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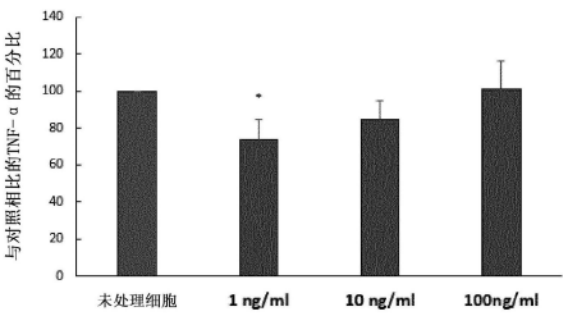
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(54) 发明名称

抗炎肽及其用途

(57) 摘要

本发明公开了一种抗炎肽,其包含选自SEQUENCE ID NO:1-16的蛋白质的抗炎片段,该抗炎片段的长度为7至37个氨基酸并且具有-9至+3的电荷;其中c-末端氨基酸不是半胱氨酸(C)或蛋氨酸(M),并且n-末端氨基酸不是半胱氨酸(C)、组氨酸(H)、脯氨酸(P)或苏氨酸(T)。抗炎片段不包含半胱氨酸(C)。抗炎片段来自SEQUENCE ID NO:1-16的蛋白质的区域,该区域特征在于长度为17至109个氨基酸并且具有-6至+4的电荷,其中该区域的c-末端氨基酸不是天冬氨酸(D)、苯丙氨酸(F)、蛋氨酸(M)或色氨酸(W),且该区域的n-末端氨基酸不是天冬氨酸(D)、组氨酸(H)、蛋氨酸(M)、脯氨酸(P)或色氨酸(W)。在SEQUENCE ID NO:71-221中提供了肽的实例。



1. 一种肽,其由SEQUENCE ID NO:349组成。
2. 根据权利要求1所述的肽,其是经修饰肽。
3. 根据权利要求2所述的肽,其通过侧链修饰、掺入保护基团、在肽合成过程中掺入非天然氨基酸和/或其衍生物和使用交联剂以及在肽上施加构象约束的其它方法而被化学修饰。
4. 一种缀合物,其包含与结合配偶体缀合、连接或融合的根据权利要求1所述的肽。
5. 根据权利要求4所述的缀合物,其中所述结合配偶体选自聚乙二醇聚合物、分子量增加化合物、亲脂性基团或抗体分子。
6. 一种缀合物,其包含与结合配偶体缀合、连接或融合的根据权利要求2所述的肽。
7. 根据权利要求6所述的缀合物,其中所述结合配偶体选自聚乙二醇聚合物、分子量增加化合物、亲脂性基团或抗体分子。
8. 一种组合物,其包含一种根据权利要求1-3中任一项所述的肽,或权利要求4-7中任一项所述的缀合物。
9. 根据权利要求8所述的组合物,其中所述组合物是粉末。
10. 根据权利要求8或9所述的组合物,其是局部组合物。
11. 根据权利要求10所述的局部组合物,其存在于制剂中,所述制剂选自包括无水组合物、水分散液、油、乳、洗剂、化妆品、擦剂、肥皂、扑粉、半固体制剂、血清 (serum)、洗发水、护发素、任何冲洗剂、滑石、摩丝、粉末剂、喷雾剂、气雾剂、溶液、混悬剂、乳剂、糖浆、酏剂、多糖膜、贴剂、绷带和粘合剂体系。
12. 根据权利要求11所述的局部用组合物,其中所述半固体制剂是糊剂。
13. 根据权利要求11所述的局部用组合物,其以个人护理产品制剂的形式存在。
14. 根据权利要求11所述的局部用组合物,其以凝胶制剂的形式存在。
15. 根据权利要求11所述的局部用组合物,其以选自乳膏、凝胶乳霜、水凝胶、软膏、香膏、泡沫和凝胶贴剂的制剂的形式存在。
16. 根据权利要求11所述的局部用组合物,其以选自油包水乳液、水包油乳液、多重乳液、水醇溶液和水乙醇酸溶液的制剂形式存在。
17. 根据权利要求10所述的局部组合物,其包含至少一种化妆上可接受的赋形剂。
18. 根据权利要求17所述的局部组合物,其中至少一种化妆上可接受的赋形剂是稀释剂、载体、粘合剂、润滑剂、悬浮剂、包衣剂、防腐剂、稳定剂、染料、载体、增溶剂、碱、润肤剂、乳化剂、香气剂、保湿剂和/或表面活性剂。
19. 一种个人护理组合物或化妆品组合物,包含权利要求8-18中任一项所述的组合物。
20. 根据权利要求19所述的个人护理组合物或化妆品组合物,其是洗发水。
21. 权利要求1-3中任一项所述的肽、权利要求4-7中任一项所述的缀合物或权利要求8-9中任一项所述的组合物在制备用于治疗或预防哺乳动物炎症或炎性紊乱的药物中的用途。
22. 根据权利要求21所述的用途,所述炎性紊乱选自皮肤炎性紊乱、关节炎性紊乱、心血管系统炎性紊乱、肺或气道炎性紊乱和肠道炎性紊乱。
23. 权利要求1-3中任一项所述的肽、权利要求4-7中任一项所述的缀合物或权利要求8-9中任一项所述的组合物在制备用于维持哺乳动物的肠道健康的药物中的用途。

抗炎肽及其用途

[0001] 分案申请

[0002] 本申请为申请号201680051932.6、申请日2016年7月18日、题为“抗炎肽及其用途”的分案申请。

背景技术

[0003] 据估计,全世界惊人地有20亿人患有某种类型的炎症(inflammation)。炎症是一个巨大的生物过程并且是我们免疫反应的必要组成部分。炎症反应可以是急性的(短暂的)或慢性的(更持久的),并且可以发生在身体的几乎每一个部位,无论它是在内部还是外部。此外,有趣的是,无论炎症的起因如何,炎症反应所致的身体内发生的生物学变化在整个身体中是相同的,这意味着不同抗炎剂所具有的减少炎症的模式在身体的所有部位都是相同的。

[0004] 通常,炎症是一种自然反应,也是使细胞摆脱损伤原因、外来侵袭或清除死亡细胞的必要反应。然而,过度的炎症对人体有很大影响,以及有时会有不利影响。实际上,炎症反应可能具有持久的不良后果,例如组织损伤。在炎症反应期间,身体释放溶酶体酶,其可以破坏组织并且甚至可能导致危及生命的超敏反应。这些病况在外部和内部均可产生持久的影响,在外部发生急性皮疹和湿疹,在体内引发诸如炎性肠病的疾病。因此,维持正常的炎症水平对我们的身心健康是非常重要的,无论是体内还是体外。不幸的是,炎症正在增加。这种增加的主要因素之一来自我们暴露于越来越多的我们身体所不习惯的外部试剂。

[0005] 当今使用的大多数抗炎治疗是药物。有两种主要类型的抗炎药,皮质类固醇(corticosteroids)和非甾体类抗炎药(NSAID)。这些包括:免疫抑制剂(甲氨蝶呤、环孢素);特定的生物药物(主要是TNF- α 抑制剂,但还包括例如环氧合酶的抑制剂);细胞毒性药物;和口服类维生素A(阿维A)。此外,还有专门减少皮肤炎症的局部治疗。实例包括乳膏和软膏(主要基于可的松),和物理治疗,如紫外线辐射。然而,这些药物具有强烈的副作用,例如胃肠毒性和类过敏反应。它们甚至可以将免疫系统抑制到容易受其它疾病和病原体影响的程度。

[0006] 因此,很明确的是需要确定具有抗炎活性的试剂,其不会免疫抑制和/或引起其它不良副作用。为此,已知一些非常特殊类型的食物可以减少炎症(Kiecolt-Glaser J.K.等人,2010,Middleton E.等人,2000,Chatterjee M.等人,2005)。实际上,这些特殊食物的特定成分是低浓度、隐性或锁住(lock away)的,并且一旦被识别和解锁,就可以按照认可的方式被放大以特异性地靶向炎症,因为我们的身体了解食物的成分并能够很容易地处理这些分子。实际上,这些特定的食物分子可以减少炎症,而不会完全阻断这种免疫系统反应,使身体处于脆弱状态。同样地对于那些对多种食物过敏的人来说,识别和解锁可减少炎症的食物的特定成分将允许这些个体获得他们原本会过敏的食物的抗炎益处。

[0007] 本发明的目的是克服至少一个上述问题。

发明内容

[0008] 豌豆基因组编码了超过70,000种不同蛋白质。申请人已经鉴定了这些蛋白质中的七种,其中的每一种均含有一种或多种抗炎片段。同样地,在由水稻基因组(rice genome)编码的超过60,000种蛋白质中,本申请人鉴定了八种蛋白质,其中的每一种均含有一种或多种抗炎片段。当与LPS刺激的人细胞一起孵育时,已证实16种鉴定的蛋白质的抗炎片段具有抗炎活性(图1至19),不会引起人类细胞活力问题(图20),并且对人类细胞没有毒性(图21)。从其衍生天然肽的特定植物蛋白质在SEQUENCE ID NO:1-15和353-355中提供,特别是来自在SEQUENCE ID NO:17-69中提供的蛋白质的区域。从其衍生肽的特定豌豆蛋白质在SEQUENCE ID NO:1-5、8和9中提供,而从其衍生肽的特定大米蛋白质(rice protein)在SEQUENCE ID NO:6、7和10-15中提供。这些蛋白质的同源物在SEQUENCE ID NO:222-267中描述。最初在豌豆蛋白质中鉴定的特定肽在SEQUENCE ID NO:71-107和110-111中示出。最初在大米蛋白质中鉴定的特定肽在SEQUENCE ID NO:108-109和112-220中示出。本文提供了本发明的在豌豆和大米蛋白质中鉴定的另外的肽,例如提供在SEQUENCE ID NO:320、331-352和356-424中。本发明的肽涵盖含有或由任何上述肽组成的肽。

[0009] EWQINEK (SEQ ID 331) -SEQ ID 7的大米蛋白质的片段

[0010] FLPQHTD (SEQ ID 332) -SEQ ID 1的豌豆蛋白质的片段

[0011] GPQYAEWQINEK (SEQ ID 333) -SEQ ID 7的大米蛋白质的片段

[0012] PGQLQSFLLSGN (SEQ ID 334) -SEQ ID 1的豌豆蛋白质的片段

[0013] PGQLQSFLLSGNQNQQNYLSGF (SEQ ID 335) -SEQ ID 1的豌豆蛋白质的片段

[0014] PQQYAEWQ (SEQ ID 336) -SEQ ID 7的大米蛋白质的片段

[0015] QLQSFLLSGNQNQQNYLSGFSK (SEQ ID 337) -SEQ ID 1的豌豆蛋白质的片段

[0016] QNQQNYLSGFSK (SEQ ID 338) -SEQ ID 1的豌豆蛋白质的片段

[0017] QSFLLSGNQNQQ (SEQ ID 339) -SEQ ID 1的豌豆蛋白质的片段

[0018] QSFLLSGNQ (SEQ ID 340) -SEQ ID 1的豌豆蛋白质的片段

[0019] RGPQQYA (SEQ ID 341) -SEQ ID 7的大米蛋白质的片段

[0020] DALEPDNR (SEQ ID 342) -SEQ ID 354的豌豆蛋白质的片段

[0021] SEEGYYGEQQQQPGMTR (SEQ ID 343) -SEQ ID 353的大米蛋白质的片段

[0022] GYYGEQQQQPGMTR (SEQ ID 344) -SEQ ID 353的大米蛋白质的片段

[0023] IDGYDTPVEGR (SEQ ID 345) -SEQ ID 15的大米蛋白质的片段

[0024] NGVLRPGQL (SEQ ID 346) -SEQ ID 14的大米蛋白质的片段

[0025] RHGEWGPSY (SEQ ID 347)

[0026] FWM (SEQ ID 348) -SEQ ID 3的豌豆蛋白质的片段

[0027] TVFDGVL RPGQL [SEQ ID 349] -SEQ ID 10的大米蛋白质的片段

[0028] RLQSQNDQRGEIIHVK [SEQ ID 350] -SEQ ID 10的大米蛋白质的片段

[0029] HGPVEMPYTL LYPSSK [SEQ ID 351] -SEQ ID 355的豌豆蛋白质的片段

[0030] L DALEPDNR [SEQ ID 352] -SEQ ID 354的豌豆蛋白质的片段

[0031] RGPQQYAEWQINE [SEQ ID 320] -SEQ ID 7的大米蛋白质的片段

[0032] 本发明的肽主要用于使炎症减轻,因此可用于预防或治疗炎性病况和维持哺乳动物的肠道健康。

[0033] 在第一方面,本发明提供了一肽,其长度通常为3至50个氨基酸,并且包含本文公开的蛋白质的片段,例如选自SEQUENCE ID NO:1-16、349或350或其同源物的片段,或所述肽的变体或片段(以下称“本发明的肽”)。在一个实施方案中,肽或其变体或片段具有生物活性。在一个实施方案中,肽或其变体或片段具有抗炎活性。

[0034] 在一个实施方案中,本发明的肽包含选自SEQUENCE ID NO:17-220、268-352和356-424的序列。

[0035] 在一个实施方案中,本发明的肽基本上由选自SEQUENCE ID NO:17-220、268-352和356-424的序列组成。

[0036] 在一个实施方案中,肽由3-50个氨基酸组成。在一个实施方案中,肽由4-50个氨基酸组成。在一个实施方案中,肽由5-50个氨基酸组成。在一个实施方案中,肽由6-50个氨基酸组成。

[0037] 在一个实施方案中,所述片段具有7至37个氨基酸和-9至+3之间的电荷。

[0038] 优选地,c-末端氨基酸不是半胱氨酸(C)或蛋氨酸(M)。

[0039] 优选地,n-末端氨基酸不是半胱氨酸(C)、组氨酸(H)、脯氨酸(P)或苏氨酸(T)。

[0040] 优选地,片段的c-末端结构域不含半胱氨酸(C)。

[0041] 优选地,片段的n-末端结构域不含半胱氨酸(C)。

[0042] 优选地,片段不含半胱氨酸(C)。

[0043] 优选地,肽不含半胱氨酸(C)。

[0044] 优选地,片段来自SEQUENCE ID NO:1-16的蛋白质的区域,该区域由以下特征表征:

[0045] -长度为17至109个氨基酸;

[0046] -电荷在-6至+4之间;

[0047] -c-末端氨基酸不是天冬氨酸(D)、苯丙氨酸(F)、蛋氨酸(M)或色氨酸(W);

[0048] -n-末端氨基酸不是天冬氨酸(D)、组氨酸(H)、蛋氨酸(M)、脯氨酸(P)或色氨酸(W)。

[0049] 优选地,该区域的c-末端结构域不含色氨酸(W)。

[0050] 优选地,SEQUENCE ID NO:1-7的蛋白质的区域选自SEQUENCE ID NO:17-33。

[0051] 优选地,SEQUENCE ID NO:8-16的蛋白质的区域选自SEQUENCE ID NO:34-70。

[0052] 优选地,SEQUENCE ID NO:1-16的蛋白质的区域选自SEQUENCE ID NO:17-70。

[0053] 优选地,片段是选自SEQUENCE ID NO:71-221,或片段的变体。

[0054] 优选地,肽由选自SEQUENCE ID NO:71-221的片段或该片段的变体组成。

[0055] 优选地,肽由选自SEQUENCE ID NO:71-221的序列组成。

[0056] 在一个实施方案中,肽包含豌豆蛋白质的片段,其中该片段选自SEQUENCE ID NO:71-107、332、334、335、337-340、342、348和351-352。

[0057] 在一个实施方案中,肽包含豌豆蛋白质的片段,其中该片段选自SEQUENCE ID NO:71-107、332、334、335、337-340、342、348和351-352。在一个实施方案中,该片段选自339、352、351、93、92、75、76、105。

[0058] 在一个实施方案中,肽包含大米蛋白质的片段,其中该片段选自SEQUENCE ID NO:108-109、112-220、320、331、333、336、341、343-346、349-350。在一个实施方案中,该片段选

自341、144、320、349、350、177、343-346。

[0059] 在一个实施方案中,肽是经修饰的肽。在一个实施方案中,肽被保护基团修饰。在一个实施方案中,肽被修饰以增加其亲脂性。在一个实施方案中,肽被修饰以增加其半衰期。在一个实施方案中,肽的N-末端或C-末端氨基酸被修饰。在一个实施方案中,肽的N-末端或C-末端氨基酸被保护基修饰。

[0060] 本发明还提供了包含缀合至结合配偶体(binding partner)的本发明肽的缀合物。在一个实施方案中,本发明的肽被反应基团修饰,该反应基团配置为允许与结合配偶体缀合。

[0061] [SEQUENCE ID NO: 1(豌豆蛋白质1)]

[0062] 优选地,肽包含SEQUENCE ID NO:1的蛋白质的生物活性片段,或其同源物,或该蛋白质片段的生物活性变体。

[0063] 优选地,肽包含SEQUENCE ID NO:1的七个区域之一的生物活性片段,即SEQUENCE ID NO:17-23,或该蛋白质片段的生物活性变体。

[0064] 优选地,肽包含选自SEQUENCE ID NO:71-91或360的生物活性片段,或该蛋白质片段的生物活性变体。

[0065] 优选地,肽包含SEQUENCE ID NO:17的区域的片段,例如SEQUENCE ID NO:71,或该蛋白质片段的生物活性变体。

[0066] 优选地,肽包含SEQUENCE ID NO:18的区域的生物活性片段,例如SEQUENCE ID NO:72,或该片段的生物活性变体。

[0067] 优选地,肽包含SEQUENCE ID NO:19的区域的生物活性片段,例如SEQUENCE ID NO:73或74中的任何一个或二者,或该片段的生物活性变体。

[0068] 优选地,肽包含SEQUENCE ID NO:20的区域的生物活性片段,例如SEQUENCE ID NO:75或76中的任何一个或二者,或该片段的生物活性变体。

[0069] 优选地,肽包含SEQUENCE ID NO:21的区域的生物活性片段,例如SEQUENCE ID NO:77-84中的一个或多个或全部,或该片段的生物活性变体。

[0070] 优选地,肽包含SEQUENCE ID NO:22的区域的生物活性片段,例如SEQUENCE ID NO:85-89中的一个或多个或全部,或该片段的生物活性变体。

[0071] 优选地,肽包含SEQUENCE ID NO:23的区域的生物活性片段,例如SEQUENCE ID NO:90,或该片段的生物活性变体。

[0072] 优选地,肽包含SEQUENCE ID NO:91,或该片段的生物活性变体。

[0073] 本发明还提供了包含本发明的至少一种肽的组合物,所述肽包含SEQUENCE ID NO:1的片段或其同源物。本发明还提供了包含本发明的至少2种,优选为3种,优选为4种,优选为5种,优选为6种,优选为7种,优选为8种,优选为9种或优选为10种肽的组合物,其中的每一种包含SEQUENCE ID NO:1的不同片段或其同源物。优选地,肽或多种肽是生物活性的。优选地,肽或多种肽是抗炎的。优选地,组合物包含本发明的第一肽和本发明的第二肽,所述第一肽包含选自SEQUENCE ID NO:17-23的第一区域的片段,所述第二肽包含选自SEQUENCE ID NO:17-23的第二区域的片段。优选地,组合物包含第一生物活性肽(其包含选自SEQUENCE ID NO:71-91的第一生物活性片段(或该片段的生物活性变体)),和第二生物活性肽(其包含选自SEQUENCE ID NO:71-91的第二生物活性片段(或该片段的生物活性变

体))。

[0074] 豌豆蛋白质1(SEQUENCE ID NO:1)的同源物包括蚕豆(*Vicia fabia*)、鹰嘴豆(*Cicerarietinum*)和兵豆(*Lens culinaris*)同源物(SEQ ID NO:222-224)。

[0075] [SEQUENCE IDNO:2(豌豆蛋白质2)]

[0076] 优选地,肽包含SEQUENCE ID NO:2的蛋白质的生物活性片段,或其同源物。

[0077] 优选地,肽包含SEQUENCE ID NO:2的两个区域之一的生物活性片段,即SEQUENCE ID NO:24或25。

[0078] 优选地,肽包含SEQUENCE ID NO:24的区域的生物活性片段,例如SEQUENCE ID NO:92,或该片段的生物活性变体。

[0079] 优选地,肽包含SEQUENCE ID NO:25的区域的生物活性片段,例如SEQUENCE ID NO:93,或该片段的生物活性变体。

[0080] 本发明还提供了包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:2的生物活性片段或其同源物。本发明还提供了包含本发明的至少两种生物活性肽的组合物,每种肽包含SEQUENCE ID NO:2的不同生物活性片段或其同源物。优选地,组合物包含含有SEQUENCE ID NO 24的区域的生物活性片段的第一生物活性肽和含有SEQUENCE ID NO 25的区域的生物活性片段的第二生物活性肽。优选地,组合物包含含有SEQUENCE ID NO 92的生物活性片段的第一生物活性肽和含有SEQUENCE ID NO 93的生物活性片段的第二生物活性肽。

[0081] 豌豆蛋白质2(SEQUENCE ID NO:2)的同源物包括兵豆(*Lens culinaris*)、法国野豌豆(*Vicia narbonensis*)和大豆(*Glycine max*) (SEQ ID NO:225-227)。

[0082] [SEQUENCEID NO:3(豌豆蛋白质3)]

[0083] 优选地,肽包含SEQUENCE ID NO:3的蛋白质的生物活性片段,或其同源物。

[0084] 优选地,肽包含SEQUENCE ID NO:3的两个区域之一的生物活性片段,即SEQUENCE ID NO:26或27。

[0085] 优选地,肽包含SEQUENCE ID NO:26的区域的生物活性片段,例如SEQUENCE ID NO:94,或该片段的生物活性变体。

[0086] 优选地,肽包含SEQUENCE ID NO:27的区域的生物活性片段,例如SEQUENCE ID NO:95,或该片段的生物活性变体。

[0087] 本发明还提供了一种至少包含本发明的生物活性肽的组合物,所述肽包含SEQUENCE ID NO:3的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少两种生物活性肽的组合物,其中每一种肽包含SEQUENCE ID NO:3的不同生物活性片段或其同源物。优选地,组合物包含含有SEQUENCE ID NO 26的区域的生物活性片段的第一肽和含有SEQUENCE ID NO 27的生物活性片段的第二肽。优选地,组合物包含含有SEQUENCE ID NO 94的生物活性片段(或该片段的生物活性变体)的第一生物活性肽和包含SEQUENCE ID NO 95的生物活性片段(或该片段的生物活性变体)的第二生物活性肽。

[0088] 豌豆蛋白质3(SEQUENCE ID NO:3)的同源物包括箭筈豌豆(*Vicia sativa*)、蒺藜苜蓿(*Medicago truncatula*)和百脉根(*Lotus japonicas*) (SEQ ID NO:228-230)。

[0089] [SEQUENCE ID NO:4(豌豆蛋白质4)]

[0090] 优选地,肽包含SEQUENCE ID NO:4的蛋白质的生物活性片段,或其同源物。

[0091] 优选地,肽包含SEQUENCE ID NO:4的五个区域之一的生物活性片段,即SEQUENCE ID NO:28-32。优选地,区域是SEQUENCE ID NO:28,优选为SEQUENCE ID NO:29,优选为SEQUENCE ID NO:30,优选为SEQUENCE ID NO:31,优选为SEQUENCE ID NO:32。

[0092] 优选地,肽包含SEQUENCE ID NO:28的区域的生物活性片段,例如SEQUENCE ID NO:96,或该片段的生物活性变体。

[0093] 优选地,肽包含SEQUENCE ID NO:29的区域的生物活性片段,例如SEQUENCE ID NO:97-103,或该片段的生物活性变体。

[0094] 优选地,肽包含SEQUENCE ID NO:30的区域的生物活性片段,例如SEQUENCE ID NO:104,或该片段的生物活性变体。

[0095] 优选地,肽包含SEQUENCE ID NO:31的区域的生物活性片段,例如SEQUENCE ID NO:105,或该片段的生物活性变体。

[0096] 优选地,肽包含SEQUENCE ID NO:32的区域的生物活性片段,例如SEQUENCE ID NO:106,或该片段的生物活性变体。

[0097] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:4的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少2种,优选为3种,优选为4种,优选为5种,优选为6种,优选为7种,优选为8种,优选为9种或优选为10种含有SEQUENCE ID NO:4的不同生物活性片段或其同源物的肽的组合物。优选地,组合物包含含有选自SEQUENCE ID NO:28-32的第一区域的生物活性片段的第一肽,和含有选自SEQUENCE ID NO:28-32的第二区域的生物活性片段的第二肽。优选地,组合物包含第一生物活性肽(其包含选自SEQUENCE ID NO:96-106的第一生物活性片段(或该片段的生物活性变体)),和第二生物活性肽(其包含选自SEQUENCE ID NO:96-106的第二生物活性片段(或该片段的生物活性变体))。

[0098] 豌豆蛋白质4(SEQUENCE ID NO:4)的同源物包括埃塞俄比亚豌豆(*Pisum abyssinicum*)、山黧豆葵(*Lathyrus annuus*)和长柔毛野豌豆(*Vicia villosa*) (SEQ ID 231-233)。

[0099] [SEQUENCE ID NO:5(豌豆蛋白质5)]

[0100] 优选地,肽包含SEQUENCE ID NO:5的蛋白质的生物活性片段,或其同源物。

[0101] 优选地,肽包含SEQUENCE ID NO:5的区域的生物活性片段,即SEQUENCE ID NO 33的区域,例如SEQUENCE ID NO:107,或该片段的生物活性变体。

[0102] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:5的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少两种肽的组合物,其包含SEQUENCE ID NO:5的至少一种生物活性片段或其同源物,例如SEQUENCE ID NO:107。

[0103] 豌豆蛋白质5(SEQUENCE ID NO:5)的同源物包括蒺藜苜蓿(*Medicago truncatula*)、游隼野豌豆(*Vicia peregrine*)和黄花豌豆(*Vicia lutea*) (SEQ ID NO:234-236)。

[0104] [SEQUENCE ID NO:6(大米蛋白质7-Q6K508)]

[0105] 优选地,肽包含SEQUENCE ID NO:6的蛋白质的生物活性片段,或其同源物。

[0106] 优选地,肽包含SEQUENCE ID NO:108的生物活性片段,或该片段的生物活性变体。

[0107] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:6的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少两种肽的组合物,其包含SEQUENCE ID NO:6的至少一种生物活性片段或其同源物,例如SEQUENCE ID NO:108(SP1)。

[0108] 大米蛋白质7 (SEQUENCE ID NO:6) 的同源物包括短花药野生稻 (*Oryza brachyantha*)、燕麦 (*Avena sativa*) 和二穗短柄草 (*Brachypodium distachyon*) (SEQ ID NO:237-239)。

[0109] [SEQUENCE ID NO:7 (大米蛋白质8-Q6K7K6)]

[0110] 优选地,肽包含SEQUENCE ID NO:7的蛋白质的生物活性片段或其同源物。

[0111] 优选地,肽包含SEQUENCE ID NO:109(SP2) 的生物活性片段,或该片段的生物活性变体。

[0112] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:7的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少两种肽的组合物,其包含SEQUENCE ID NO:7的至少一种生物活性片段或其同源物,例如SEQUENCE ID NO:109(SP2)。

[0113] 大米蛋白质8 (SEQUENCE ID NO:7) 的同源物包括粳稻组水稻 (*Oryza sativa Japonica Group*)、籼稻组水稻 (*Oryza sativa Indica Group*) 和短花药野生稻 (*Oryza brachyantha*) (SEQ ID NO:240-242)。

[0114] [SEQUENCE ID NO:8 (豌豆蛋白质6-P13919)]

[0115] 优选地,肽包含SEQUENCE ID NO:8的蛋白质的生物活性片段或其同源物。

[0116] 优选地,肽包含SEQUENCE ID NO:110(SP3) 的生物活性片段,或该片段的生物活性变体。

[0117] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:8的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少两种肽的组合物,其包含SEQUENCE ID NO:8的至少一种生物活性片段或其同源物,例如SEQUENCE ID NO:110(SP3)。

[0118] 豌豆蛋白质8 (SEQUENCE ID NO:8) 的同源物包括豌豆野生种 (*Pisum fulvum*)、埃塞俄比亚豌豆 (*Pisum abyssinicum*) 和长柔毛野豌豆 (*Vicia villosa*) (SEQ ID NO:243-245)。

[0119] [SEQUENCE ID NO:9 (豌豆蛋白质7-P02855)]

[0120] 优选地,肽包含SEQUENCE ID NO:9的蛋白质的生物活性片段,或其同源物。

[0121] 优选地,肽包含SEQUENCE ID NO:111 (SP4) 的生物活性片段,或该片段的生物活性变体。

[0122] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:9的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少两种肽的组合物,其包含SEQUENCE ID NO:9的至少一种生物活性片段或其同源物,例如SEQUENCE ID NO:111 (SP4)。

[0123] 豌豆蛋白质9 (SEQUENCE ID NO:9) 的同源物包括硬毛山黧豆 (*Lathyrus hirsutus*)、扁荚山黧豆 (*Lathyrus cicero*)、家山黧豆 (*Lathyrus sativus*) (SEQ ID NO:

246-248)。

[0124] [SEQUENCEIDNO:10(大米蛋白质1-P07728)]

[0125] 优选地,肽包含SEQUENCE ID NO:10的蛋白质的生物活性片段,或其同源物。

[0126] 优选地,肽包含SEQUENCE ID NO:10的九个区域之一的片段,即SEQUENCE ID NO:34-42。优选地,该区域是SEQUENCE ID NO:34,优选为SEQUENCE ID NO:35,优选为SEQUENCE ID NO:36,优选为SEQUENCE ID NO:37,优选为SEQUENCE ID NO:38,优选为SEQUENCE ID NO:39,优选为SEQUENCE ID NO:40,优选为SEQUENCE ID NO:41,优选为SEQUENCE ID NO:42。

[0127] 优选地,肽包含SEQUENCE ID NO:34的区域的生物活性片段,例如SEQUENCE ID NO:112或SEQUENCE ID NO:113,或该片段的生物活性变体。

[0128] 优选地,肽包含SEQUENCE ID NO:35的区域的生物活性片段,例如SEQUENCE ID NO:114,或该片段的生物活性变体。

[0129] 优选地,肽包含SEQUENCE ID NO:36的区域的生物活性片段,例如SEQUENCE ID NO:115或SEQUENCE ID NO:116,或该片段的生物活性变体。

[0130] 优选地,肽包含SEQUENCE ID NO:37的区域的生物活性片段,例如SEQUENCE ID NO:117或SEQUENCE ID NO:118,或该片段的生物活性变体。

[0131] 优选地,肽包含SEQUENCE ID NO:38的区域的生物活性片段,例如SEQUENCE ID NO:119,或该片段的生物活性变体。

[0132] 优选地,肽包含SEQUENCE ID NO:39的区域的生物活性片段,例如SEQUENCE ID NO:120、121或122,或该片段的生物活性变体。

[0133] 优选地,肽包含SEQUENCE ID NO:40的区域的生物活性片段,例如SEQUENCE ID NO:123,或该片段的生物活性变体。

[0134] 优选地,肽包含SEQUENCE ID NO:41的区域的生物活性片段,例如SEQUENCE ID NO:124、125、126、127、128或129,或该片段的生物活性变体。

[0135] 优选地,肽包含SEQUENCE ID NO:42的区域的片段,例如SEQUENCE ID NO:130、131或132,或该片段的生物活性变体。

[0136] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:10的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少2种,优选为3种,优选为4种,优选为5种,优选为6种,优选为7种,优选为8种,优选为9种或优选为10种肽的组合物,每种肽包含SEQUENCE ID NO:10的不同生物活性片段或其同源物。优选地,组合物包含含有选自SEQUENCE ID NO:34-42的第一区域的生物活性片段的第一肽,和含有选自SEQUENCE ID NO:34-42的第二区域的生物活性片段的第二肽。优选地,组合物包含第一生物活性肽(其包含选自SEQUENCE ID NO:112-132的第一生物活性片段(或该片段的生物活性变体)),和第二生物活性肽(其包含选自SEQUENCE ID NO:112-132的第二生物活性片段(或该片段的生物活性变体))。

[0137] 大米蛋白质1(SEQUENCE ID NO:10)的同源物包括短花药野生稻(*Oryza brachyantha*)和菰(*Zizania latifolia*)(SEQ ID NO:249-251)。

[0138] [SEQUENCEIDNO:11(大米蛋白质2-P07728)]

[0139] 优选地,肽包含SEQUENCE ID NO:11的蛋白质的生物活性片段,或其同源物。

[0140] 优选地,肽包含SEQUENCE ID NO:11的四个区域之一的生物活性片段,即SEQUENCE ID NO:43-46。优选地,该区域是SEQUENCE ID NO:43,优选为SEQUENCE ID NO:44,优选为SEQUENCE ID NO:45,优选为SEQUENCE ID NO:46。

[0141] 优选地,肽包含SEQUENCE ID NO:43的区域的生物活性片段,例如SEQUENCE ID NO:133,或该片段的生物活性变体。

[0142] 优选地,肽包含SEQUENCE ID NO:44的区域的生物活性片段,例如SEQUENCE ID NO:134-137,或该片段的生物活性变体。

[0143] 优选地,肽包含SEQUENCE ID NO:45的区域的生物活性片段,例如SEQUENCE ID NO:138-144,或该片段的生物活性变体。

[0144] 优选地,肽包含SEQUENCE ID NO:46的区域的生物活性片段,例如SEQUENCE ID NO:145,或该片段的生物活性变体。

[0145] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:11的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少2种,优选为3种,优选为4种,优选为5种,优选为6种,优选为7种,优选为8种,优选为9种或优选为10种肽的组合物,其中每种肽包含SEQUENCE ID NO:11的生物活性片段或其同源物。优选地,组合物包含含有选自SEQUENCE ID NO:43-46的第一区域的生物活性片段的第一肽,和含有选自SEQUENCE ID NO:43-46的第二区域的生物活性片段的第二肽。优选地,组合物包含第一生物活性肽(其包含选自SEQUENCE ID NO:133-145的第一生物活性片段(或该片段的生物活性变体)),和第二生物活性肽(其包含选自SEQUENCE ID NO:133-145的第二生物活性片段(或该片段的生物活性变体))。

[0146] 大米蛋白质2(SEQUENCE ID NO:11)的同源物包括籼稻组水稻(*Oryza sativa* Indica Group)、菰(*Zizania latifolia*)、燕麦(*Avena sativa*)(SEQ ID NO:252-254)。

[0147] [SEQUENCE ID NO:12(大米蛋白质3-P07730)]

[0148] 优选地,肽包含SEQUENCE ID NO:12的蛋白质的生物活性片段,或其同源物。

[0149] 优选地,肽包含SEQUENCE ID NO:12的八个区域之一的生物活性片段,即SEQUENCE ID NO:47-54。优选地,该区域是SEQUENCE ID NO:47,优选为SEQUENCE ID NO:48,优选为SEQUENCE ID NO:49,优选为SEQUENCE ID NO:50,优选为SEQUENCE ID NO:51,优选为SEQUENCE ID NO:52,优选为SEQUENCE ID NO:53,优选为SEQUENCE ID NO:54。

[0150] 优选地,肽包含SEQUENCE ID NO:47的区域的生物活性片段,例如SEQUENCE ID NO:146-150,或该片段的生物活性变体。

[0151] 优选地,肽包含SEQUENCE ID NO:48的区域的生物活性片段,例如SEQUENCE ID NO:151-157之一,或该片段的生物活性变体。

[0152] 优选地,肽包含SEQUENCE ID NO:49的区域的生物活性片段,例如SEQUENCE ID NO:158或SEQUENCE ID NO:159之一,或该片段的生物活性变体。

[0153] 优选地,肽包含SEQUENCE ID NO:50的区域的生物活性片段,例如SEQUENCE ID NO:160-162之一,或该片段的生物活性变体。

[0154] 优选地,肽包含SEQUENCE ID NO:51的区域的生物活性片段,例如SEQUENCE ID NO:163或164之一,或该片段的生物活性变体。

[0155] 优选地,肽包含SEQUENCE ID NO:52的区域的生物活性片段,例如SEQUENCE ID

NO:165,或该片段的生物活性变体。

[0156] 优选地,肽包含SEQUENCE ID NO:53的区域的生物活性片段,例如SEQUENCE ID NO:166-171之一,或该片段的生物活性变体。

[0157] 优选地,肽包含SEQUENCE ID NO:54的区域的生物活性片段,例如SEQUENCE ID NO:172-176之一,或该片段的生物活性变体。

[0158] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:12的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少2种,优选为3种,优选为4种,优选为5种,优选为6种,优选为7种,优选为8种,优选为9种或优选为10种肽的组合物,其中每种肽包含SEQUENCE ID NO:12的生物活性片段或其同源物。优选地,组合物包含含有选自SEQUENCE ID NO:47-54的第一区域的生物活性片段的第一肽,和含有选自SEQUENCE ID NO:47-54的第二区域的生物活性片段的第二肽。优选地,组合物包含第一生物活性肽(其包含选自SEQUENCE ID NO:146-172的第一生物活性片段(或该片段的生物活性变体)),和第二生物活性肽(其包含选自SEQUENCE ID NO:146-172的第二抗炎片段(或该片段的生物活性变体))。

[0159] 大米蛋白质3(SEQUENCE ID NO:12)的同源物包括短花药野生稻(*Oryza brachyantha*)、二穗短柄草(*Brochypodium distachyon*)(SEQ ID NO:255-257)。

[0160] [SEQUENCEIDNO:13(大米蛋白质4-Q0D7S0)]

[0161] 优选地,肽包含SEQUENCE ID NO:13的蛋白质的生物活性片段,或其同源物。

[0162] 优选地,肽包含SEQUENCE ID NO:13的区域的生物活性片段,即SEQUENCE ID NO 55,例如SEQUENCE ID NO:177,或该片段的生物活性变体。

[0163] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:13的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少两种肽的组合物,其中的至少一种肽包含SEQUENCE ID NO:13的生物活性片段或其同源物,例如SEQUENCE ID NO:177,或该片段的生物活性变体。

[0164] 大米蛋白质4(SEQUENCE ID NO:13)的同源物包括籼稻组水稻(*Oryza sativa* Indica Group)、菰(*Zizania latifolia*)、燕麦(*Avena sativa*)(SEQ ID NO:252-254)。

[0165] [SEQUENCEIDNO:14(大米蛋白质5 -P14614)]

[0166] 优选地,肽包含SEQUENCE ID NO:14的蛋白质的片段,或其同源物。

[0167] 优选地,肽包含SEQUENCE ID NO:14的七个区域之一的生物活性片段,即SEQUENCE ID NO:56-62。优选地,该区域是SEQUENCE ID NO:56,优选为SEQUENCE ID NO:57,优选为SEQUENCE ID NO:58,优选为SEQUENCE ID NO:59,优选为SEQUENCE ID NO:60,优选为SEQUENCE ID NO:61,优选为SEQUENCE ID NO:62。

[0168] 优选地,肽包含SEQUENCE ID NO:56的区域的生物活性片段,例如SEQUENCE ID NO:178-180之一,或该片段的生物活性变体。

[0169] 优选地,肽包含SEQUENCE ID NO:57的区域的生物活性片段,例如SEQUENCE ID NO:181-182之一,或该片段的生物活性变体。

[0170] 优选地,肽包含SEQUENCE ID NO:58的区域的生物活性片段,例如SEQUENCE ID NO:183,或该片段的生物活性变体。

[0171] 优选地,肽包含SEQUENCE ID NO:59的区域的生物活性片段,例如SEQUENCE ID

NO:184-190之一,或该片段的生物活性变体。

[0172] 优选地,肽包含SEQUENCE ID NO:60的区域的生物活性片段,例如SEQUENCE ID NO:191,或该片段的生物活性变体。

[0173] 优选地,肽包含SEQUENCE ID NO:61的区域的生物活性片段,例如SEQUENCE ID NO:192-195之一,或该片段的生物活性变体。

[0174] 优选地,肽包含SEQUENCE ID NO:62的区域的生物活性片段,例如SEQUENCE ID NO:196-197之一,或该片段的生物活性变体。

[0175] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:14的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少2种,优选为3种,优选为4种,优选为5种,优选为6种,优选为7种,优选为8种,优选为9种或优选为10种肽的组合物,其中每种肽包含SEQUENCE ID NO:14的生物活性片段或其同源物。优选地,组合物包含含有选自SEQUENCE ID NO:56-62的第一区域的生物活性片段的第一肽,和含有选自SEQUENCE ID NO:56-62的第二区域的生物活性片段的第二肽。优选地,组合物包含第一生物活性肽(其包含选自SEQUENCE ID NO:178-197的第一生物活性片段(或该片段的生物活性变体)),和第二生物活性肽(其包含选自SEQUENCE ID NO:178-197的第二生物活性片段(或该片段的生物活性变体))。

[0176] 大米蛋白质5(SEQUENCE ID NO:14)的同源物包括粳稻组水稻(*Oryza sativa* Japonica Group)、二穗短柄草(*Brachypodium distachyon*)(SEQ ID NO:261-263)。

[0177] [SEQUENCE ID NO:15(大米蛋白质6-Q0DEV5)]

[0178] 优选地,肽包含SEQUENCE ID NO:15的蛋白质的生物活性片段,或其同源物。

[0179] 优选地,肽包含SEQUENCE ID NO:15的七个区域之一的生物活性片段,即SEQUENCE ID NO:63-67。优选地,该区域是SEQUENCE ID NO:63,优选为SEQUENCE ID NO:64,优选为SEQUENCE ID NO:65,优选为SEQUENCE ID NO:66,优选为SEQUENCE ID NO:67。

[0180] 优选地,肽包含SEQUENCE ID NO:63的区域的片段,例如SEQUENCE ID NO:198-200之一,或该片段的生物活性变体。

[0181] 优选地,肽包含SEQUENCE ID NO:64的区域的片段,例如SEQUENCE ID NO:201-203之一,或该片段的生物活性变体。

[0182] 优选地,肽包含SEQUENCE ID NO:65的区域的片段,例如SEQUENCE ID NO:204,或该片段的生物活性变体。

[0183] 优选地,肽包含SEQUENCE ID NO:66的区域的片段,例如SEQUENCE ID NO:205-208之一,或该片段的生物活性变体。

[0184] 优选地,肽包含SEQUENCE ID NO:67的区域的片段,例如SEQUENCE ID NO:209-215之一,或该片段的生物活性变体。

[0185] 优选地,肽包含SEQUENCE ID NO:68的区域的片段,例如SEQUENCE ID NO:216-219之一,或该片段的生物活性变体。

[0186] 优选地,肽包含SEQUENCE ID NO:69的区域的片段,例如SEQUENCE ID NO:220,或该片段的生物活性变体。

[0187] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:15的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少2

种,优选为3种,优选为4种,优选为5种,优选为6种,优选为7种,优选为8种,优选为9种,或优选为10种肽的组合物,其中每种肽包含SEQUENCE ID NO:15的生物活性片段或其同源物。优选地,组合物包含含有选自SEQUENCE ID NO:63-69的第一区域的生物活性片段的第一肽,和含有选自SEQUENCE ID NO:63-69的第二区域的生物活性片段的第二肽。优选地,组合物包含第一生物活性肽(其包含选自SEQUENCE ID NO:198-220的第一生物活性片段(或该片段的生物活性变体)),和第二生物活性肽(其包含选自SEQUENCE ID NO:198-220的第二生物活性片段(或该片段的生物活性变体))。

[0188] 大米蛋白质6(SEQUENCE ID NO:15)的同源物包括普通野生稻(*Oryza rufipogon*)、药用野生稻(*Oryza officinalis*)、青稞(*Hordeum vulgare* subsp.vulgare)(SEQ ID NO:264-266)。

[0189] [SEQUENCE ID NO:16(细菌蛋白质1-P0C1U8)]

[0190] 优选地,肽包含SEQUENCE ID NO:16的蛋白质的生物活性片段,或其同源物。

[0191] 优选地,肽包含SEQUENCE ID NO:16的区域的生物活性片段,即SEQUENCE ID NO 70的区域。通常,肽是SEQUENCE ID NO 221,或该片段的生物活性变体。

[0192] 本发明还提供了一种包含本发明的至少一种生物活性肽的组合物,所述肽包含SEQUENCE ID NO:16的生物活性片段或其同源物。本发明还提供了一种包含本发明的至少两种肽的组合物,其中的至少一种肽包含SEQUENCE ID NO:16的片段或其同源物,例如SEQUENCE ID NO:212,或该片段的生物活性变体。

[0193] 细菌蛋白质1(SEQUENCE ID NO:16)的同源物包括:

[0194] >gi|580560623|gb|EVF84961.1| 谷氨酰内肽酶 [金黄色葡萄球菌 COAS6020]

[0195] >gi|580687002|gb|EVH10169.1| 谷氨酰内肽酶 [金黄色葡萄球菌 UCIM6080]

[0196] >gi|751815683|gb|KIN24957.1| 谷氨酰内肽酶 [金黄色葡萄球菌 MRSA_CVM43477]

[0197] >gi|781884797|dbj|BAR08486.1| 谷氨酰内肽酶前体 [金黄色葡萄球菌金黄色亚种]

[0198] >gi|781887762|dbj|BAR11210.1| 谷氨酰内肽酶前体 [金黄色葡萄球菌金黄色亚种]

[0199] 本发明还提供了包含至少一种且优选为多种本发明的生物活性肽的生物活性组合物,其中本发明的每种肽包含本文所描述的蛋白质的生物活性片段。在一个实施方案中,蛋白质选自SEQUENCE ID NO:1-16。通常,本发明的所述肽或每种肽选自,或包含一生物活性片段,所述生物活性片段选自,SEQUENCE ID NO:71-220,或所述片段的生物活性变体。

[0200] 在一个实施方案中,组合物包含本发明的肽,所述肽包括选自SEQUENCE ID NO:17-220、268-352和356-424的序列。

[0201] 在一个实施方案中,组合物包含本发明的肽,所述肽基本上由选自SEQUENCE ID NO:17-220、268-352和356-424的序列组成。

[0202] 通常,本发明的所述肽或每种肽选自,或包含一生物活性片段,所述生物活性片段选自,SEQUENCE ID NO:71-107和110-111,或所述片段的生物活性变体。

[0203] 通常,本发明的所述肽或每种肽选自,或包含一抗炎片段,所述抗炎片段选自SEQUENCE ID NO:108-109和112-220,或所述片段的抗炎变体。

- [0204] 在一个实施方案中,本发明的生物活性肽、变体或片段是抗炎的。
- [0205] 优选地,组合物包含本发明的至少两种不同的肽。
- [0206] 优选地,组合物包含本发明的至少三种不同的肽。
- [0207] 优选地,组合物包含本发明的至少四种不同的肽。
- [0208] 优选地,组合物包含本发明的至少五种不同的肽。
- [0209] 优选地,组合物包含本发明的至少六种不同的肽。
- [0210] 优选地,组合物包含本发明的至少七种不同的肽。
- [0211] 优选地,组合物包含本发明的至少八种不同的肽。
- [0212] 优选地,组合物包含本发明的至少九种不同的肽。
- [0213] 优选地,组合物包含本发明的至少十种不同的肽。
- [0214] 在一个实施方案中,本发明包括一种组合物,所述组合物包含SEQUENCE ID NO: 71-107和110-111中的一种或多种,或片段的抗炎变体,或抗炎片段和变体的混合物。
- [0215] 在一个实施方案中,组合物包含SEQUENCE ID NO 75、91、92、93、110和111中的至少一种、两种、三种、四种、五种或全部。
- [0216] 在一个实施方案中,组合物包含基本上全部片段SEQUENCE ID NO:71-107和110-111。
- [0217] 在一个实施方案中,本发明包括一种组合物,所述组合物包含SEQUENCE ID NO: 108-109和112-220中的一种或多种,或片段的抗炎变体,或抗炎片段和变体的混合物。
- [0218] 在一个实施方案中,组合物包含SEQUENCE ID NO 108、109和144中的至少一种、两种或三种。
- [0219] 在一个实施方案中,本发明的组合物富含分子量小于10KD的肽。在一个实施方案中,组合物几乎没有(depleted of)细胞碎片。
- [0220] 在一个实施方案中,本发明的组合物是粉末。
- [0221] 在一个实施方案中,本发明包括一组合物,其包含SEQUENCE ID NO:108-109和112-220基本上全部的片段,或片段的抗炎变体,或抗炎片段和变体的混合物。
- [0222] 在一个实施方案中,组合物是个人护理组合物。在一个实施方案中,组合物是药物组合物。在一个实施方案中,组合物是固体。在一个实施方案中,组合物是半固体(即,乳膏、凝胶或洗剂)。在一个实施方案中,组合物是液体。
- [0223] 本发明还涉及一种包含本发明的肽的人造个人护理组合物。
- [0224] 本发明还涉及一种包含本发明的肽的组合物的人造个人护理组合物。
- [0225] 在一个实施方案中,个人护理组合物是护肤产品。在一个实施方案中,个人护理组合物是护发产品。在一个实施方案中,个人护理组合物是牙膏产品。在一个实施方案中,个人护理组合物是香料产品。在一个实施方案中,个人护理组合物是除臭产品。在一个实施方案中,个人护理组合物是止汗剂产品。在一个实施方案中,个人护理组合物是肥皂。在一个实施方案中,个人护理组合物是液体肥皂。在一个实施方案中,个人护理组合物是乳膏。在一个实施方案中,个人护理组合物是洗剂。在一个实施方案中,个人护理组合物是凝胶。在一个实施方案中,个人护理组合物是粉末。
- [0226] 本发明还涉及一种用于治疗或预防哺乳动物炎症的本发明的肽。
- [0227] 本发明还涉及一种用于治疗或预防哺乳动物炎症的本发明的肽的组合物。

[0228] 本发明还涉及一种用于治疗或预防哺乳动物炎性紊乱(inflammatory disorder)的本发明的肽。

[0229] 本发明还涉及一种用于治疗或预防哺乳动物炎性紊乱的本发明的肽的组合物。

[0230] 在一个实施方案中,炎症是症状性炎症。

[0231] 在一个实施方案中,炎性紊乱是关节的炎性紊乱。在一个实施方案中,炎性疾病是心血管系统的炎性紊乱。在一个实施方案中,炎性紊乱是自身免疫性疾病。在一个实施方案中,炎性紊乱是肺和气道炎性疾病。在一个实施方案中,炎性紊乱是肠道炎性紊乱。在一个实施方案中,炎性紊乱是皮炎。在一个实施方案中,炎性紊乱是寻常痤疮。在一个实施方案中,炎性紊乱是银屑病。在一个实施方案中,炎性紊乱是类风湿性关节炎。在一个实施方案中,炎性紊乱是心血管疾病。在一个实施方案中,炎性紊乱是动脉粥样硬化。在一个实施方案中,炎性紊乱是I型糖尿病。在一个实施方案中,炎性紊乱是格雷夫斯病(Graves disease)。在一个实施方案中,炎性紊乱是格林-巴利病(Guillain-Barre disease)。在一个实施方案中,炎性紊乱是狼疮。在一个实施方案中,炎性紊乱是牛皮癣性关节炎。在一个实施方案中,炎性紊乱是溃疡性结肠炎。在一个实施方案中,炎性紊乱是哮喘。在一个实施方案中,炎性紊乱是囊肿性纤维化。在一个实施方案中,炎性紊乱是COPD。在一个实施方案中,炎性紊乱是肺气肿。在一个实施方案中,炎性紊乱是急性呼吸窘迫综合征。在一个实施方案中,炎性紊乱是结肠炎。在一个实施方案中,炎性紊乱是炎性肠病。

[0232] 本发明还涉及一种用于治疗或预防哺乳动物的疼痛的本发明的肽。

[0233] 本发明还涉及一种用于治疗或预防哺乳动物的疼痛的本发明的肽的组合物。

[0234] 本发明还涉及一种用于治疗或预防哺乳动物的代谢紊乱的本发明的肽。

[0235] 本发明还涉及一种用于治疗或预防哺乳动物的代谢紊乱的本发明的肽的组合物。

[0236] 在一个实施方案中,代谢紊乱是前期糖尿病(pre-diabetes)。在一个实施方案中,代谢紊乱是糖尿病。在一个实施方案中,代谢紊乱是1型糖尿病。在一个实施方案中,代谢紊乱是2型糖尿病。在一个实施方案中,代谢紊乱是代谢综合征。在一个实施方案中,代谢紊乱是肥胖。在一个实施方案中,代谢紊乱是糖尿病性血脂异常。在一个实施方案中,代谢紊乱是高脂血症。在一个实施方案中,代谢紊乱是高血压。在一个实施方案中,代谢紊乱是高甘油三酯血症。在一个实施方案中,代谢紊乱是高脂肪酸血症(hyperfattyacidemia)。在一个实施方案中,代谢紊乱是高胆固醇血症。在一个实施方案中,代谢紊乱是高胰岛素血症。在一个实施方案中,代谢紊乱是MODY。

[0237] 本发明还涉及一种用于维持或恢复哺乳动物的肠道健康的本发明的肽。

[0238] 本发明还涉及一种用于维持或恢复哺乳动物的肠道健康的本发明的肽的组合物。

[0239] 本发明还涉及一种用于维持或恢复哺乳动物的肌肉健康(例如,瘦肉组织量)的本发明的肽。

[0240] 本发明还涉及一种用于维持或恢复哺乳动物的肌肉健康(例如,瘦肉组织量)的本发明的肽的组合物。

[0241] 本发明还涉及一种包含本发明的肽以及药学上可接受的载体的药物组合物。

[0242] 本发明还涉及一种药物组合物,其包含本发明的肽的组合物以及药学上可接受的载体。

[0243] 这样的肽可用于个人护理和药物产品以治疗和维持整个身体的健康水平的炎症。

本发明满足了对食源性特异性肽和肽组合物的巨大需求,该食源性特异性肽和肽组合物以能够被身体处理而不会完全阻断免疫反应和引起自身免疫问题及其它不希望的副作用的方式减少炎症。本发明最终帮助了20亿炎症患者。

[0244] 本发明的肽以化妆或药学上有效的浓度用于本发明的局部用化妆或药物组合物以达到期望的效果;相对于组合物的总重量,优选形式为0.00000001% (以重量计)至20% (以重量计);优选为0.000001% (以重量计)至15% (以重量计),更优选为0.0001% (以重量计)至10% (以重量计),且甚至更优选为0.0001% (以重量计)至5% (以重量计)。理想地,优选以组合物的约0.00001% w/w至约0.5% w/w [0.1至5000ppm],且更优选为0.00005w/w至约0.05w/w [0.5至500ppm],且最优选为约0.0001w/w至约0.01w/w的 [1至100ppm]使用本发明的肽。理想地,优选以组合物的约0.0001% w/w至约0.004% w/w使用本发明的肽。

[0245] 对于本发明的肽的组合物,典型的每日剂量可以是0.2g至100g。

[0246] 本发明的肽和组合物还可用于炎症的非治疗性处理。炎症的非治疗性处理的实例包括用于减轻正常的非病理性炎症,例如运动后的肌肉和关节内的炎症。

[0247] 本发明还提供了包含本发明的肽的局部组合物。应该理解,局部组合物可以包含多种肽、片段和/或变体。在一个实施方案中,局部组合物包含基本上所有的肽。在一个实施方案中,局部组合物包含基本上所有的变体。本发明的局部组合物可以存在于制剂中,所述制剂选自包括乳膏、多重乳液 (multiple emulsions)、无水组合物、水分散液、油、乳、香膏、泡沫、洗剂、凝胶、凝胶乳霜、水醇溶液、水乙醇酸溶液、化妆品、个人护理产品、水凝胶、擦剂、血清 (sera)、肥皂、扑粉、糊剂、半固体制剂、擦剂、血清 (serum)、洗发水、护发素、软膏、任何冲洗剂、滑石、摩丝、粉末剂、喷雾剂、气雾剂、溶液、混悬剂、乳剂、糖浆、酞剂、多糖膜、贴剂、凝胶贴剂、绷带、粘合剂体系、油包水乳剂、水包油乳剂和硅酮乳剂的组。

[0248] 在本发明的一个实施方案中,乳剂含有脂质或油。乳剂可以是但不限于水包油、油包水、水包油包水和硅酮包水包油 (oil-in-water-in-silcone) 乳剂。乳剂可以含有保湿剂。乳剂可以含有消泡剂如硅酮。乳剂可以具有任何合适的粘度。乳剂还可含有乳化剂和/或消泡剂。制备乳剂的方法是本领域技术人员已知的。

[0249] 可将本发明的局部组合物掺入用于施用的医疗器械中。这种器械可以包括但不限于织物、贴片、绷带、计量器、袜子、紧身衣、内衣、敷料、手套、面罩、粘合贴剂、非粘合贴剂、封闭贴剂和微电贴剂或合适的粘合体系。在这样的实施方案中,器械与角质层如皮肤直接接触,从而释放本发明的肽。应该理解,可以本文详述的任何合适的形式掺入局部组合物。例如,本发明的局部组合物或肽可掺入器械中或存在于器械表面上,或者可以是乳膏、凝胶或蜡制剂或本文定义的任何合适的制剂并且掺入到器械中或器械表面上。器械可以适合于粘附或附着到皮肤上。

[0250] 在一个实施方案中,器械适于释放恒定量的本发明的组合物或肽。应当理解,持续释放系统中所含的组合物的量取决于例如组合物将在何处施用、本发明组合物的释放的动力学和持续时间,以及待治疗和/或待护理的状况、紊乱和/或疾病的性质。器械可以使得组合物由于身体水分、皮肤的pH或体温而通过器械的生物降解,或者通过器械与身体之间的摩擦,而被释放。

[0251] 在本发明的一个实施方案中,局部组合物还可包含至少一种化妆或药学上可接受的赋形剂。赋形剂可以与功能成分或添加剂互换使用。应该理解,虽然本发明的局部组合物

可以单独施用,但它们通常与化妆或药物赋形剂混合施用。化妆或药学上可接受的赋形剂是本领域公知的,并且是可以使用的任何已知的赋形剂,只要其适合于局部施用并且是皮肤病学可接受的而没有不适当毒性(undue toxicity)、不相容性和/或过敏反应。

[0252] 优选地,包含的任何赋形剂以痕量存在。包含的赋形剂的量将取决于许多因素,包括所用的赋形剂的类型、赋形剂的性质、局部组合物的(多种)组分、局部组合物中的活性成分或肽的量和/或局部组合物的预期用途。任何赋形剂的性质和量不应不可接受地改变本发明的肽的益处。

[0253] 在本发明的一个实施方案中,赋形剂可以是合适的稀释剂、载体、粘合剂、润滑剂、悬浮剂、包衣剂、防腐剂、稳定剂、染料、载体、增溶剂、碱、润肤剂、乳化剂、香气剂(fragrance)、保湿剂和/或表面活性剂。

[0254] 合适的稀释剂的实例包括但不限于US2014120131或US2004132667中公开的任何稀释剂。实例包括乙醇、甘油和水。

[0255] 合适的载体的实例包括但不限于乳糖、淀粉、葡萄糖、甲基纤维素、硬脂酸镁、甘露醇、山梨醇和US2014120131或US2004132667中公开的任何合适的载体。

[0256] 合适的粘合剂的实例包括但不限于淀粉、明胶、天然糖如葡萄糖、无水乳糖、自由流动乳糖、 β -乳糖、玉米甜味剂、天然和合成树胶如阿拉伯胶、黄蓍胶或海藻酸钠、羧甲基纤维素和聚乙二醇以及US2014120131或US2004132667中公开的任何合适的粘合剂。

[0257] 合适的润滑剂的实例包括但不限于油酸钠、硬脂酸钠、硬脂酸镁、苯甲酸钠、乙酸钠和氯化钠以及US2014120131或US2004132667中公开的任何合适的润滑剂。

[0258] 载体可以是本领域已知的任何合适的载体或在US2014120131或US2004132667中公开的任何合适的载体。在一些实施方案中,载体可以包括但不限于液体如水、油或表面活性剂,包括石油、动物、植物或合成来源的那些,聚合物,油如花生油、矿物油、蓖麻油、大豆油,醇,聚山梨醇酯,山梨醇酯(sorbitan ester),醚硫酸盐,硫酸盐,甜菜碱,糖苷,麦芽糖苷,脂肪醇,壬苯醇醚,泊洛沙姆,聚氧乙烯,聚乙二醇,右旋糖,甘油或洋地黄皂苷。应该理解,载体将是皮肤病学可接受的。优选的载体包含乳剂,例如水包油、油包水、水包油包水和硅酮包水包油(oil-in-water-in-silicone)乳剂。乳剂还可含有乳化剂和/或消泡剂。

[0259] 在本发明的一个实施方案中,局部组合物还可包含一种或多种附加成分。本发明的局部组合物可与一种或多种其它附加试剂连续地、同时地或相继地施用。这种附加成分可以是包含在局部组合物中有益处或者取决于局部组合物的预期用途有益处的那些。附加成分可以是活性的或功能性的或两者皆有。

[0260] 这种附加成分的实例包括但不限于以下的一种或多种:清洁剂、调节剂、防晒剂、颜料、保湿剂、增稠剂、胶凝剂、精油、收敛剂、颜料、抗结块剂、消泡剂、粘合剂、添加剂、缓冲剂、络合剂(chelating agent)、外用止痛剂、成膜剂或材料、填充剂、聚合物、乳浊剂、pH调节剂、推进剂、还原剂、螯合剂(sequestrants)、皮肤增白剂和提亮剂、皮肤调理剂、芦荟(aloe vera)、修复剂、舒缓剂、平滑剂、泛酸、处理剂、增稠剂、维生素、着色剂、药物、防腐剂、消泡剂、缓冲剂、收敛剂、聚合物、pH调节剂、除臭剂或任何其它皮肤病学可接受的载体或表面活性剂。

[0261] 应该理解,列出的附加成分可以提供多于一种益处。本文给出的分类仅仅是为了清楚和方便,并非旨在将附加成分局限于列出的特定应用或类别。

[0262] 任何附加成分应该适合施用于皮肤而没有不适当的毒性、不相容性和/或过敏反应。

[0263] 在一些实施方案中,附加成分具有葡萄糖转运活性或者有助于葡萄糖转运活性。在一些实施方案中,附加成分具有抗炎活性或有助于抗炎活性。在一些实施方案中,附加成分具有抗老化活性或有助于抗老化活性。在一些实施方案中,附加成分用于角质层健康和/或发育、皮肤健康和/或发育,和/或肌肉健康、恢复和/或发育。活性剂可以是药理学增强剂。这样的活性剂是已知的并且在市场上可得到。在这样的情况下,本发明的局部组合物可与一种或多种其它活性剂连续地、同时地或相继地施用。

[0264] 在一些实施方案中,附加成分可以是法尼醇([2E,6E],-3,7,11,-三甲基-2,6,10,十二碳三烯-1-醇)、植烷三醇(3,7,11,15,四甲基十六烷-1,2,3,-三醇)、脱屑活性物、酶、酶抑制剂、酶激活剂、植物提取物和海洋提取物、抗痤疮活性物、抗皱纹或抗萎缩活性物、抗氧化剂/自由基清除剂、络合剂、类黄酮、抗炎剂、消脂剂(anti-cellulite agent)、局部麻醉剂、晒黑活性物、皮肤提亮剂、皮肤修复剂、甜没药醇、抗微生物或抗真菌活性物、防晒活性物、颗粒材料、调理剂、结构化剂、增稠剂。

[0265] 脱屑活性物可以是增强皮肤外观或皮肤纹理的任何合适的试剂,并且如US2014120131或US2004132667中所公开的。

[0266] 抗痤疮活性物的实例如US2014120131或US2004132667中所公开的,并包括间苯二酚、水杨酸、红霉素、锌、硫、过氧化苯甲酰。

[0267] 增稠剂的实例如US2014120131或US2004132667中所公开的,并且包括羧酸聚合物、交联聚丙烯酸酯聚合物、聚丙烯酰胺聚合物、多糖。

[0268] 调理剂的实例如US2014120131或US2004132667中所公开的,并且包括保湿剂、润肤剂或皮肤调理剂。

[0269] 结构化剂的实例如US2014120131或US2004132667中所公开的,并包括为组合物提供流变特性并有助于组合物的稳定性的任何试剂。

[0270] 可以使用任何合适的抗微生物或抗真菌活性物,并且实例如US2014120131或US2004132667中所公开的。这些活性物能够破坏微生物、防止微生物的生长或作用。实例包括但不限于 β -内酰胺药物、喹诺酮药物、四环素、红霉素、硫酸链霉素、水杨酸、过氧化苯甲酰。

[0271] 颗粒材料的实例包括金属氧化物。消脂剂的实例包括黄嘌呤剂。晒黑活性物的实例包括1,3-二羟基-2-丙酮和US2014120131或US2004132667中公开的那些。局部麻醉剂的实例包括苯佐卡因、利多卡因和布比卡因以及US2014120131或US2004132667中公开的那些。

[0272] 皮肤提亮剂的实例包括本领域已知的任何试剂如曲酸、抗坏血酸和US2014120131或US2004132667中公开的那些。

[0273] 防晒活性物的实例包括任何合适的有机或无机防晒活性物。实例包括金属氧化物、2-乙基己基-对-甲氧基肉桂酸酯和US2014120131或US2004132667中公开的那些。

[0274] 皮肤修复剂的实例包括如US2014120131或US2004132667中公开的泛酸。

[0275] 抗炎剂的实例包括增强皮肤外观、肤色或颜色的任何试剂,并且包括但不限于皮质类固醇、氢化可的松、非甾体剂如布洛芬和阿司匹林,以及US2014120131或

US2004132667中公开的那些。

[0276] 类黄酮的实例包括黄烷酮、甲氧基黄酮、未取代的查耳酮及其混合物以及US2014120131或US2004132667中公开的那些。

[0277] 酶的实例包括脂肪酶、蛋白酶、过氧化氢酶、超氧化物歧化酶、淀粉酶、过氧化物酶、葡萄糖醛酸酶、神经酰胺酶、透明质酸酶。酶抑制剂的实例包括胰蛋白酶抑制剂、Bowmann Birk抑制剂、糜蛋白酶抑制剂、植物提取物、类黄酮、槲皮素查耳酮以及US2014120131或US2004132667中公开的那些及其混合物。酶激活剂的实例包括辅酶A、Q10(泛醌)、甘草甜素、小檗碱、白杨素和US2014120131或US2004132667中公开的那些及其混合物。

[0278] 抗皱纹或抗萎缩活性物的实例包括含硫的D和L氨基酸,特别是N-酰基衍生物如N-乙酰基-L-半胱氨酸、羧基酸、植酸、硫辛酸、溶血磷脂酸、皮肤剥离剂、维生素B₃、类维生素A和US2014120131或US2004132667中公开的那些及其混合物。

[0279] 抗氧化剂/自由基清除剂可以是用于提供防紫外线辐射或其它可能引起皮肤损伤的环境试剂的任何试剂,例如US2014120131或US2004132667中公开的那些。抗氧化剂/自由基清除剂的实例包括抗坏血酸,其盐和衍生物(维生素C)、生育酚及其盐和衍生物(维生素E)、丁基化羟基苯甲酸及其盐、过氧化物、没食子酸和烷基酯、山梨酸、硫辛酸、胺、吡酮酸甜菜碱(lycine pidolate)、精氨酸氧脯氨酸(pilolate)、去甲二氢愈创木酸、生物类黄酮、姜黄素、赖氨酸、蛋氨酸、脯氨酸、超氧化物歧化酶、水飞蓟素、茶提取物及其混合物。

[0280] 络合剂的实例包括EDTA、NTA、异羟肟酸(hydroxamic acid)、植酸、乳铁蛋白和US2014120131或US2004132667中公开的那些及其混合物。络合剂是指能够通过形成配合物来去除金属离子使得金属离子不能参与化学反应或催化化学反应的试剂。络合剂可用于防止紫外线辐射或可能导致皮肤损伤的其它环境因素。

[0281] 应该理解,可以添加多种附加成分。附加成分的量可为组合物的重量的约0.001%至约50%,优选为约0.01%至约20%,优选为约0.1%至约10%,约0.5%至约10%,约1%至约5%,优选为组合物的重量的2%。包括的附加成分的量将取决于许多因素,包括使用的附加成分的类型、附加成分的性质、局部组合物的(多种)成分、局部组合物中的活性物或肽的量和/或局部组合物的预期用途。任何附加成分的性质和量不应不可接受地改变本发明的肽的益处。

[0282] 局部组合物可以是无酒精的。

[0283] 在本发明的一些实施方案中,除了本发明的肽(还称为组合物的活性物)之外,组合物还包含一种或多种附加活性剂。此外或可替代地,组合物可以与一种或多种其它附加活性剂一起施用。典型的所述附加活性剂仅以痕量存在。在一些实施方案中,组合物中可能不存在附加活性剂。包含的附加活性剂的量将取决于许多因素,包括所用的附加活性剂的类型、附加活性剂的性质、局部组合物的(多种)成分、局部组合物中的活性物或肽的量和/或局部组合物的预期用途。任何附加活性剂的性质和量不应该不可接受地改变本发明的肽的益处。

[0284] 应该理解,在一种产品中被认为是“活性”成分的成分可能是另一种产品中的“功能”或“赋形剂”成分,反之亦然。还应理解的是,一些成分发挥作为活性成分和作为功能成分或赋形剂成分的双重作用。

[0285] 附加活性剂的实例包括葡萄糖转运促进药物、皮肤补充剂、皮肤治疗和/或护理

剂、抗炎剂、抗老化剂、细胞生长促进剂和药理学增强剂。这些试剂是本领域熟知的,并且可以理解,可以使用任何合适的附加活性剂。用于治疗 and/或护理皮肤的附加活性剂可包括胶原蛋白合成剂、类维生素A、去角质剂、消脂剂、弹性蛋白酶抑制剂、黑素合成刺激或抑制剂、日晒黑剂、抗老化剂、抗微生物剂、抗真菌剂、抑真菌剂、杀菌剂和修复剂。活性剂还包括抗炎剂。

[0286] 任何附加活性剂应该适合施用于皮肤而没有不适当毒性、不相容性和/或过敏反应。

[0287] 应当理解,本文给出的分类仅仅是为了清楚和方便,并非旨在将附加成分、赋形剂或活性物局限于列出的特定应用或类别。

[0288] 在特别优选的实施方案中,本发明的方法和用途包括将本发明的肽或组合物与一种或多种其它活性剂(例如,市场上可获得的现有生长促进药或药理学增强剂)组合施用。在这种情况下,本发明的化合物可与一种或多种其它活性剂连续地、同时地或相继地施用。

[0289] 本发明的效果通过将本文所述的本发明的局部组合物局部应用或施用至需要治疗或护理的人、动物或患者来实现。局部递送优选意指递送至角质层如皮肤、头发和/或指甲,但还可以意指递送至衬有上皮细胞的体腔,例如肺或气道、胃肠道、颊腔。效果可以局限于皮肤表面或可以在皮肤内或两者的组合。

[0290] 以化妆(cosmetically)或药学上有效的量施用本发明的局部组合物。换言之,以无毒但足以提供期望效果的量。应该理解,本领域技术人员将能够确定施用本发明的局部组合物的合适剂量,而无需过多的实验。可替代地,医师将根据特定状况、待治疗或护理的疾病或病症以及个体的年龄、体重和/或健康状况来确定最适合于患者的实际剂量。这将取决于多种因素,包括所采用的具体化合物的活性、该化合物的代谢稳定性和作用时间长度、年龄、体重、一般健康状况、性别、饮食、施用方式和时间、排泄速率、药物组合、特定病况的严重程度以及正在接受治疗的个体。当然,可以有更高或更低剂量范围是合适的个别情况,并且这也在本发明的范围内。例如,可以0.01至50mg/kg体重,例如0.1至30mg/kg,更优选为0.1至20mg/kg体重,更优选为0.1至10mg/kg体重,优选为0.1至5mg/kg体重的剂量施用组合物。在一个示例性实施方案中,10至300mg/天或更优选为10至150mg/天的一个或多个剂量将施用给患者。量和频率最适合于目的。根据每个受试者的需要,应用或施用的频率可以变化很大,并且推荐的应用或施用范围从每月一次到每天十次,优选为每周一次到每天四次,更优选为从每周三次到每天三次,甚至更优选为每天一次或两次。

[0291] 在优选的实施方案中,提供了局部组合物的重复使用。

[0292] 可通过但不限于摩擦或按摩到待治疗或护理的角质组织、皮肤或身体区域中应用局部组合物。在一些实施方案中,组合物留在身体的区域上或不从身体的区域去除。在其它实施方案中,在一段时间之后,例如但不限于约2分钟至60分钟、约5分钟至约30分钟,优选为约10分钟至约20分钟之后去除组合物。应用后可立即去除组合物。在本发明的一些实施方案中,可通过获得本发明的组合物和/或肽的更大渗透的方法而将本发明的组合物应用于待治疗的区域,例如但不限于离子电渗法、超声波导入、电穿孔、微电贴片、机械压力、渗透压梯度、闭塞性治疗、借助于压力的微注射或无针注射如通过氧分压注射,或其任何组合。

[0293] 本发明的肽以化妆或药学上有效的浓度用于本发明的局部用化妆或药物组合物

以达到期望的效果;相对于组合物的总重量,优选形式为0.00000001% (以重量计)至20% (以重量计);优选为0.000001% (以重量计)至15% (以重量计),更优选为0.0001% (以重量计)至10% (以重量计),且甚至更优选为0.0001% (以重量计)至5% (以重量计)。

[0294] 在本发明的一些实施方案中,组合物可以经由以下的任一来递送:脂质体、混合脂质体、油质体、泡囊(niosome)、醇质体、微胶囊、胶囊、大胶囊、纳米胶囊、纳米结构化脂质载体、海绵、环糊精、囊泡、胶束、表面活性剂的混合胶束、表面活性剂-磷脂混合胶束、微球、球、脂质球、颗粒、纳米球、纳米颗粒、微粒、固体纳米颗粒以及微乳液包括具有反胶束的内部结构的油包水微乳液和纳米乳液微球、微颗粒。

[0295] 多种方法可用于制备脂质体。参见例如,Szoka等人,Ann.Rev.Biophys.Bioeng.9:467(1980),美国专利号4,186,183、4,217,344、4,235,871、4,261,975、4,485,054、4,501,728、4,774,085、4,837,028、4,235,871、4,261,975、4,485,054、4,501,728、4,774,085、4,837,028、4,946,787、PCT公开号W0 91/17424,Deamer&Bangham、Biochim.Biophys.Acta 443:629-634(1976);Fraley,等人,PNAS 76:3348-3352(1979);Hope等人,Biochim.Biophys.Acta 812:55-65(1985);Mayer等人,Biochim.Biophys.Acta 858:161-168(1986);Williams等人,PNAS 85:242-246(1988);Liposomes(Ostro(编辑),1983,第1章);Hope等人,Chem.Phys.Lip.40:89(1986);Gregoriadis,Liposome Technology(1984) and Lasic,Liposomes:from Physics to Applications(1993)。合适的方法包括例如,超声处理、挤出、高压/均质化、微流化、洗涤剂透析、钙诱导的小脂质体载体的融合和醚融合方法,全部都是本领域熟知的。

[0296] 这些递送系统可以适合于实现本发明的化合物和/或肽的更大渗透。这可以改善药代动力学和药效学性质。递送系统可以是持续释放系统,其中本发明的化合物或肽在一段时间内逐渐释放并且优选地在一段时间内具有恒定的释放速率。通过本领域已知的方法制备递送系统。包含在持续释放系统中的肽的量将取决于组合物将被递送到何处和释放的持续时间以及待治疗或护理的状况、疾病和/或紊乱的类型。

[0297] 本发明的局部组合物可以在人类或兽医学中供人类或动物使用。

[0298] 本发明的局部组合物可以用于药物、个人护理和/或化妆用途。

[0299] 组合物可用于治疗或护理皮肤的任何疾病、紊乱或状况,包括但不限于银屑病、皮炎、过敏性皮炎、湿疹、海绵层水肿、水肿、皮肤癌、溃疡、痤疮、疤痕、蜂窝织炎、弹性组织变性、角化病、红斑痤疮、静脉曲张、炎性疾病。

[0300] 局部组合物可用于治疗或护理可见的老化迹象,包括但不限于皱纹、妊娠纹和黑眼圈、干燥、细纹、老年斑、红色斑点、皮肤下垂以及由日晒引起的状况包括晒伤、应激、污染和/或饮食。局部组合物也可以用于延缓、减缓或抑制皮肤或老化的发生。可通过医疗器械如本文所述的石膏或贴剂施用组合物。

[0301] 局部组合物可用于治疗或护理哺乳动物的伤口。在另一个实施方案中,局部组合物用于治疗或预防特征在于受损的上皮细胞或组织,和/或受损的真皮或上皮细胞或组织的疾病或状况。疾病可能是但不限于癌症和创伤。

[0302] 局部组合物可用于治疗或护理任何肌肉状况,以改善哺乳动物的肌肉状态、通常在锻炼之后促进肌肉的恢复、维持或恢复哺乳动物的肌肉健康(例如,瘦肉组织量)、增强体能表现、治疗或预防特征在于嗜睡或低能量水平的疾病或状况。

[0303] 局部组合物可用于促进组织生长、促进上皮组织生长、促进皮肤生长、促进器官生长、促进生物体生长。皮肤可以具有正常病理和/或异常病理。

[0304] 局部组合物也可以用于治疗或护理任何炎性紊乱。

[0305] 本发明的其它方面涉及一种药物组合物,其包含与一种或多种的药学上可接受的稀释剂、赋形剂或载体混合的本发明的肽或本发明的肽的组合物。尽管本发明的肽和组合物可以单独施用,但它们通常与药物载体、赋形剂或稀释剂混合施用,特别是对于人类治疗。药物组合物可以在人类或兽医学中供人类或动物使用。用于本文所述的各种不同形式的药物组合物的这种合适的赋形剂的实例可在A Wade和PJ Weller编辑的“Handbook of Pharmaceutical Excipients”,第2版,(1994)中找到。特别地,用于局部递送的制剂在David Osborne和Antonio Aman,Taylor&Francis编辑的Topical drug delivery formulations (局部药物递送制剂)中进行了描述,其全部内容通过引用并入本文。用于治疗用途的可接受的载体或稀释剂是制药领域熟知的,并且在例如,Remington's Pharmaceutical Sciences,Mack Publishing Co. (A.R.Gennaro编辑,1985)中进行了描述。合适的载体的实例包括乳糖、淀粉、葡萄糖、甲基纤维素、硬脂酸镁、甘露醇、山梨醇等。合适的稀释剂的实例包括乙醇、甘油和水。药物载体、赋形剂或稀释剂的选择可以根据预期的施用途径和标准药学实践进行选择。药物组合物可以包含作为载体、赋形剂或稀释剂的,或除载体、赋形剂或稀释剂之外的,任何合适的粘合剂、润滑剂、悬浮剂、包衣剂、增溶剂。合适的粘合剂的实例包括淀粉、明胶、天然糖如葡萄糖、无水乳糖、自由流动乳糖、 β -乳糖、玉米甜味剂、天然和合成树胶如阿拉伯胶、黄蓍胶或海藻酸钠、羧甲基纤维素和聚乙二醇。合适的润滑剂的实例包括油酸钠、硬脂酸钠、硬脂酸镁、苯甲酸钠、乙酸钠、氯化钠等。可以在药物组合物中提供防腐剂、稳定剂、染料和甚至调味剂。防腐剂的实例包括苯甲酸钠、山梨酸和对羟基苯甲酸的酯。还可以使用抗氧化剂和悬浮剂。

[0306] 本发明的肽或组合物可适用于局部、口服、直肠、肠胃外、肌内、腹膜内、动脉内、支气管内、皮下、皮内、静脉内、鼻、阴道、颊或舌下施用途径。对于口服给药,特殊用途由压缩片剂、丸剂、片剂、凝胶剂、滴剂和胶囊剂组成。优选地,这些组合物每剂含有1-250mg,且更优选为10-100mg的活性成分。其它施用形式包括可静脉内、动脉内、皮下、皮内、腹膜内或肌内注射的溶液剂或乳剂,并且由无菌或可灭菌的溶液制备。本发明的药物组合物也可以是栓剂、阴道环、子宫托、悬浮剂、乳剂、洗剂、软膏剂、乳膏剂、凝胶剂、喷雾剂、溶液剂或扑粉剂的形式。本发明的组合物可以配制用于局部递送。局部递送通常意指递送至皮肤,但还可以意指递送至衬有上皮细胞的体腔,例如肺或气道、胃肠道、颊腔。特别地,用于局部递送的制剂在David Osborne和Antonio Aman,Taylor&Francis编辑的Topical drug delivery formulations (局部药物递送制剂)中进行了描述,其全部内容通过引用并入本文。用于递送到气道的组合物或制剂在O'Riordan等人的 (Respir Care, 2002, Nov. 47)、EP2050437、W02005023290、US2010098660和US20070053845中进行了描述。用于将活性剂递送至回肠特别是近端回肠的组合物和制剂包括微粒和微胶囊,其中活性剂被包封在由聚合物或乳蛋白形成的保护基质内,该保护基质耐酸但易于溶解在回肠的更碱性的环境中。在EP1072600.2和EP13171757.1中描述了这种递送系统的实例。经皮给药的替代方法是通过使用皮肤贴剂。例如,可将活性成分掺入到由聚乙二醇或液体石蜡的含水乳液组成的乳膏中。还可以将活性成分以1至10%重量的浓度掺入到由白蜡或白软石蜡基质以及可能需要的稳定剂和防

腐剂组成的软膏剂中。

[0307] 可注射形式每剂可包含10-1000mg,优选为10-250mg的活性成分。

[0308] 可以单位剂型(unit dosage)形式,即以含有单位剂量或多个或亚单位的单位剂量的分离部分(discrete portion)的形式配制组合物。

[0309] 本领域普通技术人员可以容易地确定待施用给主体的本发明组合物之一的合适剂量,而无需过多的实验。通常,医生将确定最适合于个体患者的实际剂量,并且这将取决于多种因素,包括所使用的具体化合物的活性、该化合物的代谢稳定性和作用时间长度、年龄、体重、一般健康状况、性别、饮食、施用方式和时间、排泄速率、药物组合、特定状况的严重程度以及正在接受治疗的个体。本文公开的剂量是平均情况的示例。当然可以有个别情况,其中更高或更低的剂量范围是合适的,并且这些也在本发明的范围之内。根据需要,可以0.01至30mg/kg体重,例如0.1至10mg/kg,更优选为0.1至1mg/kg体重的剂量施用试剂。在一个示例性实施方案中,为了治疗炎性疾病,10至300毫克/天或更优选为10至150毫克/天的一个或多个剂量将施用给患者。

[0310] 在特别优选的实施方案中,本发明的方法和用途包括将本发明的肽或组合物与一种或多种其它活性剂(例如,市场上可获得的现有抗炎药或药理学增强剂)组合施用。在这种情况下,本发明的组合物可与一种或多种其它活性剂连续地、同时地或相继地施用。

[0311] 在本发明的一个实施方案中,本发明的肽可以以包含所述肽的缀合物的形式施用,并且可以任选地包含连接子和配偶体分子,例如蛋白质如旨在增加体内缀合物的半衰期的抗体分子。在一个实施方案中,所述肽可被修饰以用一个或多个氨基酸替换,其中氨基酸用于连接配偶体分子。例如,为了缀合配偶体分子如PEG分子的目的,可以用赖氨酸残基替换氨基酸。

[0312] 定义

[0313] 对于所有目的,本文提到的所有出版物、专利、专利申请和其它参考文献都通过引用全部并入本文,如同每个单独的出版物、专利或专利申请都被具体和单独地指示以通过引用并入并且其内容被完整引用一样。

[0314] 在本文中使用的情况下,除非另外明确指出,否则以下术语除了在本领域可能具有的任何更宽(或更窄)的含义之外,还旨在具有以下含义:

[0315] 除非上下文另有要求,否则在本文中单数的使用应理解为包括复数,且反之亦然。关于实体使用的术语“一(a)”或“一(an)”应被理解为是指一个或多个该实体。因此,术语“一(a)”(或“一(an)”)、“一个或多个”和“至少一个”在本文中可互换使用。

[0316] 如本文所用,术语“包括(comprise)”或其变型如“包括(comprises)”或“包括(comprising)”应被理解为指示包括任何引述的整体(integer)(例如,特征、要素、特性、性质、方法/过程步骤或限制)或整体组(例如,特征、要素、特性、性质、方法/过程步骤或限制),但不排除任何其它整体或整体组。因此,如本文所用,术语“包括(comprising)”是包含性的或开放性的,并且不排除另外的未提及的整体或方法/过程步骤。

[0317] 如本文所用,术语“疾病”用于定义损害生理功能并与特定症状相关的任何异常状况。该术语广泛地用于涵盖其中无论病因性质(或实际上是否确定疾病的病因学基础)的生理功能受损的任何紊乱、疾患、异常、病理、生病、病况或综合征。因此,它涵盖了由感染、创伤、损伤、手术、放射消融、中毒或营养缺陷引起的状况。

[0318] 如本文所用,术语“治疗(treatment)”或“治疗(treating)”是指干预(例如,向主体施用试剂),其治愈、改善或减轻疾病的症状或消除其病因(或减轻其病因的影响)(例如,减少溶酶体酶的病理水平的积累)。在这种情况下,该术语与术语“治疗(therapy)”同义使用。

[0319] 此外,术语“治疗(treatment)”或“治疗(treating)”是指干预(例如,向受试者施用试剂),其预防或延迟疾病的发作或进展或降低(或根除)其在受治疗人群中的发病率。在这种情况下,术语治疗与术语“预防(prophylaxis)”同义使用。

[0320] 如本文所用,试剂的有效量或治疗有效量定义了与合理的利益/风险比相称的可以施用于主体而没有过度的毒性、刺激性、过敏反应或其它问题或并发症的量,但其足以提供期望的效果,例如表现为主体状况的永久或暂时改善的治疗或预防。该量因主体不同而变化,其取决于个体的年龄和总体状况、施用方式和其它因素。因此,虽然不可能规定确切的有效量,但本领域技术人员能够使用常规实验和背景常识在任何个体情况下确定适当的“有效”量。在这种情况下的治疗性结果包括根除或减轻症状、减轻疼痛或不适、延长存活、改善活动性和临床改善的其它标志。治疗性结果不一定是完全治愈。

[0321] 术语“哺乳动物”应该理解是指高等哺乳动物,特别是人类。然而,该术语还包括非哺乳动物,例如鱼。

[0322] 本文使用的术语“肽”是指通常通过肽键连接的由多至50个氨基酸单体组成的聚合物。肽的长度可以是3至50个氨基酸。肽的长度可以是4至50个氨基酸。肽的长度可以是5至50个氨基酸。肽的长度可以是7至50个氨基酸。作为本发明和用于本发明的肽(包括其片段和变体)可全部或部分地通过化学合成或通过从核酸表达来产生。例如,可以根据本领域已知的充分确认(well-established)的标准液体或优选为固相肽合成方法容易地制备本发明的肽和用于本发明的肽(参见例如,J.M.Stewart和J.D.Young,Solid Phase Peptide Synthesis,第2版,M.Bodanzsky和A.Bodanzsky中的Pierce Chemical Company,Rockford,Illinois(1984),The Practice of Peptide Synthesis,Springer Verlag,New York(1984))。必要时,本发明中使用的任何肽可以被化学修饰以增加它们的稳定性。经化学修饰的肽或肽类似物包括肽的任何功能化学等价物,其特征在于相对于本发明的实践,其在体内或体外的稳定性和/或功效提高。术语肽类似物还是指如本文所描述的肽的任何氨基酸衍生物。可通过包括但不限于侧链的修饰、在肽合成过程中掺入非天然氨基酸和/或其衍生物和使用交联剂以及在肽或其类似物上施加构象约束的其它方法的程序来制备肽类似物。侧链修饰的实例包括氨基的修饰,例如还原烷基化,通过与醛反应,随后用 NaBH_4 还原;用乙酰亚胺酸甲酯酰胺化;用乙酸酐乙酰化;用氰酸酯对氨基进行氨基甲酰化;用2,4,6-三硝基苯磺酸(TNBS)对氨基进行三硝基苄基化;用琥珀酸酐和四氢邻苯二甲酸酐对氨基进行的烷基化;以及用吡哆醛-5'-磷酸酯对赖氨酸进行吡哆化(pyridoxylation),随后用 NABH_4 还原。精氨酸残基的胍基可以通过与试剂如2,3-丁二酮、苯甲酰甲醛和乙二醛形成杂环缩合产物来修饰。羧基可以通过经由O-酰基异脲形成的碳二亚胺活化,然后随后的衍生化例如到相应的酰胺来修饰。巯基可以通过(多种)方法来修饰,诸如与碘乙酸或碘乙酰胺的羧甲基化;过甲酸氧化成磺基丙氨酸;与其它硫醇化合物形成混合二硫化物;与马来酰亚胺反应;马来酸酐或其它取代的马来酰亚胺;使用4-氯汞苯甲酸、4-氯汞苯磺酸、氯化苯汞、2-氯汞-4-硝基苯酚和其它汞制剂形成汞衍生物;在碱性pH下用氰酸酯进行的氨基甲酰化。色氨

酸残基可通过例如用N-溴琥珀酰亚胺来氧化或用2-羟基-5-硝基苄基溴或磺酰卤来对吡啶环进行烷基化来修饰。酪氨酸残基可以通过用四硝基甲烷来硝化以形成3-硝基酪氨酸衍生物来改变。组氨酸残基的咪唑环的修饰可以通过用碘乙酸衍生物进行烷基化或用焦碳酸二乙酯进行N-乙酯基化来完成。在肽合成期间掺入非天然氨基酸和衍生物的实例包括但不限于使用正亮氨酸、4-氨基丁酸、4-氨基-3-羟基-5-苯基戊酸、6-氨基己酸、叔丁基甘氨酸、正缬氨酸、苯基甘氨酸、鸟氨酸、肌氨酸、4-氨基-3-羟基-6-甲基庚酸、2-噻吩基丙氨酸和/或氨基酸的D-异构体。肽结构修饰包括产生包含由D-氨基酸编码的反向序列的逆反肽(retro-inverso peptide)。

[0323] “经修饰肽”：在本发明的一个实施方案中，该肽是经修饰肽。术语经修饰肽与术语肽的衍生物可互换使用。经修饰肽包括已经被一个或多个如本文所定义的基团替换的肽。该修饰可以是任何修饰，其提供具有增加的穿透细胞的能力的本发明的肽和/或组合物。该修饰可以是增加本发明的组合物或肽的半衰期的任何修饰。在一个实施方案中，该基团是保护基。保护基可以是N-末端保护基、C-末端保护基或侧链保护基。该肽可具有这些保护基团中的一个或多个。本领域技术人员知道使氨基酸与这些保护基团反应的合适技术。这些基团可以通过本领域已知的制备方法添加，例如US2014120141的段落[0104]至[0107]中概述的方法。这些基团可能保留在肽上或可能脱除。保护基可以在合成过程中加入。在本发明的一个实施方案中，肽可以被选自以下的基团取代：一个或多个直链或支链、长链或短链、饱和或不饱和，被羟基、氨基、氨基酰基、硫酸根或硫化物基团取代或未取代，具有1至29个碳原子。N-酰基衍生物包括衍生自乙酸、癸酸、月桂酸、肉豆蔻酸、辛酸、棕榈酸、硬脂酸、山萘酸、亚油酸、亚麻酸、硫辛酸、油酸、异硬脂酸、反油酸、2-乙基己酸(2-ethylhexanoic acid)、椰子脂肪酸、牛油脂肪酸、硬化牛油脂肪酸、棕榈仁脂肪酸、羊毛脂脂肪酸或类似的酸。这些可以是取代的或未取代的。当被取代时，它们优选被羟基或含硫基团取代，例如但不限于 SO_3H 、 SH 或 S-S 。在本发明的一个实施方案中，肽是 $\text{R}_1\text{-X-R}_2$ ， R_1 和/或 R_2 基团分别与肽序列的氨基末端(N-末端)和羧基末端(C-末端)结合。在一个实施方案中，肽是 $\text{R}_1\text{-X}$ 。或者，肽是 X-R_2 。优选地， R_1 是H、 C_{1-4} 烷基、乙酰基、苯甲酰基或三氟乙酰基。X是本发明的肽； R_2 是OH或 NH_2 。在一个实施方案中， R_1 选自H、非环取代的或未取代的脂肪族基团、取代的或未取代的脂环族、取代的或未取代的杂环基、取代的或未取代的杂芳基烷基、取代的或未取代的芳基、取代的或未取代的芳烷基、叔丁氧基羰基、9-苄基甲氧基羰基(Fmoc)和 $\text{R}_5\text{-CO-}$ 形成的基团，其中 R_5 选自H、非环取代的或未取代的脂肪族基团、取代的或未取代的脂环族、取代的或未取代的芳基、取代的或未取代的芳烷基、取代的或未取代的杂环基和取代的或未取代的杂芳基烷基形成的基团； R_2 选自 $\text{-NR}_3\text{R}_4$ 、 -OR_3 和 -SR_3 形成的基团，其中 R_3 和 R_4 独立地选自H、非环取代的或未取代的脂肪族基团、取代的或未取代的脂环族、取代的或未取代的杂环基、取代的或未取代的杂芳基烷基、取代的或未取代的芳基和取代的或未取代的芳烷基形成的基团；并且条件是 R_1 和 R_2 不是 α -氨基酸。根据另一个优选的实施方案， R_2 为 $\text{-NR}_3\text{R}_4$ 、 -OR_3 或 -SR_3 ，其中 R_3 和 R_4 独立地选自以下形成的基团：H、取代的或未取代的 $\text{C}_1\text{-C}_{24}$ 烷基、取代的或未取代的 $\text{C}_2\text{-C}_{24}$ 烯基、叔丁氧基羰基、9-苄基甲氧基羰基(Fmoc)、取代的或未取代的 $\text{C}_2\text{-C}_{24}$ 炔基、取代的或未取代的 $\text{C}_3\text{-C}_{24}$ 环烷基、取代的或未取代的 $\text{C}_5\text{-C}_{24}$ 环烯基、取代的或未取代的 $\text{C}_8\text{-C}_{24}$ 环炔基、取代的或未取代的 $\text{C}_6\text{-C}_{30}$ 芳基、取代的或未取代的 $\text{C}_7\text{-C}_{24}$ 芳烷基、3-10元的取代的或未取代的杂环基环，以及2-24个碳原子和1-3个非碳原子的取代或未取代的

杂芳基烷基,其中烷基链具有1-6个碳原子。任选地, R_3 和 R_4 可以通过饱和或不饱和的碳-碳键键合,与氮原子形成环。更优选地, R_2 是 $-NR_3R_4$ 或 $-OR_3$,其中 R_3 和 R_4 独立地选自自由以下形成的基团:H、取代的或未取代的 C_1 - C_{24} 烷基、取代的或未取代的 C_2 - C_{24} 烯基、取代的或未取代的 C_2 - C_{24} 炔基、取代的或未取代的 C_3 - C_{10} 环烷基、取代的或未取代的 C_6 - C_{15} 芳基和3-10元的取代的或未取代的杂环基、具有3至10元的环和1至6个碳原子的烷基链的取代的或未取代的杂芳基烷基。更优选地, R_3 和 R_4 选自自由以下形成的基团:H、甲基、乙基、己基、十二烷基或十六烷基。甚至更优选地, R_3 是H且 R_4 选自自由H、甲基、乙基、己基、十二烷基或十六烷基形成的基团。根据甚至更优选的实施方案, R_2 选自 $-OH$ 和 $-NH_2$ 。根据本发明的另一个实施方案, R_1 选自自由H、乙酰基、月桂酰基、肉豆蔻酰基或棕榈酰基形成的基团,且 R_2 为 $-NR_3R_4$ 或 $-OR_3$,其中 R_3 和 R_4 独立地选自H、甲基、乙基、己基、十二烷基和十六烷基,优选地 R_2 是 $-OH$ 或 $-NH_2$ 。更优选地, R_1 是乙酰基或棕榈酰基,并且 R_2 是 $-NH_2$ 。在一个优选的实施方案中,酰基与肽的至少一个氨基酸的N-末端键合。在本发明的一个实施方案中,肽被修饰以包含侧链保护基。侧链保护基可以是包括苄基的基团或基于苄基的基团、基于叔丁基的基团、苄氧基-羰基(Z)基团和烯丙氧基羰基(alloc)保护基中的一种或多种。侧链保护基可以衍生自非手性氨基酸如非手性甘氨酸。非手性氨基酸的使用有助于稳定所得的肽,并且还有利于本发明的简易合成路线。优选地,肽还包含经修饰的C-末端,优选为酰胺化的C-末端。非手性残基可以是 α -氨基异丁酸(甲基丙氨酸)。应该理解,所使用的特定侧链保护基将取决于肽的序列和所使用的N-末端保护基的类型。

[0324] “缀合物”:在本发明的一个实施方案中,肽缀合、连接或融合至结合配偶体,例如一种或多种聚乙二醇聚合物或其它化合物,如分子量增加化合物或亲脂性基团。分子量增加化合物是将所得缀合物的分子量增加通常10%至90%或20%至50%的任何化合物,并且可具有200至20,000,优选为500至10,000的分子量。分子量增加化合物可以是PEG、任何水溶性(两亲性或亲水性)聚合物部分、PEG的均聚物或共聚物、PEG(mPEG)和聚氧乙烯甘油(POG)的单甲基取代的聚合物、聚氨基酸如聚赖氨酸、聚谷氨酸、聚天冬氨酸,特别是L构型的那些,药理学无活性的蛋白质如白蛋白、明胶、脂肪酸、多糖、脂质氨基酸和葡聚糖。聚合物部分可以是直链或支链的,并且其可以具有500至40000Da、5000至10000Da、10000至5000Da的分子量。化合物(结合配偶体)可以是任何合适的细胞穿透化合物,如tat肽、穿膜肽、pep-1。化合物(结合配偶体)可以是抗体分子。化合物(结合配偶体)可以是亲脂性部分或聚合物部分。亲脂性取代基和聚合物取代基是本领域中已知的。亲脂性取代基包括形成酯、磺酰酯、硫酯、酰胺或磺酰胺的一部分的酰基、磺酰基、N原子、O原子或S原子。亲脂性部分可以包括具有4至30个C原子,优选为8至12个C原子的烃链。它可以是线性的或支链的、饱和的或不饱和的。烃链可被进一步取代。它可以是环烷烃或杂环烷烃。该肽可以在N-末端、C-末端或两者处被修饰。聚合物或化合物(结合配偶体)优选与氨基、羧基或巯基连接,并且可以通过任何氨基酸残基的侧链的N-末端或C-末端连接。聚合物或化合物(结合配偶体)可以与任何合适的残基的侧链缀合。聚合物或化合物(结合配偶体)可以通过间隔物缀合。间隔物可以是天然或非天然氨基酸、琥珀酸、赖氨酸、谷氨酸、天门冬氨酸、甘氨酸、 β -丙氨酸、 γ -氨基丁酰基。聚合物或化合物(结合配偶体)可以通过酯、磺酰酯、硫酯、酰胺、氨基甲酸酯、脲、磺酰胺缀合。本领域技术人员知道制备所述缀合物的合适方法。

[0325] “片段”是指蛋白质片段,通常选自SEQUENCE ID NO:1-16和353-355,且特别是选

自那些选自SEQUENCE ID NO:17-70的蛋白质的区域。在一个实施方案中,片段的长度通常为3至37个连续的氨基酸。在一个实施方案中,片段的长度通常为5至37个连续的氨基酸。在一个实施方案中,片段的长度通常为5至37个连续的氨基酸。片段通常具有-9至+3的电荷;通常为通常不是半胱氨酸(C)或蛋氨酸(M)的c-末端氨基酸;并且通常为通常不是半胱氨酸(C)、组氨酸(H)、脯氨酸(P)或苏氨酸(T)的n-末端氨基酸。使用Cameselle,J.C.,Ribeiro,J.M.和Sillero,A.(1986).Derivation and use of a formula to calculate the net charge of acid-base compounds.Its application to amino acids,proteins and nucleotides (推导和使用公式来计算酸碱化合物的净电荷。其应用于氨基酸、蛋白质和核苷酸).Biochem.Educ.14,131-136的方法测定肽、片段或区域的电荷。

[0326] 应用于肽的术语“天然”意指一肽,其包括(a)植物蛋白质的片段,植物蛋白通常为大米或豌豆蛋白质,或豌豆蛋白质的变体包括小扁豆(lentil)、甜豌豆或鹰嘴豆,或大米蛋白质的变体包括燕麦、草、玉米、野生稻和香蕉,或(b)植物蛋白质的片段的变体,例如植物蛋白质的同源物的片段。本发明的肽或片段可从植物蛋白质中分离或合成制备。

[0327] 应用于片段的“C-末端结构域”意指片段的c-末端处的前三个氨基酸。

[0328] 应用于片段的“N-末端结构域”意指片段的n-末端处的最后三个氨基酸。

[0329] 应用于肽或片段的“生物活性”意指当施用给哺乳动物时具有健康促进作用,例如葡萄糖转运促进、抗细菌、抗炎或促进细胞生长或增殖中的一种或多种。在一个实施方案中,术语“生物活性”意指抗炎。

[0330] 应用于肽或变体或片段的“葡萄糖转运促进”或“葡萄糖转运促进活性”意指当在以下体外测定中以2 μ M的浓度使用时,与未处理对照相比,能够增加GLUT4易位至骨骼肌中的肽、变体或片段。在10%的FBS和2 μ g/ml的杀稻瘟菌素中培养L6-GLUT4myc细胞。使细胞生长48-72小时,然后在24-孔板中在2%的FBS中以每孔15,000个细胞接种,并在实验之前使其分化6至8天。使L6-GLUT4myc细胞血清饥饿3小时,然后分别使用100nM的胰岛素孵育30分钟,或者使用200、20、2.0和0.2 μ M的SP以及2、1、0.5和0.25mg/ml的肽组合物孵育3小时。基于先前的发现选择3小时的孵育期,该发现确定了使用含有支链氨基酸的二肽孵育3小时增加了L6肌管1中的葡萄糖摄取。为了确定在同一时间点的GLUT4myc易位,将处理交错进行。通过抗体偶联比色测定法测量细胞表面上的myc标记的GLUT4的量。简略地说,在分别使用胰岛素孵育30分钟或用合成肽或肽组合物孵育3小时后,通过使用3%的多聚甲醛(PFA)孵育来固定L6-GLUT4myc细胞。然后,加入0.1M的甘氨酸溶液以淬灭PFA,并用5%的山羊血清阻断细胞。将肌管单层暴露于抗myc抗体,然后使用过氧化物酶缀合的驴抗小鼠IgG孵育。向每个孔中加入1mL的邻苯二胺二盐酸盐(OPD)试剂,并通过加入250 μ l/孔的3M的HCl终止该反应。为了确定GLUT4易位至细胞表面,使用492nm处的吸光度,在酶标仪上通过分光光度法测定每一条件的测量的等分试样。优选地,与未处理的对照相比,所述肽或片段能够使GLUT4易位增加至少50%(即,GLUT4易位的相对单位增加为1%-1.5%)。

[0331] 应用于肽或片段的“抗细菌”或“抗细菌活性”意指在以下基于琼脂板的生长抑制测定中能够可见地抑制细菌生长的肽或片段:溶于DMSO中的肽储液=5mg/mL。将细菌接种物调整至McFarland 0.5标准,并将MHA板擦拭。将空白盘置于板中,并加入10 μ L的每种化合物(在64 μ g/mL-最大测试浓度下)。将板在37 $^{\circ}$ C下孵育16-18小时。还进行了适当的对照(DMSO;单独的Mueller-Hinton培养基;以及两种抗生素片-环丙沙星和四环素)。

[0332] 应用于肽或片段的“抗炎”意指当用100 μ M的肽或片段处理LPS刺激的J774.2巨噬细胞时,能够显著减少巨噬细胞的TNF α 分泌(与未处理的LPS刺激的J774.2巨噬细胞相比)的肽或片段。将J774.2巨噬细胞用100 μ M的合成肽处理24小时,然后用(A) LPS(10ng/ml)刺激5小时或(B) LPS(10ng/ml)刺激5小时,然后用ATP(5mM)刺激1小时。收集上清液并通过ELISA测定TNF α 的水平。

[0333] 应用于肽或片段的“细胞生长促进”或“细胞生长或增殖促进”意指在以下测定中能够增加使用20 μ M的肽或片段的溶液处理的人类皮肤的弹性蛋白产生或细胞增殖的肽或片段。从腹部整形手术制备皮肤外植体。将一些外植体用酒精脱脂以获得脱水皮肤。将这些外植体维持在供应商Bioprédic International提供的维持培养基中5天。测试项目每天施用两次,其中每个外植体5 μ L。在测试结束时,在两个外植体上用MTT实现活力对照,将第三外植体固定在4%的甲醛中用于组织学和细胞染色。对于每次分析(D1和D5),进行脱脂外植体、用测试项目处理的外植体、DMSO 0.3%对照和水对照的组织学分析。在实验室收到之后,在3小时期间用5 μ L的酒精将维持培养基中的每个皮肤外植体脱脂。3小时后,将所有皮肤外植体每天用测试项目处理两次,并将它们在37 $^{\circ}$ C $\pm$ 2 $^{\circ}$ C,5%的CO₂下孵育1天或5天。在第1天和第5天使用MTT用活力对照实现系统的完整性。由实验室Gredeco实现组织学分析,并由同一实验室实现弹性蛋白和Ki67的免疫染色。由实验室Intertek实现丝聚蛋白的免疫染色。使用免疫过氧化物酶技术两层(ABC试剂盒,Vector Laboratories)进行弹性蛋白(兔单克隆抗体,克隆P15502,LSBio)的检测,并通过AEC(3-氨基-9-乙基咔唑)显示。使用半定量组织学评分评估弹性纤维中的免疫组织化学染色强度。使用抗Ki67抗体通过免疫组织化学分析上皮细胞增殖。使用间接免疫过氧化物酶技术三层进行免疫检测,扩增(DAKO试剂盒)并通过AEC(3-氨基-9-乙基咔唑)显示。对标记细胞(表皮基底层的角质形成细胞)的数量进行计数,并提供基底细胞的总数以计算标记细胞的百分比。用免疫过氧化物酶染色(ABC试剂盒,Fisher)进行丝聚蛋白的特异性染色。相对于溶剂的阴性对照(水或DMSO 0.3%)评估表皮中的免疫组织化学标记的强度。

[0334] 应用于本发明组合物的“富含具有小于10KD的分子量的肽”意指组合物中分子量小于10KD的肽的干重%大于组合物中分子量为10KD或更高的多肽/蛋白质的干重%。

[0335] 参考蛋白质的“同源物”应被理解为意指来自与参考蛋白质具有至少60%序列同源性的不同植物物种的蛋白质。因此,例如,豌豆蛋白质P13918的同源物包括:

[0336] >gi|137584|sp|P08438.1|VCL_VICFA RecName:完整=豌豆球蛋白;标志:前体[蚕豆]

[0337] >gi|22057|emb|CAA68559.1|豌豆球蛋白(vicilin)[小蚕豆]>gi|383931031|gb|AFH56916.1|豌豆球蛋白[蚕豆]

[0338] >gi|502105533|ref|XP_004492829.1|预测的:豌豆球蛋白样亚型X1[鹰嘴豆(Cicer arietinum)]鹰嘴豆(ChickPea)

[0339] >gi|29539109|emb|CAD87730.1|过敏原Len c 1.0101[兵豆(Lens culinaris)]小扁豆(Lentil)

[0340] 抗炎片段的“变体”应被认为意指具有与抗炎片段基本相同的氨基酸序列的片段,并且其具有如上定义的抗炎活性。因此,例如,该术语应该被认为包括一个或多个氨基酸残基被改变的片段。优选地,这种改变涉及插入、添加、缺失和/或替换5个或更少的氨基酸,更

优选为4个或更少,甚至更优选为3个或更少,最优选为仅1或2个氨基酸。设想用天然和经修饰的氨基酸插入、添加和替换。变体可具有保守氨基酸变化,其中被引入的氨基酸在结构上、化学上或功能上类似于被替换的氨基酸。通常,变体具有与亲本抗炎片段至少70%的氨基酸序列同源性,优选为至少80%的序列同源性,更优选为至少90%的序列同源性,并且理想地为至少95%、96%、97%、98%或99%的序列同源性。

[0341] 在本说明书中,术语“序列同一性”应理解为包含序列同一性和相似性二者,即与参考序列共享70%的序列同一性的变体(或同源物)是其中变体(或同源物)的任何70%的比对残基在整个序列长度上与参考序列中的相应残基相同或是其保守替换的变体(或同源物)。序列同一性是两个不同序列之间完全匹配的字符(character)的量。因此,缺口不计算在内,并且测量与两个序列中较短的一个相关。就“序列同源性”而言,该术语应被理解为意指当变体(或同源物)的比对残基的百分比与参考序列中的相应残基相同或是其保守替换时并且在变体(或同源物)与参考序列共享相同的功能的情况下,与参考序列共享限定的百分比相似性或同一性的变体(或同源物)。该比对和百分比同源性或序列同一性可以使用本领域已知的软件程序来确定,例如,一个比对程序是使用默认参数的BLAST。这些程序的详细信息可以在以下Internet网址获悉:<http://www.ncbi.nlm.nih.gov/blast/Blast.cgi>。

[0342] SEQUENCE ID NO:109的变体(抗炎肽(I_37))

[0343] 以下提供SEQUENCE ID NO:109(RGPQQYAEWQINEK)的变体,包括具有1、2或3个保守氨基酸替换,1、2至3个非保守氨基酸替换,1-2个氨基酸添加,1、2或3个氨基酸缺失的变体:

[0344] 一个保守氨基酸替换:

[0345] RGPQQYAEWQINER, RGPQQYAEWQINDK, RGPQQFAEWQINEK, KGPQQYAEWQINEK, RGPEQYAEWQINEK, RGPQEYAEWQINEK, RGPQQYADWQINEK, RGPQQYAEYQINEK (SEQ ID NO268-275)

[0346] 两个保守氨基酸替换:

[0347] KGPEQYAEWQINEK, KGPQEYAEWQNEK, KGPQQFAEWQINEK,

[0348] RGPEQFAEWQINEK, KGPQQYAEWQINER, RGPQQYAEWQINDR,

[0349] RGPQQYADWQINDK, RGPQQFAEWQINER (SEQ ID NO276-283)

[0350] 三个保守氨基酸替换:

[0351] RGPQQYAEWQVNEK, RGPQQFAEWQINEK, KGPQQFAEWQNER,

[0352] KGPQQFAEWQVNEK, RGPQQFAEWQVNDK, RGPQQYADWQINDR,

[0353] KGPQQYADWQINDK, RGPQQFADYQINEK (SEQ ID NO284-291)

[0354] 一个非保守氨基酸替换

[0355] RGPQQYARWQINEK, RGPQQYAEWQINEE, HGPQQYAEWQINEK,,

[0356] RGPYQYAEWQINEK, RGPQQYMEWQINEK, RGPQQYAEWCINEK,

[0357] RGPQPYAEWQINEK (SEQ ID NO292-298)

[0358] 两个非保守氨基酸替换

[0359] RGGQQYAEWQINED, RGPQQYARWKINEK, RGGQQYAEWQINEK,

[0360] RGPLQYAEWQNNNEK, EGPQQYAEWQINED, RGPQQYAEWQINLL,

[0361] RGPQQGGEWQINEK (SEQ ID NO 299-305)

[0362] 三个非保守氨基酸替换

[0363] RGPQQYAEWQIGGG, RGPQQKYEWQINEK, RGPQAQYEWQINEK,
[0364] RPHQQYAEWQINEK, RGPQHHEWQINEK, RGPPQYAPPQINEK,
[0365] RGPQCYEWCINEK, RGPTQYAEQGINEG (SEQ ID NO 306-313)
[0366] 一个或两个氨基酸添加
[0367] RGPQQYAEWQINEKG, RGPQQYAEWQINEKY, RGPQQYAFTEWQINEK,
[0368] RGPQSQAWEWQINEKPM, RGPQQYAEWQINEKKK, RRRRGPPQYAEWQINEK (SEQ ID NO314-319) .。

[0369] 术语“变体”通常涵盖本发明的肽的片段。“本发明的肽的片段”或“肽片段”意指具有至少3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21或22个氨基酸并且通常具有生物活性,例如抗炎活性、细胞生长或增殖促进活性、葡萄糖转运促进活性或抗细菌活性的本发明的肽之一的片段。在一个实施方案中,该片段由至少30%、40%、50%、60%、70%、80%或90%的参考序列(reference sequence)组成。在SEQUENCE ID NO 320-330中提供了本发明的片段的实例。

[0370] RGPQQYAEWQINE, RGPQQYAEWQIN, RGPQQYAEWQI, GPQQYAEWQINEK, PQQYAEWQINEK, QQYAEWQINEK, QQYAEWQI, PQQYAEWQINE, PQQYAEWQIN, RGPQQYA, EWQINEK (SEQ ID NO 320-330)

[0371] “炎性紊乱”意指影响人类的免疫介导的炎性病症并且通常特征在于一种或多种细胞因子的异常表达(dysregulated expression)。炎性紊乱的实例包括皮肤炎性紊乱、关节炎性紊乱、心血管系统的炎性紊乱、某些自身免疫病、肺和气道炎性紊乱、肠道炎性紊乱。皮肤炎性紊乱的实例包括皮炎,例如特应性皮炎和接触性皮炎、寻常痤疮和银屑病。关节炎性紊乱的实例包括类风湿性关节炎。心血管系统炎性紊乱的实例是心血管疾病和动脉粥样硬化。自身免疫疾病的实例包括1型糖尿病、格雷夫斯病、格林-巴利病、狼疮、银屑病关节炎和溃疡性结肠炎。肺和气道炎性紊乱的实例包括哮喘、囊性纤维化、COPD、肺气肿和急性呼吸窘迫综合征。肠道炎性紊乱的实例包括结肠炎和炎性肠病。其它炎性紊乱包括癌症、枯草热、牙周炎、变态反应、超敏反应、缺血、抑郁症、全身性疾病、感染后炎症和支气管炎。

[0372] 在本说明书中,术语“代谢紊乱”应被理解为包括前期糖尿病、糖尿病;1型糖尿病;2型糖尿病;代谢综合征;肥胖;糖尿病血脂异常;高脂血症;高血压;高甘油三酯血症;高脂脂肪酸血症;高胆固醇血症;高胰岛素血症和MODY。

[0373] “维持或恢复肠道健康”意指减少和/或调节肠道中且更具体地为上皮细胞中的促炎反应。健康的微生物组提供抵御致病病毒和细菌的一定的保护,并且需要它们的存在以引导我们的免疫系统的发展。已经表明,这些细菌可以对人体的应激、生病或年龄的信号作出反应,这些信号可以通过炎症表现出来,并因此开启它们的致病基因并导致或促成疾病。具有减少炎症反应和将炎症反应维持在健康水平的能力,可以帮助维护健康细菌。消化问题包括北美洲的头号健康问题近年来似乎更频繁地出现。维持消化健康的一个方法是维持适当的发炎和肠道菌群。

[0374] “维持或恢复肌肉健康”意指帮助保持或恢复运动过程中出现的损伤所引起的哺乳动物肌肉健康。通过减少炎症,肽促进运动过程中的损伤恢复,并减轻肌肉酸痛/疼痛和运动相关的损伤。它们还可以用来减少和防止肌肉痉挛,并允许从肌肉痉挛的较快恢复。痉挛可由躯体应激、心理应激和/或重复性劳损应激造成的。通过减少炎症,肽有助于减少肌

肉肌病,并有助于预防哺乳动物的肌肉减少症,促进运动过程中的损伤恢复,并减轻肌肉酸痛/运动相关的疼痛和损伤。它们还可以用来减少和防止肌肉痉挛,并允许从肌肉痉挛快速恢复。痉挛可能是由躯体应激、心理应激和/或重复性压迫损伤应激造成的。通过减少炎症,肽有助于减少肌肉肌病,并有助于预防哺乳动物的肌肉减少症。

[0375] 在本说明书中,术语“组合物”应被理解为意指由人手工制造的东西,并且不排除天然存在的组合物。示例性的组合物包括个人护理组合物和药物组合物。

[0376] 在本说明书中,应用于肽或片段的清单的术语“基本上全部”应被理解为意指肽或片段的至少60%、70%、80%、90%或95%。

[0377] 在本说明书中,术语“个人护理组合物”应被理解为意指被配制用于人类清洁或处理人体,特别是皮肤、牙齿、指甲、脚和头发的组合物。实例包括洗发水、护发素、护肤霜和乳液、粉末、牙膏、沐浴露或乳霜、身体乳、除臭剂和止汗剂。

附图说明

[0378] 图1至18:本发明的十八种合成肽对THP1细胞中TNF-分泌的作用。在三个板上一式两份地(6孔/条件)准备所有实验。使用Students t检验计算显著性(与对照相比 $p < 0.05$,与对照相比 $^{**}p < 0.01$,与对照相比 $^{***}p < 0.001$)

[0379] 图19.用合成肽处理后J774.2巨噬细胞的活力。在进行阿尔玛蓝(alar blue)测定之前,用100 μ M的合成肽将J774.2巨噬细胞处理24小时。数据表示为 $n = 3 \pm$ SEM的平均值。

[0380] 图20.肽组合物对细胞存活的影响。在进行alar blue测定之前,用(A)1mg/ml或(B)0.5mg/ml的肽组合物将J774.2巨噬细胞处理24小时。数据显示为(A) $n = 1 \pm$ SEM和(B) $n = 3 \pm$ SEM。

[0381] 图21:DMSO载体对来自J774.2巨噬细胞的TNF α 和IL-1 β 分泌的影响。将J774.2巨噬细胞用终浓度为0.3%和1%的DMSO(相当于用于溶解肽的量)处理24小时,并确定刺激后对TNF α 和IL-1 β 的影响。数据表示为 $n = 3 \pm$ SEM的平均值。 $(^{***}p < 0.001 \text{ w.r.t LPS})$ 。

[0382] 图22.本发明的六种肽对来自J774.2巨噬细胞的TNF α 和IL-1 β 分泌的影响。将J774.2巨噬细胞用100 μ M的合成肽处理24小时,然后用(A)LPS(10ng/ml)刺激5小时或(B)LPS(10ng/ml)刺激5小时,然后用ATP(5mM)刺激1小时。收集上清液并通过ELISA测定(A)TNF α 和(B)IL-1 β 的水平。 $(^{***}p < 0.001 \text{ w.r.t LPS}, ^{**}p < 0.01 \text{ w.r.t LPS}, ^{*}p < 0.05, ^{###}p < 0.001 \text{ w.r.t. LPS/ATP}, ^{##}p < 0.01 \text{ w.r.t LPS/ATP}$ 和 $^{\#}p < 0.05 \text{ w.r.t LPS/ATP})$ 。孔中的DMSO的最终浓度:SP1-0.3%,SP2-0%,SP3-0.3%,SP4 -1%,SP5-1%,SP6-0.3%,阳性对照-0%。数据表示为 $n = 3 \pm$ SEM的平均值。

[0383] 图23:本发明的肽组合物对TNF α 和IL-1 β 分泌的影响。将J774.2巨噬细胞用0.5mg/ml的肽组合物处理24小时,然后用(A)LPS(10ng/ml)刺激5小时或(B)LPS(10ng/ml)刺激5小时,然后用ATP(5mM)刺激1小时。收集上清液并通过ELISA测定(A)TNF α 和(B)IL-1 β 的水平。 $(^{***}p < 0.001 \text{ w.r.t 未处理的+LPS}, ^{###}p < 0.001 \text{ w.r.t. 未处理的+LPS/ATP})$ 。数据表示为 $n = 3 \pm$ SEM的平均值。

[0384] 图24.合成肽与DMSO载体对TNF α 的影响。将J774.2巨噬细胞用100 μ M的合成肽处理24小时,然后用LPS(10ng/ml)处理5小时。收集上清液并通过ELISA测定TNF α 的水平。 $^{###}p <$

0.001w.r.t 0.3% DMSO+LPS, ## $p < 0.01$ w.r.t. 0.3% DMSO+LPS, +++ $p < 0.001$ w.r.t 1% DMSO+LPS, ++ $p < 0.01$ w.r.t 1% DMSO+LPS/ATP)。孔中的DMSO的最终浓度:阳性对照-0%, SP1-0.3%, SP2-0%, SP3 -0.3%, SP4-1%, SP5-1%, SP6-0.3%。

[0385] 图25. 在LPS刺激之前, 将用本发明的大米肽的组合物(I_2_HR)处理24小时的THP-1分化的巨噬细胞与未处理的细胞比较。与未处理的细胞相比, I_2_HR处理的细胞中的TNF- α 分泌减少了92%。在100ug/ml和500ug/ml浓度的I_2_HR下观察到显著的结果, 表明I_2_HR的效力。

[0386] 图26至28. 本发明的三种合成肽对THP1细胞中的TNF-分泌的影响。在三个板上一式两份地(6孔/条件)准备所有实验。使用Students t检验计算显著性(与对照相比 $p < 0.05$, 与对照相比** $p < 0.01$, 与对照相比*** $p < 0.001$)。

具体实施方式

[0387] 实施例1-炎症反应

[0388] 响应于内毒素如脂多糖(LPS)的刺激, 巨噬细胞分泌TNF- α 。TNF- α 被认为与全身性炎症有关, 且TNF- α 产生的调节异常被认为与许多疾病有关。Biolegend测定是一种夹心ELISA试剂盒, 其被设计用于从细胞培养上清液、血清或血浆中精确定量人TNF- α 。

[0389] 在含有10%的胎牛血清(FCS)、1%的青霉素/链霉素(Pen/strep)、1%的L-谷氨酰胺、100nM的PMA的RPMI中, 将THP-1单核细胞以10,000个细胞/孔接种在96孔板中, 并在实验之前使其分化72小时。

[0390] 分化后, 分别用100ng/ml、10ng/ml或1ng/ml的合成肽将细胞孵育24小时。

[0391] 处理后, 用10ng/ml的LPS刺激细胞5小时, 使用Biolegend测定ELISA试剂盒确定上清液中TNF- α 的量。

[0392] 结果以未处理的对照的百分比形式计算。光密度读数的增加表明更大的量的TNF- α 释放到细胞培养物上清液中。

[0393] 结果提供在图1至21中并总结于下表1中。在三个板上一式两份地(6孔/条件)准备所有实验。使用Student t检验计算显著性(与对照相比 $p < 0.05$, 与对照相比** $p < 0.01$, 与对照相比*** $p < 0.001$)。

[0394] 表1

图号	SEQ ID	TNF- α 减少
图1	339	26%
图2	352	23%
图3	341	21%
图4	351	18%
图5	144	16%
图6	93	14%
图7	320	13%
图8	92	13%
图9	75	11%
图10	76	9%

图11	349	6%
图12	350	
图13	105	9%
图14	177	
图15	345	23%
图16	353	20%
图17	344	20%
图18	346	18%
图26	85	80%
图27	91	80%
图28	420	80%

[0396] 实施例2-炎性反应

[0397] 测定本发明的六种合成肽SP1至SP6 (SEQUENCE ID NO:108、109、110、111、85和91) 和四种肽组合物对使用细胞系的体外炎性反应的影响。

[0398] 肽组合物I_1_HR (大米) 含有以下肽 (通过SEQ ID确定): 116、197、207、112、211、158、201、203、114、183、130、113、182、167、166、152、220、213、215、154、219、218、165、123、185、190、209、181、198、200、147、172、184、124、153、205、115、196、151、161、160、216、210、208、146、133、204、212、206。

[0399] 肽组合物I_2_HR (大米) 含有以下肽 (通过SEQ ID确定): 189、177、174、129、176、202、193、195、194、192、182、128、220、127、134、136、135、180、179、178、219、218、145、120、175、190、149、126、187、191、121、122、159、132、162、137、150、186、188、164、118、125、163、157、156、117。

[0400] 肽组合物E_1_HR (豌豆) 含有以下肽 (通过SEQ ID确定): 74、76、106、102、101、100、92、96、83、89、90、104、82、75、79、78、77、99、103、72、86、105、94、93、81、97、80、88、85、87、71、107、73、84、98、95。

[0401] 肽组合物E_2_HR (豌豆) 含有本发明的肽的同源物。

[0402] 用100 μ M的每种合成肽 (Sp) 和0.5mg/ml的每种肽组合物处理J774.2小鼠巨噬细胞系,并在脂多糖 (LPS) 作为炎性刺激物诱导炎症后测定对两种促炎症标志物-肿瘤坏死因子 α (TNF α) 和白细胞介素-1 β (IL-1 β) 的影响。将单因素方差分析与多重比较的dunnet检验一起使用,并将每个平均值与单个对照平均值进行比较。

[0403] 实施例3-合成肽:细胞活力

[0404] 首先将合成肽在合适的溶剂中稀释。二甲亚砜 (DMSO) 是选择用于预测水溶性差的肽的溶剂。每个孔中的DMSO的最终浓度:SP1 (1_155_HR) -0.3%、SP2 (1_374_HR) -0%、SP3 (E_155_HR) -0.3%、SP4 (E_54_HR) -1%、SP5 (E_41_HR) -1%、SP6 (E_788_HR) -0.3%、阳性对照-0%。在进行alar blue测定之前,首先用100 μ M的每种SP处理细胞24小时。用任何肽都没有发现活力问题。

[0405] 实施例4-肽组合物:制备和毒性

[0406] 通过将pH调节至6-7和无菌过滤来制备肽组合物。测定肽组合物对细胞活力的影响。J774.2巨噬细胞用1mg/ml和0.5mg/ml的每种肽组合物处理、用过氧化氢处理以诱导细

胞死亡作为阳性对照,以及用一已知是无毒的肽作为阴性对照。然后,进行alamar blue测定,并且细胞存活在图19中显示为未处理(100%)的百分比。由于1mg/ml的肽损害细胞存活,因而将0.5mg/ml的肽组合物用于进一步测定。

[0407] 实施例5-炎性标志物

[0408] 测定DMSO对TNF α 和IL-1 β 分泌的影响。1%的DMSO显著增加TNF α 的水平(图3A,***p<0.001w.r.t LPS),并且在分析肽对TNF α 的影响时将其考虑在内。对于DMSO和IL-1 β 分泌没有观察到显著的效果。

[0409] 实施例6-炎性反应

[0410] 用本发明的大米肽的组合物(I_2_HR)处理24小时的THP-1分化的巨噬细胞,然后用LPS刺激,与未处理的细胞进行比较。与未处理的细胞相比,I_2_HR处理的细胞中的TNF- α 分泌减少了92%。在100ug/ml和500ug/ml浓度的I_2_HR下观察到显著的结果,表明I_2_HR的效力。

[0411] 本发明不限于前面描述的实施方案,在不脱离本发明的精神的情况下,其可以在结构和细节上进行改变。

序列信息

豌豆蛋白质 1: P13918 - 1 -

MAATTMKASFLLMLMGISFLASVCVSSRSDPQNPFIFKSNKFQTLFENENGHIRLLQKFDQRSKIFENLQNYRLLLEYKSKPHTIFLPQHTDA
DYILVVLGSKAILTVLKPDNRNSFNLERGDTIKLPAGTIAYLVNRDDNEELRVLDLAIPVNRPGQLQSFLLSGNQNNQNYLSGFSKNILEASFN
TDYEEIEKVLLEEHEKETQHRRLKDKRQSQEENVIVKLSRGQIEELSKNAKSTSKSVSSSEPFNLRSRGPIYSNEFGKFFEITPEKNPQLQ
DLDFVNSVEIKEGSLLLPHYNSRAIVIVTVNEGKGFELVQGQRNENQQEQRKEDDEEEQGEIEINKQVQNYKAKLSSGDVFPAGHPVA
VKASSNLDLLGFGINAENNQRNFLAGDEDNVISQIRPVKELAFPGSAQEVDRILENQKQSHFADAQPQQRERGRSRETRDLSSV [SEQ
ID 1]

区域: 253 至 274 - PFNLRSRGPIYSNEFGKFFEIT [SEQ ID 17]

肽: SRGPIYSNEFGK [SEQ ID 71]

区域: 110 至 126 - KPDDNRNSFNLERGDTIK [SEQ ID 18]

肽: NSFNLER [SEQ ID 72]

区域: 134 至 160 - YLVNRDDNEELRVLDLAIPVNRPGQLQ [SEQ ID 19]

肽: VLDLAIPVNR [SEQ ID 73]

肽: DDNEELR [SEQ ID 74]

区域: 331 至 381 - QEQRKEDDEEEQGEIEINKQVQNYKAKLSSGDVFPAGHPVAVKASSNL [SEQ ID 20]

肽: LSSGDVFPAGHPVAVK [SEQ ID 75]

肽: EDDEEEQGEIEINK [SEQ ID 76]

区域: 175 至 242 - SGFSKNILEASFNTDYEEIEKVLLEEHEKETQHRRLKDKRQSQEENVIVKLSRGQIEELSKNAKST [SEQ
ID 21]

肽: NILEASFNTDYEEIEKVLLEEHEKETQHR [SEQ ID 77]

肽: NILEASFNTDYEEIEKVLLEEHEK [SEQ ID 78]

肽: NILEASFNTDYEEIEK [SEQ ID 79]

肽: RQSQEENVIVK [SEQ ID 80]

肽: QSQEENVIVK [SEQ ID 81]

肽: LSRGQIEELSK [SEQ ID 82]

肽: GQIEELSK [SEQ ID 83]

肽: VLLEEHEK [SEQ ID 84]

[0412]

区域: 35 至 108 - PFIFKSNKFQTLFENENGHIRLLQKFDQRSKIFENLQNYRLLLEYKSKPHTIFLPQHTDADYILVVLGSKAILTV
[SEQ ID 22]

肽: SKPHTIFLPQHTDADYILVVLGSK [SEQ ID 85]

肽: PHTIFLPQHTDADYILVVLGSK [SEQ ID 86]

肽: SNKFQTLFENENGHIR [SEQ ID 87]

肽: SKIFENLQNYR [SEQ ID 88]

肽: IFENLQNYR [SEQ ID 89]

区域: 423 至 450 - QEVDRILENQKQSHFADAQPQQRERGRS [SEQ ID 23]

肽: ILENQKQSHFADAQPQQR [SEQ ID 90]

肽: PGQLQSFLLSGNQNNQNYLSGFSK [SEQ ID 91]

豌豆蛋白质 2: P02856 - 2 -

DRRQELSNENVLVKVSRRQLEELSKNAKSSSRSSVSSESGPFNLRSRSDPLYSNNSGKFFELTPEKNQQLQDLDFVNSVDLKEGSLLLPNYNS
RALLVLVLVNEGKGFELVQQRNENQKGK [SEQ ID 2]

区域: 53 至 87 - NNSGKFFELTPEKNQQLQDLDFVNSVDLKEGSL [SEQ ID 24]

肽: FFELTPEKNQQLQDLDFVNSVDLK [SEQ ID 92]

区域: 14 至 30 - KVSRRQLEELSKNAKSS [SEQ ID 25]

肽: QLEELSK [SEQ ID 93]

豌豆蛋白质 3: P15838 - 3 -

MATKLLALSFCFLLLGGCFALREQPEQNECQLERLNALEPDNRIESEGGLIETWNPNNKQFRCAGVALSRATLQHNAALRRPYSNAPQEI
FIQQNGYFGMVFPGPETFEPEQEQEGRRYRDRHQVNRFRREGDIIAVPTGIVFWMYNDQDTPVIAVSLDIRSSNNQLDQMPRR
FYLAGNHEQEFLRYQHQQGGKQEQENEGNNIFSGFKRDFLEDAFNVNRHIVDRQLQGRNEDEEKGAIVKVGGLSIISPEKQARHQGRSR
QEEDEDEDEERQPRHQGRSRQEEDEDEERQPRHQRRRGEEDKKERRGSQKGSRRQGDNGLEETVCTAKLRNLNIGPSSSPDIYNPE
AGRIKTVTSLDLPVLRWLKLSAEHGSLLHKNAFMVPHYNLANSIIYALKGRARLQVVNCNGNTVFDGELEAGRALTVPQNYAVAAKSLSD
RFSYVAFKTNDRAGIARLAGTSSVINNLPLDVVAATFNLQRNEARQLKSNNPFKFLVPARQSENRA [SEQ ID 3]

区域: 267 至 287 - QRGSRQEEDEDEERQPRHQ [SEQ ID 26]

肽: QEEDEDEER [SEQ ID 94]

区域: 190 至 222 - QEFLRYQHQQGGKQEQENEGNNIFSGFKRDFLE [SEQ ID 27]

肽: YQHQQGGKQEQENEGNNIFSGFK [SEQ ID 95]

豌豆蛋白质 4 : Q9M3X6 - 4 -

MATTIKSRFPLLLLLGIIFLASVVCVTYANYDEGSEPRVPAQRRERGRQEGEKEEKRHGEWRPSYEKEDEEEGQRRERGRQEGEKEEKRHGE
WRPSYEKQDEEEKQKYRYQREKEDEEEKQKYQYQREKKEQKEVQPGRRWEREEDEEQVDEEWRGSGRRREDPEERARLRHREERTKR
DRRHQREGEEERSESQERRNPFLFKSNKFLTLFENENGHIRLLQRFDRKSDLFENLQNYRLVEYRAKPHTIFLPQHIDADLILVVLGSKAILT
VLSPNDRNSYNLERGDTIKLPAGTTSYLVNQDDEEDLRLVDLVIPVNGPGKFEAFDLAKNKNQYLRGFSKNILEASYNTRYETIEKVLLLEE
KDRKRRQGEETDAIVKVSREQIEELKKLAKSSSKSLPSEFEPINLRSHKPEYSNKFGLFEITPEKKYPQLQDLDFVSCVEINEGALMLPHY
NSRAIVLLVNEGKGNLELLGLKNEQEREDRKERNNEVQRYEARLSPGDVVIIPAGHPVAITASSNLLNGFGINAENNERNFLSGSDDNV
ISQJENPVKELTFPGSVQEIINRLIKNQKQSHFANAEPQEQGSGQKRSPLSSILGTFY [SEQ ID 4]

区域 : 284 至 317 - YNLERGDTIKLPAGTTSYLVNQDDEEDLRLVDLV [SEQ ID 28]

肽 : GDTIKLPAGTTSYLVNQDDEEDLR [SEQ ID 96]

区域 : 321 至 400 -

NGPGKFEAFDLAKNKNQYLRGFSKNILEASYNTRYETIEKVLLLEEQEKDRKRRQQGEETDAIVKVSREQIEELKKLAKSS [SEQ ID 29]

肽 : RQQGEETDAIVK [SEQ ID 97]

肽 : VLLEEQEKDRK [SEQ ID 98]

肽 : NILEASYNTR [SEQ ID 99]

肽 : FEAFDLAK [SEQ ID 100]

肽 : EQIEELKK [SEQ ID 101]

肽 : EQIEELK [SEQ ID 102]

肽 : NKNQYLR [SEQ ID 103]

区域 : 503 至 549 - RYEARLSPGDVVIIPAGHPVAITASSNLLNGFGINAENNERNFLSG [SEQ ID 30]

肽 : LSPGDVVIIPAGHPVAITASSNLLNGFGINAENNER [SEQ ID 104]

区域 : 89 至 112 - HGEWRPSYEKQDEEEKQKYRYQR [SEQ ID 31]

肽 : PSYEKQDEEEKQK [SEQ ID 105]

区域 : 62 至 80 - PSYEKEDEEEGQRRERGRQ [SEQ ID 32]

肽 : EEDEEEGQR [SEQ ID 106]

豌豆蛋白质 5 : D3VNE1 - 5 -

MAATPIKPLMLLAIAFLASVCVSSRSQENPFIFKSNRFQTLYENENGHIRLLQKFDKRSKIFENLQNYRLLEYKSKPRTLFLPQYTDADFILVV
LSGKATLTVLKSNDNRNSFNLERGDTIKLPAGTIAYLANRDDNEDLRLVLDLTIPVNKPGQLQSFLSGTQNPQSLSGFSKNILEAAFNTNYEEI
EKVLLQQEQEPQHRRSLKDRRQEIENEENVIVKVSREQIEELSKNAKSSSKSVSSSESGPFNLRSRNPISNKFGLFFEITPEKNQQLQDLDF
VNSVDIKEGSLLPNYSRAIVIVTVTEGKGDFELVGQRNENQKGKENDKEEEQEEETSKQVQLYRAKLSPGDVVFVIPAGHPVAINASSDLNLI
GFGINAENNERNFLAGEEDNVISQVERPVKELAFPGSSHEVDRLLKNQKQSYFANAQPLQRE [SEQ ID 5]

肽 : 75 至 104 - KSKPRTLFLPQYTDADFILVVLGKATLTV [SEQ ID 33]

肽 : TLFLPQYTDADFILVVLGK [SEQ ID 107]

大米蛋白质 7 : Q6K508

MATTTSLSSCLCALLAPLSQGVDAWESRQGASRQCRFDRLQAFELRKVRSEAGDTE
YFDERNEQFRCAGVFVIRRVIEPQGLVVPYRNTPALAYIIQGGKGYVGLTFPGCPATHQQ
QFQLFEQRQSDQAHKFRDEHQKIHEFRQGDVVALPASVAHWFYNGGDTPAVVVVYDIKS
FANQLEPRQKEFLAGNNQRGQQIFEHSIFQHSQGQNFSGFNTEVLSEALGINTEASKRL
QSQNDQRGDIIRVKHGLQLLKPTLTQRQEEHRQYQQVYQYREGQYNGLDENFCTIKARVNI
ENPSRADYYNPRAGRITLLNNQKFPILNLIGMGAARVNLYQNALLSPFWNINAHSVVYII
QGSVRVQVANNGGRSVFNGVLHQQGLLIIPQNHAVIKKAEHNGCQYVAIKTISDPTVSWV
AGKNSILRALPVDVIANAYRISRDEARRLKNNRADEIGPFTPRFPQKSQRGYQFLTEGLS
LIGM [SEQ ID 6]

肽 : GYVGLTFPGCPATHQQQFQLFEQR [SEQ ID 108]

大米蛋白质 8 : Q6K7K6

MASMSTILPLCLGLLFFQVSMAQFSFGGSPLQSPRGFRGDQDSRHQCRFEHLTALEATH
QQRSEAGFTEYYNIEARNEFRCAQSVRRLLVESKGLVLPMYANAHKLVIYVQGRGVFGM
ALPGCPETFQSVRSPFEQEVATAGEAQSSIQKMRDEHQQLHQFHQGDVIAVPAGVAHWLY
NNGDSPVVAFTVIDTSSNANQLDPKRREFFLAGKPRSSWQQQSYSYQTEQLSRNQNFAG
FSPDLLSEALSVSKQTVLRLQGLSDPRGAIIRVENGLQALQPSLQVEPVKEEQTQAYLPT
KQLQPTWLRSGGACQQNVLDEIMCAFKLRKNIDNPQSSDIFNPHGGRITRANSQNFIL
NIIQMSATRIVLQNNALLTPHWTVNAHTVMYVTAGQGGHIQVVDHRGRSVFDGELHQQQIL
LIPQNFVAVVVKARREGFAWVSFKTNHNAVDSQIAGKASILRALPVDVIANAYRLSREDSR
HVKNRNGDEMAVFAPRRGPPQYAEWQINEK [SEQ ID 7]

肽 : RGPQQYAEWQINEK [SEQ ID 109]

[0413]

豌豆蛋白质 6: P13919

MATTIKSRFPLLLLLGIIFLASVSVTYANYDEGSEPRVPAQREGRQEGEKEEKRHGEW
RPSYEKEDEEEGQREGRQEGEKEEKRHGEWGSPYEKQDEEEKQKYRYQREKEDEEEK
QKYQYQREKKEQKEVQPGRRERWEREEDEEQVDEEWGRSQRREDPEERARLRHREERTKRD
RRHQREGEEERSSSEQERRNPFLFKSNKFLTFENENGHIRLLQRFDKRSDFENLQNY
RLVEYRAKPHTIFLPQHIDADLILVVLGSKAILTVLSPNDRNSYNLERGDTIKLPAGTTS
YLVNQDDEEDLRLVDLVIPVNGPGKFEAFDLAKNKNQYLRGFSKNILEASYNTRYETIEK
VLLEEQEKDRRRQGEETDAIVKVS [SEQ ID 8]

肽 : LVDLVIPVNGPGKFEAFDLAK [SEQ ID 110]

豌豆蛋白质 7: P02855

MATTIKSRFPLLLLLGIIFLASVSVTYANYDEGSEPRVPAQREGRQEGEKEEKRHGEW
RPSYEKEDEEEGQREGRQEGEKEEKRHGEWGSPYEKQDEEEKQKYRYQREKEDEEEK
QKYQYQREKKEQKEVQPGRRERWEREEDEEQVDEEWGRSQRREDPEERARLRHREERTKRD
RRHQREGEEERSSSEQERRNPFLFKSNKFLTFENENGHIRLLQRFDKRSDFENLQNY
RLVEYRAKPHTIFLPQHIDADLILVVLGSKAILTVLSPNDRNSYNLERGDTIKLPAGTTS
YLVNQDDEEDLRLVDLVIPVNGPGKFEAFDLAKNKNQYLRGFSKNILEASYNTRYETIEK
VLLEEQEKDRRRQGEETDAIVKVS [SEQ ID 9]

肽 : KNPQLQDLDFVNYVEIK [SEQ ID 111]

大米蛋白质 1: P14323 - 1 -

MASSVFSRFSIYFCVLLCHGSMALFNPNSTNPWHSPRQGSFRECFRDLQAPEPLRKVRSEAGVTEYFDEKNELFQCTGTIVIRRVIPQGG
LLVPRYTINIPGVVYIIQGRGSMGLTFPGCPATYQQQFQQFSSQGGSQSKFRDEHQKIHQFRQGDIVLAPAGVAHWFYNDGDAPIVAVY
VYDVNNNANQLEPRQKEFLLAGNNNRAQQQQVYGSSIEHQSGQNIQSGFGVEMLSEALGINAVAAKRLQSQNDQRGEIIVKNGQLQLLK
PTLTQQQEQAQAQDQYQQVQYSERQQTSSRWNGLEENFCTIKVRVNIENPSRADSYNPRAGRITSVNSQKFPILNLQMSATRVNLYQN
AILSPFWNVNAHSLVYMIQGRSRVQVVSNGKTVFDGVLPRGQLLIIPQHYAVLKAEREGCQYIAIKTNANAFVSHLAGKNSVFRALPVD
VVANAYRISREQARSLKNNRGEHGAFTPRFQQQYYPGLSNESESETSE [SEQ ID 10]

区域 : 138 至 159 - SQSQKFRDEHQKIHQFRQGDIV [SEQ ID 34]

肽 : DEHQKIHQFR [SEQ ID 112]

肽 : FRDEHQK [SEQ ID 113]

区域 : 336 至 358 - VNSQKFPILNLQMSATRVNLYQ [SEQ ID 35]

肽 : FPILNLQMSATR [SEQ ID 114]

区域 : 423 至 462 - YIAIKTNANAFVSHLAGKNSVFRALPVDVVANAYRISREQ [SEQ ID 36]

肽 : TNANAFVSHLAGK [SEQ ID 115]

肽 : ALPVDVVANAYR [SEQ ID 116]

区域 : 175 至 205 - APIVAVYVDVNNNANQLEPRQKEFLLAGNN [SEQ ID 37]

肽 : VYVDVNNNANQLEPRQKEFL [SEQ ID 117]

肽 : VYVDVNNNANQLEPRQKEFL [SEQ ID 118]

区域 : 318 至 334 - ENPSRADSYNPRAGRIT [SEQ ID 38]

肽 : ADSYNPR [SEQ ID 119]

区域 : 265 至 296 - GLQLLKPTLTQQQEQAQAQDQYQQVQYSERQQ [SEQ ID 39]

肽 : KPTLTQQQEQAQAQDQ [SEQ ID 120]

肽 : QAQAQDQYQQVQY [SEQ ID 121]

肽 : QAQDQYQQVQY [SEQ ID 122]

区域 : 45 至 62 - CRFDRLQAPEPLRKVRSE [SEQ ID 40]

肽 : LQAPEPLR [SEQ ID 123]

区域 : 361 至 408 - ILSPFWNVNAHSLVYMIQGRSRVQVVSNGKTVFDGVLPRGQLLIIPQ [SEQ ID 41]

肽 : SRVQVVSNGK [SEQ ID 124]

肽 : WNVNAHSLVY [SEQ ID 125]

肽 : NVNAHSLVY [SEQ ID 126]

肽 : IQGRSRVQVVSNGK [SEQ ID 127]

肽 : GKTVDGVLPRGQL [SEQ ID 128]

肽 : FGKTVFDGVLPRGQL [SEQ ID 129]

区域 : 476 至 499 - AFTPRFQQQYYPGLSNESESETSE [SEQ ID 42]

肽 : FQQQYYPGLSNESESETSE [SEQ ID 130]

肽 : QQYYPGLSN [SEQ ID 131]

肽 : QQYYPGLSN [SEQ ID 132]

大米蛋白质 2: P07728 - 2 -

MASINRPIVFFTVCLLNCGLAQQLLGQSTSQWQSSRRGSPRECFRDLQAPEPIRSVRSQAGTTEFFDVSNEQFQCTGVSVVRRVIEPR

[0414]

GLLLPHYTNGASLVYIIQGRGITGPTFPGPCESYQQQFQQSGQAQLTESQSQSKFKDEHQKIHRFRQGDVIALPAGVAHWVCYNDGEVPV
VAIYVTDLNNGANQLDPRQRDFLLAGNKRNPQAYRREVEERSQNFSGFSTELLSEALGVSSQVARQLQCQNDQRGEIVRVEHGLSLQPY
ASLQEQEQGQVQSREHYQEGGYQQSQYSGSCSNGLDETFTCLRVQRNIDNPNRADTYNPRAGRVTNLNTQNFILSLVQMSAVKVNLY
QNALLSPFWNINAHSVVYITQGRARVQVNNNGKTVFNGELRRGQLLIIPQHYAVVKKAAQREGCAYIAFKTNPNSMVSHIAGKSSIFRAL
PNDVLANAYRISREEAQLKHNRGDEFGAFTPIQYKSYQDVYNAEES [SEQ ID 11]

区域 : 332至 362 - PRAGRVTNLNTQNFILSLVQMSAVKVNLYQ [SEQ ID 43]

肽 : VTNLNTQNFILSLVQMSAVK [SEQ ID 133]

区域 : 375至 406 - HSVVYITQGRARVQVNNNGKTVFNGELRRGQ [SEQ ID 44]

肽 : ITQGRARVQVNNNGKTVF [SEQ ID 134]

肽 : ITQGRARVQVNNNGKTVFNGE [SEQ ID 135]

肽 : ITQGRARVQVNNNGKTVFNG [SEQ ID 136]

肽 : RVQVNNNGKTVF [SEQ ID 137]

区域 : 440至 471 - HIAGKSSIFRALPNDVLANAYRISREEAQLK [SEQ ID 45]

肽 : RALPNDVLANAYRISREE [SEQ ID 138]

肽 : SIFRALPNDVLANAYR [SEQ ID 139]

肽 : SIFRALPNDVLANAY [SEQ ID 140]

肽 : SIFRALPNDVLAN [SEQ ID 141]

肽 : SSIFRALPNDVLANAYR [SEQ ID 142]

肽 : SIFRALPNDVLANAYRISREE [SEQ ID 143]

肽 : SIFRALPND [SEQ ID 144]

区域 : 180至 208 - VPVVAIYVTDLNNGANQLDPRQRDFLLAG [SEQ ID 46]

肽 : IYVTDLNNGANQLDPRQRD [SEQ ID 145]

大米蛋白质 3 : P07730 - 2 -

MASINRPIVFFTVCLFLCDGSLAQQLLGQSTSQWQSSRRGSPRGCRFDRQLQAFEPISVRSQAGTTEFFDVSNELFQCTGVSVVRRVIEPR
GLLLPHYTNGASLVYIIQGRGITGPTFPGPCETYQQQFQQSGQAQLTESQSQSHKFKDEHQKIHRFRQGDVIALPAGVAHWVCYNDGEVPV
VAIYVTDINNGANQLDPRQRDFLLAGNKRNPQAYRREVEEWSQNFSGFSTELLSEAFGISNQVARQLQCQNDQRGEIVRVERGLSLQPY
ASLQEQEQGQMQRHYQEGGYQQSQYSGSCPNGLDETFTCMRVQRNIDNPNRADTYNPRAGRVTNLNSQNFILNLVQMSAVKVN
LYQNALLSPFWNINAHSVVYITQGRAQVQVNNNGKTVFNGELRRGQLLIPQHYVVKKAQREGCAYIAFKTNPNSMVSHIAGKSSIFR
ALPTDVLANAYRISREEAQLKHNRGDEFGAFTPLQYKSYQDVYNVAEES [SEQ ID 12]

区域 : 311至 362 - TFCTMRVRQNIIDNPNRADTYNPRAGRVTNLNSQNFILNLVQMSAVKVNLYQ [SEQ ID 47]

肽 : VTNLNSQNFILNLVQMSAVK [SEQ ID 146]

肽 : QNIDNPNR [SEQ ID 147]

肽 : ADTYNPR [SEQ ID 148]

肽 : NIDNPNRADTYNPRAGRVTNL [SEQ ID 149]

肽 : RVRQNIIDNPNRADTYNPRAGRVTNL [SEQ ID 150]

区域 : 427至 499 -

YIAFKTNPNSMVSHIAGKSSIFRALPTDVLANAYRISREEAQLKHNRGDEFGAFTPLQYKSYQDVYNVAEES [SEQ ID 48]

肽 : TNPNSMVSHIAGKSSIFR [SEQ ID 151]

肽 : HNRGDEFGAFTPLQYK [SEQ ID 152]

肽 : SYQDVYNVAEES [SEQ ID 153]

肽 : ISREEAQR [SEQ ID 154]

肽 : SIFRALPTDVLANAYRISREE [SEQ ID 155]

肽 : YRISREEAQLKHNRGDEF [SEQ ID 156]

肽 : YRISREEAQLKHNRGDE [SEQ ID 157]

区域 : 143至 178 - SQSHKFKDEHQKIHRFRQGDVIALPAGVAHWVCYNDG [SEQ ID 49]

肽 : FKDEHQKIHR [SEQ ID 158]

肽 : QGDVIALPAGVAHW [SEQ ID 159]

区域 : 381至 409 - TQGRAQVQVNNNGKTVFNGELRRGQLLI [SEQ ID 50]

肽 : TVFNGELRR [SEQ ID 160]

肽 : TVFNGELR [SEQ ID 161]

肽 : QVQVNNNGKTVF [SEQ ID 162]

区域 : 101至 124 - NGASLVYIIQGRGITGPTFPGCPE [SEQ ID 51]

肽 : YIIQGRGITGPTF [SEQ ID 163]

肽 : VYIIQGRGITGPTF [SEQ ID 164]

区域 : 46至 66 - CRFDRQLQAFEPISVRSQAGT [SEQ ID 52]

肽 : LQAFEPISVR [SEQ ID 165]

区域 : 253至 292 - QNDQRGEIVRVERGLSLQPYASLQEQEQGQMQRHYQE [SEQ ID 53]

肽 : GLSLQPYASLQEQEQGQMQR [SEQ ID 166]

肽 : GEIVRVER [SEQ ID 167]

肽 : RGLSLQPYASLQ [SEQ ID 168]

肽 : RGLSLQPYASLQEQ [SEQ ID 169]

肽 : RGLSLQPYASLQEQE [SEQ ID 170]

[0415]

肽: RGLSLLQPYASLQE [SEQ ID 171]
区域: 199 至 233 - PRQRDFLLAGNKRNPQAYRREVEEWSQNIFSGFST [SEQ ID 54]
肽: RNPQAYR [SEQ ID 172]
肽: FLLAGNKRNPQAY [SEQ ID 173]
肽: EVEEWSQNIF [SEQ ID 174]
肽: LAGNKRNPQAYR [SEQ ID 175]
肽: FLLAGNKRNPQA [SEQ ID 176]

大米蛋白质 4: Q0D7S0 - 3 -

MASNKVVSFVLLAVVSVLAATATMAEYHHQDQVYTPGPLCQPGMGYPMYPLPRCRALVKRQCVGRGTAAAAEQVRRDCCRQLAAV
DDSWCRCEAISHMLGGIYRELGAPDVGHMSEVFRGCRRLERAAASLPFCNVNDIPNGGGGVGYWLRASGY [SEQ ID 13]

区域: 102 至 124 - GGIYRELGAPDVGHMSEVFRGC [SEQ ID 55]
肽: ELGAPDVGHMSE [SEQ ID 177]

大米蛋白质 5: P14614 - 4 -

MATIAFSRLSIYFCVLLCHGSMAGLFGPNVNPWHNPRQGGFRECFRDLQAFELRRVRSEAGVTEYFDEKNEQFQCTGTGTVIRRVIEPQ
GLLVPRYSNTPGMVYIIQGRGSMGLTFPGCPATYQQQFQFLPEGQSQSQKFRDEHQKIHFQRGGDIVALPAGVAHWFYNEGDAVVVA
LYVFDLNNNANQLEPRQKEFLLAGNNNREQQMYGRSIEHSGQNIFSGFNNELLSEALGVNALVAKRLQGQNDQRGEIIRVKNGLKLLRP
AFAQQQEQAQQQEQAQYQVYSEEQQPSTRCNGLDENFCTIKARLNIENPSHADTYNPRAGRITRLNSQKFPILNLVQLSATRVNLY
QNAILSPFWNVNAHSLVYIVQGHARVQVVSNLGKTVFNGVLRPGQLLIIPQHYYVVLKKAHEGQCQYISFKTNANSMVSHLAGKNSIFRAM
PVDVIANAYRISREQARSLKNNRGEELGAFTPRYQQQTYPGFSNESENEALE [SEQ ID 14]

区域: 372 至 397 - HSLVYIVQGHARVQVVSNLGKTVFNG [SEQ ID 56]

肽: IVQGHARVQVVSNLGK [SEQ ID 178]

肽: IVQGHARVQVVSNL [SEQ ID 179]

肽: IVQGHARVQVVS [SEQ ID 180]

区域: 464 至 486 - ARSLKNNRGEELGAFTPRYQQQT [SEQ ID 57]

肽: NNRGEELGAFTPR [SEQ ID 181]

肽: GEELGAFTPR [SEQ ID 182]

区域: 337 至 359 - LNSQKFPILNLVQLSATRVNLYQ [SEQ ID 58]

肽: FPILNLVQLSATR [SEQ ID 183]

区域: 210 至 293 -

[0416] QMYGRSIEHSGQNIFSGFNNELLSEALGVNALVAKRLQGQNDQRGEIIRVKNGLKLLRPAFAQQQEQAQQQEQAQYQVYQ [SEQ ID 59]

肽: SIEHSGQNIFSGFNNELLSEALGVNALVAK [SEQ ID 184]

肽: LQGQNDQR [SEQ ID 185]

肽: SGFNNELLSEALGVNALVAK [SEQ ID 186]

肽: PAFAQQQEQAQQQEQAQY [SEQ ID 187]

肽: VAKRLQGQNDQRGEI [SEQ ID 188]

肽: ALVAKRLQGQNDQRGEI [SEQ ID 189]

肽: LQGQNDQRGEIIR [SEQ ID 190]

区域: 24 至 47 - AQLFGPNVNPWHNPRQGGFRECRF [SEQ ID 60]

肽: PNVNPWHNPRQGGF [SEQ ID 191]

区域: 164 至 186 - GVAHWFYNEGDAVVVALYVFDLN [SEQ ID 61]

肽: FYNEGDAVVVALY [SEQ ID 192]

肽: FYNEGDAVV [SEQ ID 193]

肽: FYNEGDAVVVAL [SEQ ID 194]

肽: FYNEGDAVVVA [SEQ ID 195]

区域: 424 至 463 - YISFKTNANSMVSHLAGKNSIFRAMPVDVIANAYRISREQ [SEQ ID 62]

肽: TNANSMVSHLAGK [SEQ ID 196]

肽: AMPVDVIANAYR [SEQ ID 197]

大米蛋白质 6: Q0DEV5 - 5 -

MSALTTSQATSATGFGIADRSAPSSLLRHGFQGLKPRSPAGGDATSLSVTTSARATPKQQRSVQRGSRFPVSVVYATGAGMNVFVGA
EMAPWSKTGGLDVLGGLPPAMAANGHRVMVISPRYDQYKDAWDTSVVAEIKVADRYERVFFHCYKRGVDRVDFIDHPSFLEKVWGK
TGEKIYGPDTGVDYKDNQMRFSLLCQAALAPRILNLLNNPYFKGTYGEDVVFVCNDWHTGPLASYLKNNYQPNGIYRNAKVAFCIHNS
YQGRFAFEDYPELNLSEFRSSFDIDGYDTPVEGRKINWMKAGILEADRLTVSPYYAEELISGIARGCELDNIMRLTGITGIVNGMDVSE
WDPSKDKYITAKYDATTAEAKALNKEALQAEAGLPVDRKIPLIAFIGRLEEQKGPDMMAAIPELMQEDVQIVLLGTGKKKFEKLLKSME
KYPGKVRVVKFNAPLAHLIMAGADVLAVPSRFPCGLIQGMRYGTPCACASTGGLVDTVIEGKTGFHMGRLSVDCVVEPSDVKKV
AATLKRAIKVVGTPAYEEMVRNMCNMQDLSWKGPKNWENVLLGLGVAGSAPGIEGDEIAPLAKENVAAP [SEQ ID 15]

区域: 571 至 608 - KGPKNWENVLLGLGVAGSAPGIEGDEIAPLAKENVA [SEQ ID 63]

肽: NWENVLLGLGVAGSAPGIEGDEIAPLAK [SEQ ID 198]

肽: NVLLGLGVAGSAPGIEGDE [SEQ ID 199]

肽: NWENVLLGLGVAGSAPGIEGDEIAPLAK [SEQ ID 200]

区域 : 458 至 488 - RAVVKFNAPLAHLIMAGADVLAVPSRFPCG [SEQ ID 64]
肽 : FNAPLAHLIMAGADVLAVPSR [SEQ ID 201]
肽 : FNAPLAHLIM [SEQ ID 202]
肽 : FNAPLAHLIMAGADVLAVPSR [SEQ ID 203]
区域 : 545 至 566 - KRAIKVVGTPAYEEMVRNCMNQ [SEQ ID 65]
肽 : VVGTPAYEEMVR [SEQ ID 204]
区域 : 93 至 147 - APWSKTGGLGDLVGLGGLPPAMAANGHRVMVISPRYDQYKDAWDTSVVAEIKVADRY [SEQ ID 66]
肽 : TGGLGDLVGLGGLPPAMAANGHR [SEQ ID 205]
肽 : YDQYKDAWDTSVVAEIK [SEQ ID 206]
肽 : DAWDTSVVAEIK [SEQ ID 207]
肽 : VMVISPR [SEQ ID 208]
区域 : 305 至 413 -
INWMKAGILEADRVLTSPYYAEELISGIARGCELDNIMRLTGITGIVNGMDVSEWDPSKDKYITAKYDATTAEAKALNKEALQAEAGLPVDR
KIPLIAFIGRLEEQK [SEQ ID 67]
肽 : LTGITGIVNGMDVSEWDPSKDK [SEQ ID 209]
肽 : VLTSPYYAEELISGIAR [SEQ ID 210]
肽 : EALQAEAGLPVDRK [SEQ ID 211]
肽 : YDATTAEAK [SEQ ID 212]
肽 : IPLIAFIGR [SEQ ID 213]
肽 : AGILEADR [SEQ ID 214]
肽 : IPLIAFIGR [SEQ ID 215]
区域 : 158 至 202 - RGVDRVFIDHPSFLEKVGWGTGEKIYGPDTGVDYKDNQMRFSLLC [SEQ ID 68]
肽 : VFIDHPSFLEK [SEQ ID 216]
肽 : GPDGTGVDYKDNQM [SEQ ID 217]
肽 : IYGPDTGVDYKDNQMR [SEQ ID 218]
肽 : IYGPDTGVDYK [SEQ ID 219]
区域 : 206 至 226 - LEAPRILNLNPNPYFKGTYGE [SEQ ID 69]
肽 : ILNLPNPYFK [SEQ ID 220]

蛋白质 **P02855**

肽 : KNPQLQDLDI [SEQ ID 356]

[0417]

蛋白质 **P07730**

肽 : GQSTSQWQSSR [SEQ ID 357]

肽 : QSTSQWQSSR [SEQ ID 358]

蛋白质 **P07728**

肽 : QSTSQWQSSR (也在P07730中) [SEQ ID 359]

蛋白质 **P13918**

肽 : EEEEQGEEIINK [SEQ ID 360]

蛋白质 **P14323**

肽 : PSTNPWHSPR [SEQ ID 361]

肽 : AQAQDQYQQVQYSE [SEQ ID 362]

肽 : SEAGVTEYFDEKNELFQCTGTFVIRR [SEQ ID 363]

肽 : QAQAQDQYQQVQYSE [SEQ ID 363]

肽 : GSMGLTFPGCPAT (也在P14614中) [SEQ ID 365]

肽 : GSMGLTFPGCPATY (也在P14614中) [SEQ ID 366]

蛋白质 **P14614**

肽 : LGAFTPRY [SEQ ID 367]

肽 : LGAFTPRYQQ [SEQ ID 368]

肽 : ALGVNALVAKRLQGQN [SEQ ID 369]

肽 : LGAFTPRYQ [SEQ ID 370]

肽 : GSMGLTFPGCPAT (也在P14323中) [SEQ ID 371]

肽 : GSMGLTFPGCPATY (也在P14323中) [SEQ ID 372]

蛋白质 **P15838**

肽 : SNNPFKFLVPARQS [SEQ ID 373]

蛋白质 **Q6K508**

肽 : CAGVFVIRR [SEQ ID 374]

豌豆蛋白质2 (SEQ ID 2) 的同源物

>gi|29539111|emb|CAD87731.1| 过敏原 Len c 1.0102 [兵豆]

SRSDQENPFIFKSNRFQTIYENENGHIRLLQKFKRSKIFENLQNYRLLLEYKSKPHTLFLPQYTDADFILVVLGKAVLTVLNSNDRNSFNLERGDT
IKLPAGTIAYLANRDDNEDLRVLDLAI PVNPNPGQLESFLLSGTQNPQPSFLSGFNKSILEAAFNTDYEEIEKVLEDDQEQEPQHRRSLDRRQEI
ENVIVKVSREQIKELSKNAKSSSKSVSSESEPFNLRNPIYSNKFQKFEITPEKNPQLQDLDFVNSVEIKEGSLLLPNYNSRAIVIVTVNEGKGY
FELVGQRNENQREENDEEEQEEETSTQVQRYRAKLSPGDVFVVPAGHPVAINASSDLNLIGFGINAKNNQRNFLAGEEDNVISQIQRPVKEL
AFPGSSREVDRLTNQKQSHFANAQPLQIE [SEQ ID 225]

>gi|1297072|emb|CAA96514.1|豌豆球蛋白前体[法国野豌豆]

MAAITMKVSFPLMLLGISFLASVCVSSRSDQENPFIFKSNKFQTLFENDNGHIRLLQKFDERSKILENLQNYRLLLEYKSKPRTIFLPQQTNADFIL
VVLGKAILTVLPDDRNSFNLERGDTIKLPAGTIAYLVNKDDNEDLRVLDLAI PVNPGDQLQSFLSGSENQQSILSGFSKSVLEASFNTGYEEIE
KVLLEEREKETQHRRSLDRKQHSQDEEDVIVKLSRGQIEELSRNAKSSSKSVSSESEPFNLRNPIYSNKFQKFEITPEKNPQLQDLVIVNSV
EIKEGSLLLPHYNSRAIVIVTVNDGKGDFEIVGQRNENRQGGQRKEDDEEEQGDENTNTQVQNYKAKLSRGDVFVVPAGHPVSIKASSNLDLLG
FGINAKNNQRNFLAGEEDNVISQIDRPVKELAFPGSAQEVDRLLLENQKQSHFANAQPPQQRERGSHTDRHLLSILDAF [SEQ ID 226]

>gi|28629838|gb|AAO45103.1| β -伴大豆球蛋白 α' 亚基[大豆 (Glycine max)]

QYGHVRVLQRFNKRSQQQLNLRDYRILEFNSKPNTLLPHHADADYLIVLNGTAILTVNNDDRDSYNLQSGDALRVPAGTYYVVPNDNE
NLRMITLAIPVKNKGRFESFLLSSTQAQSYLQGFSGFNILEASYDTKFEEINKVLFGREEGQQQGEERLQESVIVEISKQIRELSKHAKSSSRKTIS
SEDKPFNLRSDPIYSNKLGLFEITPEKNPQLRDLDFVLSVDMNEGALFLPHFNSKAIVVLVINEGEANIELVGIEQQQRQQEQEPPLEVRK
YRAELSEQDIFVIPAGYPVVVNATSDLNFFAFGINAENNRNFLAGSKDNVISQIPSQVQELAFPGSAKDIENTLIKSQSESYFVDAQPPQKEEGN
KGRKGPLSSILRAFY [SEQ ID 227]

豌豆蛋白质3 (SEQ ID 3) 的同源物

[0420]

>gi|483449|emb|CAA83677.1| 球蛋白A[箭筈豌豆 (Vicia sativa)]

MAKLLALSLSFCFLFSSCFALREQSQQNECQLERINALEPDNRIESEGGIETWNPNNRQFRCARVALSRATLQRNALRRPYYSNAPQEIIYQQ
GNGYFGMVFPGPCPETHEEPQQSEQGEGRRYRDSHQVNRFRREGDIIAVPTGIAFWMYNDQDTPVIAISLTDGTSSNNQLDQMPPRFYLAG
NQEQFLRYQHQQGGKQEQDNDGNNIFSGFKRDFLEDAFNVRHIVDRQLQGRNEDEEKGAIVKVKGGSLIAPPERQARHERGSRQEDED
EKEERQPSHHKSRDEDEDDKEKRHSQKQSGRRQGDNGLEETVCTAKLRANIGSSSPDIYNPQAGRIKTVTSLDLPVLRWLKLSAEHGSLSHK
NAMFVPHYNLANSVIYALKGRARLQVVNCNGNTVFDGELEAGRALTVPQNYAVAAKSLSERFTYVAFKTD DRASIRLAGTSSVIDDLPLDV
VAATFNMQRNEARQLKSNPNFKFLVPPRQSEMRAA [SEQ ID 228]

>gi|657379551|gb|KEH23931.1| 球蛋白A2[蒺藜苜蓿 (Medicago truncatula)]

MAKLLALSLSLFCFLFSGCFaireHQPHKQPPQNECQLEQLNALEPDNRIESEGGIETWNPNNRQFRCAGVALSRCTLQRNLSRRPFYSNA
PQEIFIQQGSGYFGMVFPGPCPETFEPEQSEQRERRIRESEQGESRRIRESEQGEGRRFRDSHQVNRFRREGDLIAVPTGTVFWMYNDQDTP
VIAVSLIDTGSFQNLDEMPPRFYLAGNQEQFLQYQQQVVRGRGEQRRGREQENEGGNIFSGFKRDFLEDALNVRHIVDRQLQGRNEDE
EKGAIKVRGGSLFVTPPERQSRHQGGSIIEDEDEDEWRRPHHQSRRGEEERPCRRGQKCRSNGLEETICTARLRQNISSSSPDIIYNPE
AGRIKTVTSFDLPALRWLRLSAEHGTLRNAMFVPHYNLANSIAYLRGRARLQVVNCNGNTVFDGELEAGRVLIVPQNFAVAAKSMSDRF
QYVSFKTNDNAIARLAGTQSTLSGVPMDVLAATYNMDRNEARQLKNNNLYKFLVPPRESERRAAA [SEQ ID 229]

>gi|206712292|emb|CAR78996.1| 球蛋白贮藏蛋白质5 [百脉根]

MAYKLFALSLSFCFLFSGCFairQQSQQQNECQLERLNALKPDNRIESEAGYIETWNPNTNNQFRCAGVALSRCTLRRNGLKRPSYSNAPQEIFI
QQGSGIFGMIFPGPCPETVEEPFESDQQRDRHQVNRFRREGDVIAVPPGVVFWMYNEETPVIAVSLIDTGSYLNQLDQMPPRFYLSGNQ
EQEFLQYQREQVREGREENQGGNIFSGFGGEFLEDALNIDRNIVHKLQGRDEEQDKGAIVRVKGGLSVITPPERQSHRRGSEEEEEDEEDRPS
RHQSRGSGRRNGLEETICTVLRNMIGKSSSPDIFNPQAGRIKATGDFPALRFLKLSAEHGSLLNRNAMVVPHYNLNANSIYALRGRAWIQV
VNCKGNRIFDGELEEQVLIVPQNFFVAARMSDKFNVAFTNDMPMTAKLAGATSEIQAMPLEVIQNAFNLEREQAQKQVFNRRNFVFLV
PPREQSQRRAA [SEQ ID 230]

豌豆蛋白质4 (SEQ ID 4) 的同源物

>gi|164512526|emb|CAP06312.1| cvc [埃塞俄比亚豌豆 (*Pisum abyssinicum*)]

MATTVESRFPLLLFPGIIFLASVCVTYANYDEGSETRVPGQREGRGRQEGEKEEKHRHGEWRPSYEKEEDEEEKQKYRYQREKEDEEEKQKYRYQR
EKKEEKEVQPGRRERWEREEDEEQVDEEWGRSQRRQDPEERARLRHREERTKRDRRHKREGEEERSSSESQEQRNPFLLFKSNKFLTLFENENG
HIRRLQRFDKRSDLFENLQNYRLVEYRAKPHITFLPQHIDADLILVVLNGKAILTVLSPNDRNSYNLERGDTIKIPAGTTSYLVNQDDEEDLRVVD
FVIPVNRPGKFEAFGLSENKNQYLRGFSKNILEASLNTKYETIEKVLLLEEQEKPPQQLRDRKRRQQGGERDAIKVSREQIEELRLKAKSSSKSLPS
EFEPFNLRSHKPEYSNKFGLFEITPEKKYPQLQDLILVSCVEINKGALMLPHYNSRAIVVLLVNEGKGNLELLGLKNEQKEREDRKERNNEVQ
RYEARLSPGDVVIIIPAGHPVAISSNLNLLGFGTNAENNQRNFLSGSDDN [SEQ ID 231]

>gi|164512538|emb|CAP06318.1| cvc [山黧豆葵 (*Lathyrus annuus*)]

MATTIKSRFPLLLGIIFLASVCVTWANYDEGSEPRVPGQREGRGRQEGEKEEKHRHGEWRPSYEEYDEGLEPKVPGKRERGRQEGEKEEKHRH
EWRPSYEKEEDEEEKQKYNQYQREKKEHKEVQPGRRERWERKQDEKQVEEDEEPGEEQWGRSKRHEDPEERARLRHREKTKSYVEDNEETSS
KEGRNPFLLFKSNKFLTLFENENGHIRRLQRFDERSDIFENLQNYRLVEYRAKPHITMFLPQHIDADLILVVLNGKAILTVLSPNDRNSYNLERGDT
VKLPAGTTSYLVNQDDEEDLRVVDLAIIPVNRPGKFEAFGLSANKNQYLRGFSKNILEASLNTKYETIEKVLEERRDQKGRQQGQETNAIVKVS
EQIEELRLKAKSSSKSLSESEPLNLSQNPYSNKFGLFEITPQKKYPQLQDLVDSISCEINKGALLPHYNSRSIGILLVNEGKGNLELVGFKN
EQQRQRENEETNKKLQRYEARLSSGDVVIIPEGHPVAISSNLNLLGFGINAANNQRNFLTGSDDN [SEQ ID 232]

>gi|164512558|emb|CAP06328.1| cvc 长柔野豌豆

[0421]

MATTIKSRFPVLLLLGIIFLTVCVTYANYDEGREPSVPGQREGRGRQEGEKEEKHRHGEWRPSEDEEEKYKYEGRVPGQREGRGRQEGEKEEK
HGKWRPSEDEEEKYRYEEGSEPRGPGQRETGRQEGEKEKQRPEREPSYEKEEDEEEKQKYQYHREKKEQREVRPGRERFERHEDEEQWRG
IQRHEDPEERARERYRAEIAKQVVEEREERDIPHEREQRNPFLLFKSNKFQTLFQNGYIRRLQRFDKRSDLFENLQNYRLVEYRAKPHITFLPQ
HIDADLIIVVLSGRAITVLSPDDRNSYNLERGDTIKLPAGTTSYLVNQDDEEDLRVVDLAIIPVNRPGKVESFLLSGNKNQYLRGFSKNILEASFNT
NYETIERVLLLEEQDKESQSIGQKRRSQRQETNALVKVSREQLEDLRLAKSSSQEGLSSQFEPINLSQNPYSNKFGLVFEITPEKKYPQLQDL
DLFVSSVDIKEGALMLPHYNSRAIVVLLVNEGRGNLELVGLKNEQKEQREKEDEQQRNQNQVQRYEARLSPGDVVIIIPAGHPVAVRASSDLNL
LAFGINAENNQRNFLAGSDDN [SEQ ID 233]

豌豆蛋白质5 (SEQ ID 5) 的同源物

>gi|357507721|ref|XP_003624149.1|前豌豆球蛋白 (provicilin) [蒺藜苜蓿] >gi|87162569|gb|ABD28364.1| Cupin, RmlC- 型
[蒺藜苜蓿] >gi|355499164|gb|AES80367.1| 豌豆球蛋白47kDa蛋白质 [蒺藜苜蓿]

MAIKAPFQLMLLGIIFLASVCVSSRRDRHDQENPFFNANHFQTLFENENGHIRLLQRFDKRSKIFENLQNYRLLEYHSPHTLFLPQHNDAD
FILAVLSGKAILTVLNPDRNSFNLERGDTIKLPAGSIAYLANRDDNEDLRVLDLAIIPVNRPGKFQSFSLSGSQNQSFSSGFSKNILEAAFNANY
EEIERVLEEHEQEPQHRRGLRKDRRQQSQDSNVIVKVSREQIEELSRHAKSSRRSGSSESAPFNLSREPIYSNEFGNFFETPEKNPQLKDLDIL
VNYAEIREGSLLLPHFNSRATVIVVDEGKGEFELVGQRNENQQEQREDEEQEEERSQQVQRYRRLSPGDVVIIIPAGHPVAVASSDLSLL
GFGINAENNERNFLAGEEDNVISQIERPVKEVAFPGSAQDVESLLKNQRQSYFANAQPQREREGRSQRQRELISILGVF [SEQ ID 234]

>gi|164512560|emb|CAP06329.1|共豌豆球蛋白 (convicilin) [游隼野豌豆 (*Vicia peregrine*)]

MATTFKSRSFLLLLGIIFLAFVCVTCANYDEGSEPRVPGQREGRGRQEGEKEEQSRERHPQREPSREKEEDEEEKQKYDEGTEPRVPGQREGR
QEGEKEEQRRERHPGQREPSQEDEEREESDRRQEGSSKSEEQRNPFLLFKSNKFLTLFQNGNGHIRLLQRFDKRSDLFENLQNYRLLEYRAKPH
TIFLPQHIDADLILVVLNGRAITVLSPDDRNSYNLERGDTIKLPAGTTSYPLNQDDEEDLRVVDLAIIPVNRPGKVESFLLSGNKNQYLRGFS
ENILEASFNTKYETIEKVLLLEEQDKESQQPRGQRLQRETNALVKVSREQVEELKRLARTSSKKGVSSEFEPFNLRSHGPKYSNKFGLFEITPEKKYPQ
LQDLDISVSSVEINEGALFLPHYNSRAIVVLLVDEGKGNLELVGFKNEQKEQREKEDEQEERNKQVQRYEARLSPGDVVIIIPAGHPVAVASSN
LNLLGFGINAENNQRNFLTGSDDN [SEQ ID 235]

>gi|164512562|emb|CAP06330.1| 共豌豆球蛋白[黄花豌豆 (*Vicia lutea*)]

MATTIKLRFPLLLLGVILLASVCTCANYDEGSEPRVPGRPEGEKEEKHRGKLRPSYEKEEDEGEKQRYHYEKEQKEAQPRREKKEQKEEEKQ
VEESRESQRYEDPGERARERYRAEIIKRQVEKEREERDRRHQREGEEEGSSSRNPFLFKSNNFLTFENENGHIRLLQRFDKRSDLFENLQNY
RLVEYRAKPHITFLPQHIDADLILVVLGSKAILTVLSPNNRNSYNLKRGDITKLPAAGTTSYLLNSDDEEDLRMVDLAISVNRPGKVESFNLSGNKN
QYLRGFSKNILEASFNTKYETIEKVLLEEQDKESQQSIGQKRISQRQETNALVKVSREQIEPKRLARSSSRKGVSEFEPINLRSQRPKYSNKFQKF
YEISPEKKYPQLQDLVSVSSVEINEGALLPHYNSRAIVTVLVNEGKGNLELIGFQNEQQGQREKEDEQQHERNKKVQRYDARLSSGDVVIIIP
AGHPVAVSASSNLDLLGFGINAENSQRNFLTGSDDN [SEQ ID 236]

大米蛋白质1 (SEQ ID 6) 的同源物

>gi|573919041|ref|XP_006647142.1| 预测的: 谷蛋白型-B4-样[短花药野生稻]

MATTTFSRFSIYFCVLLCHGSMALFSPNLNPWHSSRRGSRDCRDLQAFELRRVRSEAGVTEYFDERNEQFQCTGTIVIRRVIEPQGLL
VPRYTNTPGVVYIMQGRGSMGLTFPGCPATYQQFQQFLPEGQSQSQKFRDEHQKIHQFRQGDIVLPAAGVAHWFYNEGDTPVVALYVFD
INNSANQLEPRQKDFLLAGNNNREQQVYGRSIEKHSQGNIFSGFNHELLSEALGISTLAARKLQGGNDHRGEIIRVRNGLQLLKPTFTTQQEQ
AQSQYQVQYSEKQEQESTRCNGLDENFCTINARLNIENPSRADTYNPRAGRITHLNNQKFPIILNLVQMSATRVNLYQNAILSPYWNVNAHSLV
YMVQGHARVQVSVNLGKTVFNSVLRPGQLLIIPQHYVVLKKAEREGCQYIAFKTNANSIVSQLAGKNSILRAMPVDVVANAYRISREQARDLK
NNRGEELGAFTPKFEQQSYPLSNESESEASE [SEQ ID 237]

>gi|2764800|emb|CAA54153.1| 12s球蛋白[燕麦]

MATTSFSPSVLFYSCIFLLYNGSMAQLFGQSFTPWQSSRQGGKLGCKFDRLQAFELRQVRSQAGVTEYFDEQNEQFRCTGVFVIRRVIEPQGLL
LLPQYHNAPGLVYILQGRGYTGLTFPGCPATFQQQFQPFDDQAQDQSQSHLKDQHRVHRFKQGDVIALPAGIVHWGYNDGDAPVVAIYVF
DVNNNANQLEPRQKEFLLAGNNKEDQQFGQNFISGFNIQLLSEALGISQQAQRIQSQKEQGEIIRVTQALQFLKPTMSQQLVEHQAYQP
IQSQEGQSTQYQVGQSTQYQEGQSTQYQAGQSQDRSFNGLEENFCLEARQNGNPKRADTHNPRAGRITRLHGQNFPIILNLVQMSATRV
NLYQNAILSPFWNINAHSVVYMIQGHGAQVQVNNNGQTVFNDRLRQGLLIVPQHYVVLKKAEREGCQYISFKTNPNMSMVSHIAGKSSILRA
LPVDVLANAYRISRQEARNLKNNRGQESGVFTPKFTQTSFQPYPEGEDESSLTNKASE [SEQ ID 238]

>gi|357130026|ref|XP_003566659.1| 预测的: 12S种子贮藏球蛋白1-样[二穗短柄草]

>gi|357130028|ref|XP_003566660.1| 预测的: 12S种子贮藏球蛋白1-样[二穗短柄草]

MAHTSFSSVLSYFCIFLLFHGSMALQVPGQSTWQSPRQGGSRCSFDRLQTIEPLTQVRSQAGLTEYFDEQNEQFRCAGVSVIRRVIEPRGLLL
PRYHNTPLGLVYILEGSGFVGLAFPGCPETFLEQFQSSRQTQSTLGQSQSQSQKLGDVHQRVHQFTQGDVVALPAGVAHWFYNGGDAPV
VAVYVFDVNNNANQLEPRQKEFLLAGNYNGVLQSGRNILNLNAQLLSQAQGINEQTSRIIQNQNDGRGEIVRVEYGLQFLTPVVTQQQK
QPFLPIEPQEGQSSRNGLNFCLEPRQNIEDPNRADTYNPRAGSIARLNGQNFPIILNLVQMSATRVNLQKNAIVSPFWNINAHSVVYVIQ
QASVQVNNQGRNVFNGLRRGQLLIIPQNYVVLKKAESQYQYIAFKTNANSMVSHIAGKNSILRALPVDVIANAYRISRQEAQNLKNNRGE
EIGVLTPNFPQSSCQSYPIGDDVSSSTPKAQE [SEQ ID 239]

大米蛋白质2 (SEQ ID 7) 的同源物

>gi|222622792|gb|EEE56924.1| 假定蛋白质 OsJ_06602 [粳稻组水稻]

MAQFSFGGSPQLQSPRGFRGDQDSRHQCRFEHLTALEATHQQRSEAGFTEYNIENARNEFRCAVSVRRLLVVEKGLVLPYANAHKLVIYVQ
GRGVFGMALPGCPETFQSVRSPFEQEVATAGEAQSSIQKMRDEHQLHQFHQGDVIAVPAGVAHWLYNNGDSPVVAFTVIDTSNNANQL
DPKRREFFLAGKPRSSWQQSYQTEQLSRNQNIQFAGFSPDLLSEALSVSKQTVLRLQGLSDPRGAIIRVENGLQALQPSLQVEPVKEEQTA
YLPTKQLQPTWLRSGGACGQQNVLDIEMCAFKLRKNIDNPQSSDIFNPHGGRITRANSQNFPIILNIIQMSATRIVLQNNALLTPHWTVNAHT
VMYVTAGQGHQVVDHGRSVFDGELHQQQILLIPQNFVAVVKARREGFAVVSFKTNHNAVDSQIAGKASILRALPVDVVANAYRISREDS
RHVKFNRGDEMAVFAPRRGPPQYAEWQINEK [SEQ ID 240]

[0422]

>gi|218190679|gb|EEC73106.1| 假定蛋白质 Osl_07091 [籼稻组水稻]

MAQFSFGGSPQLQSPRGFRGDQDSRHQCRFEHLTALEATHQQRSEAGFTEYYNIEARNEFRFCAGVSVRRLLVVEKGLVLPYANAHKLVIYVQ
GRGVFGMALPGCPETFQSVRSFPEQEVATAGEAQSSMQKMRDEHQQLHQFHQGDVIAVPAGVAHWLYNNGDSPVVAFTVIDTSNNANQ
LDPKRREFFLAGKPRSSWQQQSYSYQTEQLSRNQNI FAGFNPDLLEALS VSKQTVLRLQGLSDPRGAIIRVENGLQALQPSLQVEPVKEEQTQ
AYLPTKQLQPTWSRSGGACGQQNGLDEIMCAFKLRKNIDNPQSSDIFNPHGGRITRANSQNFILNIIQMSATRIVLQNNALLTPHWTVNAH
TVMYVTAGQGRIQVVDHGRSVFDGELHQQLILLIPQNFVAVVVKARREGFAWVVSFKTNHNAVDSQIAGKASILRALPVDVAVANAYRLSREDS
RRVKFNRGDMAVFAPRRGPQQYAEWQINEK [SEQ ID 241]

>gi|573922051|ref|XP_006648611.1| 预测的: 谷蛋白型-A1样 [短花药野生稻]

MVDMSIVVPVCLTIFLLSQVCIQVQVSDGSPLYSSRGFRGGSASQQQCRFEHLAALEVTHQEKSEAGSIEYYNTEARDEFRCARVSARRLVIESR
GLVLPYANAHKLVIYVQGRGVFGMALPGCPETFQSVRSFEMATGDAESSTRKLRDEHQKIHQFRQGDVIAVPPGVAHWLYNNGDSPVVA
FSVIDFGNNAQLDPKPREFFLAGKPWWQVQVSYQSEQQSKHQNIFAGFNPDLLEALS VSRQTAMRLQELNDQRGAIIRVEQGLQAL
DPSFQAEQEQEQPQEYLSQQQPTWSQSGACVQNNGLDEIMCAFKVSKNINSAQSTDIFNPRGGRITRANSQNFVNLIIQMSATRTV
LQNNALLTPHWTVNAHTVMYVTAGQGRIQVVDHGRVTVDGELRQQQLIPQNFVAVVKARHEGFSWVVSFKTSHNAIDSQIAGKGSILRA
LPVDVLAKAYMLSREESRTLKYNRADETLVFAPRPEIQLYAESEK [SEQ ID 242]

豌豆蛋白质6 (SEQ ID 8) 的同源物

>gi|164512534|emb|CAP06316.1| cvc [豌豆野生种 (*Pisum fulvum*)]

[0423]

MATTTKSRFPLLLLGIIIFLASVVCVTYANYDEGSEPRVPGRRERGRQEKEEKRHGEWRPSYEKEEDEEGQRRERGRQEKEEKRHGEWG
PSYEKQDEDEEEKKYRYQREKEDEEEKKYRYQREKKEQKEVQPGRRERWEREEDEEHVDEEWGRSQRHEDPEERARLRYREERTKDRRRHQ
REGEEERSSSQERRNPFLFKSNKFTLFENENGHIRLLQRFDKRSDLFENLQNYRLVEYRAKPHTIFLPQHIDADLILVLSGKAILTVLSPNAR
NSYNLERGDTIKLPAGTTSYLVNQDDEEDLRVLDLVIPVNGPGKFEAFDL SKNKNQYLRGFSKNILEASYNKYETIEKVLEEQEKTD AIVKVSRE
QIEELRKHAKSSSKKIFPSEFEPINLRNHKPEYSNKFGLFEITPEKKYPQLQDLDFVSCVEINEGALMLPHYNSRAIVVLLVNEGKGNLELLGLEN
EQQEREDRKERNNEVQRYEARLSPGDVVIIIPAGHPVAITASSNLNLLAFGINAENNQRNFLSGSDDN [SEQ ID 243]

>gi|164512526|emb|CAP06312.1| cvc [埃塞俄比亚豌豆]

MATTVESRFPLLLPFGIIFLASVVCVTYANYDEGSETRVPQGRRERGRQEKEEKRHGEWRPSYEKEEDEEEKKYRYQREKEDEEEKKYRYQR
EKKEEKEVQPGRRERWEREEDEEQVDEEWGRSQRQDPEERARLRHREERTKDRRRHKREGEEERSSSQEQRRNPFLFKSNKFTLFENENG
HIRRLQRFDKRSDLFENLQNYRLVEYRAKPHTIFLPQHIDADLILVVLNGKAILTVLSPNDRNSYNLERGDTIKIPAGTTSYLVNQDDEEDLRVVD
FVIPVNRPGKFEAFGLSENKNQYLRGFSKNILEASLNTKYETIEKVLEEQEKKPQLRDRKRRQQGGERDAIIVKVSREQIEELRLAKSSSKSLPS
EFEPFNLRSHKPEYSNKFGLFEITPEKKYPQLQDLDFVSCVEINKGALMLPHYNSRAIVVLLVNEGKGNLELLGLKNEQQEREDRKERNNEVQ
RYEARLSPGDVVIIIPAGHPVAISASSNLNLLGFTNAENNQRNFLSGSDDN [SEQ ID 244]

>gi|164512558|emb|CAP06328.1| cvc [长柔野豌豆]

MATTIKSRFPVLLLLGIIIFLTSVVCVTYANYDEGREPSVPGQRRERGRQEKEEKRHGEWRPSEDEEEKKYEEGRVPGQRRERGRQEKEEKR
HGKWRPSEDEEEKKYRYEESGSEPRGPGQRETGRQEKEEKQRPEREPSYEKEEDEEEKKYQYHREKKEQREVPRGRERFERHEDEEQWRG
IQRHEDPEERARERYRAEIAKQVEEEREERDIPHEREQRNPFLFKSNKFTLFQNGYIRRLQRFDKRSDLFENLQNYRLVEYRAKPHTIFLPQ
HIDADLILVLSGRAILTVLSPDDRNSYNLERGDTIKLPAGTTSYLVNQDDEEDLRVVDLAIPVNRPGKVESFLLSGNKNQYLRGFSKNILEASFNT
NYETIERVLEEQDKESQSIGQKRRSQRQETNALVKVSREQLEDLRLAKSSSQEGLSSQFEPINLRSQNPKNYKNKFGLVFEITPEKKYPQLQDL
DLFVSSVDIKEGALMLPHYNSRAIVVLLVNEGRGNLELVGLKNEQQEQREKEDEQQRNNQVQRYEARLSPGDVVIIIPAGHPVAVRASSDLNL
LAFGINAENNQRNFLSGSDDN [SEQ ID 245]

豌豆蛋白质7 (SEQ ID 9) 的同源物

>gi|164512536|emb|CAPO6317.1| cvc [硬毛山黧豆]

MAIIKSRFPLLLLLGIIFLASVCATWANYDEGSEPRVPGQRRERGRQEGEKAESHEKWRSYEEYDEGSEPRVPGKRERGRQEGEKEEKRHGE
WRPSHEEYDEGSEPRVPTHGERGRQEGEKEEKRHEEWRPSYEKEDEEKEKYQREKKEQKEVQPGREKWERKQDEKHVEEDEDQEEE
QWRGSKRREDPEERARLRREERTKSNVEETEERRNPFLFSKNKFLTLFENENGHIRRLQRFDERSDIFENLQNYRLVEYKAKPHTMFLPQHID
ADLIIVVLNGKAILTVLSPNDRNSYNLERGDTIKLPAGTTSYLVNQDDEEDLRVVDLAIPVNRPGKFEAFGLSANKNQYLRGFSKNILEAFLNTKY
ETIEKVLLEEQERRDRKGRQQQETNAIVKVSREQIEELRKLAKSSSKSLLSESEPINLRSQNPKYSNKFGLFEITPEKKYPQLQDLVDVSISSVEI
NEGAPLLPHYNSRAIVLLVNEGKGNLELVGFKNEQQRQRENERNKVQRYEARLSPGDVVVIPAGHPVAISASLNLNLVGFVNAENNQR
NFLTGSDDN [SEQ ID 246]

>gi|164512542|emb|CAPO6320.1| cvc [扁荚山黧豆]

MATIIKSRFPLLLLLGIIFLASVCVTLANYDEGSEPRVPAQRERGRQEGEKEEKRHGEWRPSHEKEYDEGSEPRVPGRRERGRQEGEKEEKRHGE
WRPSYEKEYDEGSEPRVPGRRERGRQEGEKEEKRHGEWRPSYEKEYDEEKKQYQYEREKEEQKEVQPGRRERWERKEDEEKEEDQWRGSQ
RHEDPEERARLRKERTKKYVEEDTEETSSESQGRNPFLFSKNKFLTLFENENGYIRRLQRFDERSDIFENLQNYRLVEYRAKPHTIFLPQHIDA
DLILVILNGKAILTVLSPNDRNSYNLERGDTIKLPAGTTSYLVNEDDEEDLRVVDLIPVNRPGKFEAFDLNQYLGGSFSKSVLEASLNTKYETIEKVL
LEEQQKQGGQETNAIVKVSREQIEELRKLAKSSSKSLLSELEPNLRSHPKYSNKFGLFEITPEKKYPQLQDLVDVSISSVEINEGALLPHYNSRA
IVVVLVNEGKGNLELLGVQNEDEQKERKERNKEVQRYEARLSPGDVVIPSGHPVAVSASSNLNLLGFGINAENNQRNFLSGSDDN [SEQ ID
247]

>gi|164512544|emb|CAPO6321.1| 共豌豆球蛋白[家山黧豆]

MATIIKSRFPLLLLLGIIFLASVCVITYANYDEGSEPRVPAQRERGRQEGEKEEKRHGEWRPSSEKEYDEGSEPRVPGRRERGRQEGEKEEKRHGE
WRPSYEKEYDEEKKQYQYEREKEEQKEVEPGRERWERKEDEEKEEDQWRGSQRHEDPEERARLRKERTKKYVEEDTEETSSESQGRNP
FLFSKNKFLTLFENENGYIRRLQRFDERSDLFENLQNYRLVEYRAKPHTIFLPQHIDADLILVILNGKAILTVLSPNDRNSYNLERGDTIKLPAGTTS
YLVNEDDEEDLRVVDLIPVNRPGKFEAFDLNQYLGGSFSKSVLKASLNTKYETIEKVLLEEQQKQGGQETNAIVKVSREQIEELRKLAKSSSKSLLS
ELEPNLRSHPKYSNKFGLFEITPEKKYPQLQDLVDVSISSVEINEGALLPHYNSRAIVVLLVNEGKGNLELLGVQDEDEQKERKERNKEVQRY
EARLSPDVIIPAGHPVAVSASSNLNLLGFGINAENNERNFLSGSDDN [SEQ ID 248]

[0424]

大米蛋白质3 (SEQ ID 10) 的同源物

>gi|573918992|ref|XP_006647120.1| 预测的: 谷蛋白型-B2-样 [短花药野生稻]

MATTVFSRFSTYFCVLLCHGSMALFNPSTNPWHNPRQGSSRECFDRQLQPFELRKVRSEAGVTEYFDEKNELFQCTGTFTVIRRVIPQGLL
VPRYTNPGLVYIIMQGRGSMGLTFPGCPATYQQQFQQFLPQEQSQSKFRDEHQIHKQFRQGDIVALPAGVAHWFYNDGDAPVAVVYVDV
KNSANQLEPRQREFLLGGNNMRAQQVYGSSAEQHSRQNFISGFGVEILSEALGISTVTTKRLQSQNDQRGEIHHVKNGLQLKPTLTQQQEQA
QAQYQEVQYSEQQQTSSRWNGLDENFTIKARMNIENSTRADTYNPRAGRITSLNSQKFPILNLVQMSATRVNLYQNAILSTFWNVNAHSL
VYTIQGRARVQVVSNGKTVFDGELRPGQLLIIPQHYVVLKKAQREGFRYIAIKTNANAFVSQLVGKNSVFRSLPVDVIANVYRISREQARSLKN
NRGEEHGAFAPRSQQSYPGFSNQSESESE [SEQ ID 249]

>gi|573919041|ref|XP_006647142.1| 预测的: 谷蛋白型-B4样 [短花药野生稻]

MATTTFSRFSTYFCVLLCHGSMALFSPTLNPWHSSRRGSRDCRDLQAFELRRVRSEAGVTEYFDERNEQFQCTGTFTVIRRVIEPQGLL
VPRYTNPGLVYIIMQGRGSMGLTFPGCPATYQQQFQQFLPEGQSQSKFRDEHQIHKQFRQGDIVALPAGVAHWFYNEGDTPVVALYVFD
INNSANQLEPRQKDFLLAGNNNREQQVYGRSIEKHSQGNIFSGFNHELLSEALGISTLAARKLQGGNDHRGEIIRVRNGLQLKPTFTQQQEQA
AQSQYQVQYSEKQEQESTRCNGLDENFTINARLNIENPSRADTYNPRAGRITHLNNQKFPILNLVQMSATRVNLYQNAILSPYWNVNAHSLV
YMVQGHARVQVVSNGKTVFNSVLRPGQLLIIPQHYVVLKKAQREGCQYIAFKTNANSIVSQLAGKNSILRAMPVDVIANAYRISREQARDLK
NNRGEEELGAFTPKFEQQSYPGLSNESESEASE [SEQ ID 250]

>gi|109894635|gb|ABG47337.1| 谷蛋白前体[菰]

MNMATINGPTIFFTVCLFLLCHGSLAQLLGQSTSQWQSSHRGSSRQCRFDRLQAFEPVRSVRSQAGTTEFFDASNELFQCAGVSIVRRRIEPRG
LLLPQYTNGATIMYIIQGRGITGQTFPGCPESYQQQFQQSQMAQLTGSQSQSQKFDEHQKINRFRQGDVIALPAGVAHWCYNDGEVPPVA
IYVIDINNAANQLDPRQRDFLLAGNMRSQAYRREVENQSQNIFSGFSAELLSEALGISTGVARQLQCQNDQGEIVRVEHGLSLLQPYASLQE
QEQQEQEPREYQVTQHQQSQYGGGCSNGLDETFCAMRIWQNIIDNPNLADTYNPRAGRVTNLNSQKFPILNLIQMSAVKVNLYQNALLSP
FWNINSHSVVYVTQGCARVQVNNNGKTVFNGELRRGQLLIIPQHYVVVKAQREGCAYIAFKTNPNSMVSHIVGKSSIFRALPTDVLANAY
RISREDAQRLKHNRGDELGAFTPLQYKSYQDVSSVAASS [SEQ ID 251]

大米蛋白质4 (SEQ ID 11) 的同源物

>gi|531874314|gb|AGT59174.1| 谷蛋白, 部分[籼稻组水稻]

CRFDRLQAFEPVRSVRSQAGTTEFFDVSNEQFQCTGVSAVRRVIEPRGLLPHYTNGASLVYIIQGRGITGPTFPGPCPESYQQQFQQSGQAQLT
ESQSQSHKFKDEHQKINRFRQGDVIALPAGVAHWCYNDGEVPPVAIYVTDLNNGANQLDPRQRDFLLAGNKRNPQAYRREVEERSQNI
FSTELLSEALGVSSQVARQLQCQNDQGEIVRVEHGLSLLQPYASLQEQQGQVQSRERYQEGYQQSQYSGSCNGLDETCTMKVRQNI
DNPNRADTYNPRAGRVTNLNTQNFILNLVQMSAVKVNLYQNALLSPFWNINAHSVVYITQGRARVQVNNNGKTVFNGELRRGQLLIIPQ
HYAVVKAQREGCAYIAFKTNPNSMVSHIAGKSSIFRALPNDVLANAYRISREDAQRLKHNRGDEFGAFTPIQYKSYQDVYNAEASS [SEQ ID
252]

>gi|109894635|gb|ABG47337.1| 谷蛋白前体[菰]

MNMATINGPTIFFTVCLFLLCHGSLAQLLGQSTSQWQSSHRGSSRQCRFDRLQAFEPVRSVRSQAGTTEFFDASNELFQCAGVSIVRRRIEPRG
LLLPQYTNGATIMYIIQGRGITGQTFPGCPESYQQQFQQSQMAQLTGSQSQSQKFDEHQKINRFRQGDVIALPAGVAHWCYNDGEVPPVA
IYVIDINNAANQLDPRQRDFLLAGNMRSQAYRREVENQSQNIFSGFSAELLSEALGISTGVARQLQCQNDQGEIVRVEHGLSLLQPYASLQE
QEQQEQEPREYQVTQHQQSQYGGGCSNGLDETFCAMRIWQNIIDNPNLADTYNPRAGRVTNLNSQKFPILNLIQMSAVKVNLYQNALLSP
FWNINSHSVVYVTQGCARVQVNNNGKTVFNGELRRGQLLIIPQHYVVVKAQREGCAYIAFKTNPNSMVSHIVGKSSIFRALPTDVLANAY
RISREDAQRLKHNRGDELGAFTPLQYKSYQDVSSVAASS [SEQ ID 253]

[0425]

>gi|472867|emb|CAA52764.1| 11S 球蛋白 [燕麦]

MATTSFSPMLFYFCIFLLFHGSMALFGQSSTPWQSSRQGGRLGCRFDRLQAFEPVRSVRSQAGITEYFDEQNEQFRCTGVSVIRRVIEPQGL
VLPQYHNAPALVYIIQGRGITGQTFPGCPATFQQQFQPFQDQSQFAQQGRQSQTIKDEHQKINRFRQGDVIALPAGVAHWCYNDGDPIVA
IYVFDVNNANQLEPRQKEFLAGNNKREQSGNNIFSLVQLLSEALGISQQAQRIQSQNDQGEIIRVSQGLQFLKPIVSQQVPGEQQV
YQPIQTQEGQATQYQVQSTQYQVGKSTPYQGGQSSQYAGQSWDQSFNGLENFCSLEARKNIENPQHADTYNPRAGRITRLNKNFPIL
NIVQMSATRVNLYQNAILSPFWNINAHSVIYMIQGHARVQVNNNGQTVFNDILRRGQLLIVPQHFFVLKKAEREGCQYISFKTNPNSMVSH
IAGKSSILRALPIDVLANAYRISRQEARNLKNNRGEFGAFTPKLTQKGFQSYQDIEEGSSSPVRASE [SEQ ID 254]

大米蛋白质5 (SEQ ID 12) 的同源物

>gi|225959|prf||1404367A 谷蛋白

MASTNRPIVFFTVCLFLLCDGSLAQLLGQSTSQWQSSRRGSPRQCRFDRLQAFEPVRSVRSQAGTTEFFDVSNEQFQCTGVSVVRRVIEPRGL
LLPHYTNGASLVYIIQGRGITGPTFPGPCPETYQQQFQQSGQAAGLTESQSQSHKFKDEHQKINRFRQGDVIALPAGVAHWCYNDGEVPPVAIYV
TDINNGANQLDPRQRDFLLAGNKRNPQAYRREVEEWSQNIIFSGFSTELLSEAFGISNQVARQLQCQNDQKGEIVRVERGLSLLQPYASLQE
EQGQMMSREHYQEGGYQQSQYSGGCPNGLDETFCVNKVRQNIIDNPNRADTYNPRAGRVTNLNSQNFILNLVQMSAVKVNLYQNTDTWIS
MGQEENALLSPFWNINAHSVIYITQGRAQVQLRRGQLLIVPQHFFVLKKAEREGCAYIAFKTNPNSMVSHIAGKSSIFRALPTDVLANAYRIS
REEAQLKHNRGDEFGAFTPLQYKSYQDVYNAEASS [SEQ ID 255]

>gi|573943558|ref|XP_006654150.1| 预测的: 谷蛋白型-A3样 [短花药野生稻]

MKSSIVFSTICLVLLCHGSLAQLLSQSTSQWQSSRRGSPRQCRFDRLQAFEPVRSVRSQAGVTEFYDVSNEQFQCTGVSVVRRVIEPRGLLPHY
SNGATLVYIIQGRGITGPTFPGPCPETYQQQFQQSGEAQPFEGQSHKFRDEHQKINRFRQGDVIALPAGVAHWCYNDGEVPPVAIYVTDIYNS
ANQLDPRHRDFFLAGNNKVAQQLYRSEARENSKNIFGGFVELLSEALGISRGVARQLQCQNDQGEIVRVEHGLALLQPYASVQEQQQEQV
QSRDYEQTQYQQKQPGGSCNGLDETCTMRLRQNIIDNPNLADTYNPKAGRITYLNGQKFPILNLVQMSAVKVNLYQNAVLSPFWNINAH

VVYITQGRARVQVNNNGKTVFDGELRQGQLLIIPQHVVVLKKAQREGCSYIALKTNPNISIVSHIAGKNSIFRALPGDVTNAYRISREEAKRIK
HNRGDESGVFAPSHAYRSYQDMSVAA [SEQ ID 256]

>gi|721641733|ref|XP_010231907.1| 预测的: 12S种子贮藏球蛋白1-样[二穗短柄草]

MAHTSFSSFLSYFCLFLLFHGSMACVVGQVSTWQSSRQGGSRDCSFDRLQAIEPVTQVRSQAGLTFEYFDEQNEQFRCAGVFVIRRVIEPRGLL
LPRYHNTPLGLVYILQNGFVGLTFPGCPETFREYQFQFRQTQSTLGGQSQSQKLGDVHQRVHQFTQGDVVALPTGVAHWIYNGGDAPVV
IVYVFDVNNNANQLEPRQKEFLGNGYNGVLQYQGNIFSGFNAQLLSQAFGINEQTSQRIQNDGRGDIIRVDNGLQFLKPVVTQQQPEQ
PFMPIQHQTGQSSRNGLLEENFCSLEPRQNIEDPNRADTYNPRAGSITRLNGQNFPIILNLVQMSATRVNLQKNAILSPFWNNINAHSVVYIQG
HALVQVNNQGHNVFNGLLHRGQLLIIPQNYVVLKKAEGYQYIAFKTNANSMVSHIAGKNSILRALPVDVIANAYRISRQEAQNLKNNRGE
ETGVLTPNFSQSTCQSYQTEDVQSLRPMSE [SEQ ID 257]

大米蛋白质6 (SEQ ID 13) 的同源物

>gi|169244463|gb|ACA50505.1| 种子过敏性蛋白RAG2[粳稻组水稻]

MASNKVVSALLIIVSLAATATMADHHKQVVSLSGERCQPGMGYPMSLPRCAVVKRQCVGHGAPGGAVDEQLRQDCCRQLAAVD
DSWCRCALNHMVGGIYRELGATDVGHMPMAXVFPGRRGDLERAAASLPAFCNVDPNGTGVCYWLGPRTPTGH [SEQ ID 258]

>gi|5777592|emb|CAA44001.1| 低分子量球蛋白 [水稻 (Oryza sativa)]

MASNKVVSALLIIVSLRRDGTADHHKQVVSLSGERCQPGMGYPMSLPRCAVVKRQCVGHGAPGGAVDEQLRQDCCRQLAAVDD
SWCRCALNHMVGGIYRELGATDVGHMPMAEVFPGRRGDLERAAASLPAFCNVDPNGTGVCYWLGPRTPTGH [SEQ ID 259]

[0426]

>gi|115471175|ref|NP_001059186.1| Os07g0214600 [粳稻组水稻] >gi|23616954|dbj|BAC20657.1|
过敏原 RA16 [粳稻组水稻] >gi|113610722|dbj|BAF21100.1| Os07g0214600 [粳稻组水稻
] >gi|125557687|gb|EAZ03223.1| 假定蛋白质 Osl_25372 [籼稻组水稻]

MASNKVVISALLVVVSVLAATTTMADHHQEQVYTPGQLCQPGIGYPTPLPRCRAVVKRQCVAPGTVDEQVRRGCCRLAAIDSSWCRC
DALNHMLRIIYRESGAADAGHPMAEVFRGCRRGDIERAAASLPAFCNVDPNGVGGVCYWLPGTGY [SEQ ID 260]

大米蛋白质7 (SEQ ID 14) 的同源物

>gi|115445309|ref|NP_001046434.1| Os02g0248800 [粳稻组水稻] >gi|37993738|gb|AAR06952.1|
谷蛋白B型 [粳稻组水稻] >gi|47497729|dbj|BAD19794.1| 谷蛋白B型 [粳稻组水稻
] >gi|113535965|dbj|BAF08348.1| Os02g0248800 [粳稻组水稻] >gi|215768942|dbj|BAH01171.1|
未命名蛋白质产物 [粳稻组水稻] >gi|284431772|gb|ADB84627.1| 谷蛋白 [粳稻组水稻
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MTISVFSRFSIYFCVLLLCNGSMAQLFDPATNQWQTHRQGSFRECERFERLQAFELQNVSEAGVTEYFDETNELFQCTGTFFVIRRVIQPQGLL
IPRYANTPGMVYIIQGRGSMGLTFPGCPATYQQSQQLFQGEGSQKFIDEHQKIHQFRQGDIVVLPVTVGVAHWFYNDGDTPVVALVYDI
NNSANQLEPRHREFLAGKNNRVQVYGRSIQQHSGQNIIFNGFSVEPLSEALNINTVTTKRLQSQNDQGRGEIHHVKNGLQLLKPTLTQRQE
QAQYQEVQYSEKPTSSRWNGLEENLCTIKTRLNIENPSRADSYDPRAGRITSLDSQKFILNIIQMSATRVNLYQNAILTPFWNVNAHSLMYV
IRGRARVQVVSFNGKTVFDGVLRLPEQLLIIPQNYVVLKKAQHEGCQYIAINTANAFVSHLAGVDSVFHALPVDVIANAYCISREEARRLNNR
GDEYGPFPRLQQQIYPEFSNESKETSE [SEQ ID 261]

>gi|428674402|gb|AFZ41188.1| 谷蛋白, 部分[粳稻组水稻]

LLCHG5MAQIFSLGINPWQNPRQGG5RECRFDRLOAFEPLRKVRHEAGVTEYFDEKNEQFQCTGTLVIRRIIEPQGLLLPRYSNTPGLVYIIQGT
GVLGLTFPGCPATYQKQFRHFGLEGGSQRQGGKLRDENQKIHQFRQGDVVALPSGIPHWFYNEGDTPVVALFVFDVNNNANQLEPRQKEFL
LAGNNIEQQVSNPSINKHSGQNFNGFNTKLLSEALGVNIEVTRRLQSQNDRRGDIIRVKNGLRLIKPTITQQQEQTQDQYQQIQYHREQRSTS
KYNGLDENFCAIRARLNENPNHADTYNPRAGRITNLNSQKF5ILNLVQMSATRVNLYQNAILSPFWNINAHSLVYTIQGRARVQVVSNHGKA
VFNGVLRPGQLLIIPQNYVVMKKAELGFQFIAFKTNPNAMVNHIAGKNSVLRAMPVDVIANAYRISRQEARSLKNNRGEEIGAFTPRYQQQ
KIHQEYSNPNESETQ [SEQ ID 262]

>gi|226510|prf||1515394A 种子贮藏球蛋白

MATTRFPSLLFYSCIFLLCNGSMAQLFGQSFTPWQSSRQGGRLGCRFDRLOAFEPLRQVRSQAGITEYFDEQNEQFRCAGVSVIRRVIEPQGLL
LPQYHNAPGLVYLQGRGFTGLTFPGCPATFQQQFQPFQDQARFAQGSQSKNLKDEHQRVHHIKQGDVVALPAGIVHWYNDGDAPIVAV
YVFDVNNNANQLEPRQKEFLLAGNNKREQFGQNFISGFSVQLLSEALGISQQAQKIQSQNDQRGEIIRVSQGLQFLKPFVSQQGPVEHQA
YQPIQSQQEQSTQYQVGQSPQYQEGQSTQYQSGQSWDQSFNGLEENFCSLEARQNIENPKRADTYNPRAGRITHLSKNFPTLNLVQMSA
TRVNLQYQNAILSPYWNINAH5VMHMIQGRARVQVNNHGGQTVFNDILRRGQLLIIPQHYVVLKKAEREGCQYISFKTTPNSMVSYIAGKTSIL
RALPVDVLANAYRISRQESQNLKNNRGEEFGAFTPKFAQTGSQSYQDEGESSTEKASE [SEQ ID 263]

大米蛋白质8 (SEQ ID 15) 的同源物

>gi|83375868|gb|ABC17777.1| 蜡状[普通野生稻]

MSALTTSQLATSATGFGIADRSAPSSLLRHGFQGLKPRSPAGGDATSLSVTTSARATPKQQR5VQRG5RRF5PSVVVYATGAGMNVV5VGAEM
APWSKTGGLGDLVGLPPAMAANGHRVMVISPRYDQYKDAWDT5VVAEIKVADRYERV5FFHCYKRGVDRVFDHPSFLEK5WGKTGEKI
YGPDTGVDYKDNQMRFSLLCQAPRILN5NNNPYFKGT5YGEDV5FVCNDWHTG5PLASYLKNNYQPNGIYRNAK5VAFCIHNISYQGRF5AFEDYP
ELNLSERFRSS5DFIDGYDTPVEGRKINW5MKAGILEADRVLT5SPY5AEELISGIARGCELDNIMRLTGITGIVNGMDV5EWDPSKDKYITAKYD
ATTAIEAKALNKEALQAEAGLPVDRKIPLIAFIGRLEE5QKGP5DVMAAAIPELMQEDVQIVLLGTGKKKFEKLLK5MEEKYP5GKVR5AVVKFNAPLA
HLIMAGADV5LAVPSRF5EPCGLIQLQGMRYGTPCACASTGGLVD5TVEGKTGFHMGRL5VDC5KVVEPSDV5KVAATLKRAIKV5GTPAYEEMV
RNCMNQDLSWK5GPAKNWENVLLGLGVAGSAPGIEGDEIAPLAKENVAAP [SEQ ID 264]

[0427]

>gi|297614332|gb|ADI48504.1| 糖原合成酶 [药用野生稻]

MSALTTSQLATSATGFGIADRSAPSSLLRHGFQGLKPRSPAGGDASSLSVTTSARATPKQQR5VQRG5RRF5PSVVVYATGAGMNVV5VGAEM
APWSKTGGLGDLVGLPPAMAANGHRVMVISPRHDQYKDAWDT5VVAEIKVADRYERV5FFHCYKRGVDRVFDHPSFLEK5WGKTGEKI
YGPDTGVDYKDNQMRFSLLCQAA5EAPRILN5NNNPYFKGT5YGEDV5FVCNDWHTG5PLPSYLKNNYQPNGIYRNAK5VAFCIHNISYQGRF5AF
EDYPELNLSERFRSS5DFIDGYDTPVEGRKINW5MKAGILES5DRVLT5SPY5AEELISGIARGCELDNIMRLTGITGIVNGMDV5EWDPSKDKYIA
AKYDATT5AIEAKALNKEALQAEAGLPVDRKIPLIAFIGRLEE5QKGP5DVMAAAIPELMQENVQIVLLGTGKKKFEKLLK5MEEKYP5GKVR5AVVKF
NAPLAHLIMAGADV5LAVPSRF5EPCGLIQLQGMRYGTPCACASTGGLVD5TVEGKTGFHMGRL5VDC5KVVEPSDV5QKVATTLKRAIKV5GTPAYEM
NEMVRN5CMNQDLSWK5GPAKNWENVLLGLGVAGSAPGVEGEEIAPLAKENVAAP [SEQ ID 265]

>gi|389620054|gb|AFK93486.1| 颗粒结合淀粉合成酶 [青稞]

MAALAT5QLATSGTVLGVTD5RFR5PGFQGLR5PRNPADAALGMRTIGASAPKQ5SRKAH5RGS5RRL5SV5VRATG5GMNL5VF5VGAEMAPW5
KTGGLGDLVGLPPAMAANGHRVMVISPRYDQYKDAWDT5V5EIKVAD5EYERV5FFHCYKRGVDRVFDH5PW5FLEK5VRGKT5KEIY5GPDA
GTDYEDN5QQR5F5LLCQAA5EAPRILN5NNNPYF5SGPYGEDV5FVCNDWHTG5LLAC5YLK5SNYQ5SNGIY5RTAK5VAFCIHNISYQGRF5S5D5FAQL
NLPDRF5K5S5DFIDGYDKPVEGRKINW5MKAGILQADKVLTV5PY5AEELIS5DEARGCELDNIMRLTGITGIVNGMDV5EWD5PTKDKFLAVNYDI
TTALEAKALNKEALQAEVGLPVDRKVPLVAFIGRLEE5QKGP5DVMAAAIPEILKEEDVQIILLGTGKKKFEKLLK5MEEKF5PGKVR5AVV5RFNAPLAH
QMMAGADLLAVTSRF5EPCGLIQLQGMRYGTPCV5CASTGGLVD5TVEGKTGFHMGRL5VDC5NV5VEPADV5KKVATTLKRAV5V5GTPAYQEM
VKNCMIQDLSWK5GPAKNWEDV5LEL5GVEG5EPGIV5GEEIAPL5MENVAAP [SEQ ID 266]

[0428]

52

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[0584]	Glu	Pro	Arg	Gln	Lys	Glu	Phe	Leu	Leu	Ala	Gly	Asn	Asn	Asn	Arg	Ala

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[0608]	Val Val Ser Asn Phe Gly Lys Thr Val Phe Asp Gly Val Leu Arg Pro		
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[0612]	Glu Arg Glu Gly Cys Gln Tyr Ile Ala Ile Lys Thr Asn Ala Asn Ala		
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[0614]	Phe Val Ser His Leu Ala Gly Lys Asn Ser Val Phe Arg Ala Leu Pro		
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[0616]	Val Asp Val Val Ala Asn Ala Tyr Arg Ile Ser Arg Glu Gln Ala Arg		
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[0618]	Ser Leu Lys Asn Asn Arg Gly Glu Glu His Gly Ala Phe Thr Pro Arg		
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[0620]	Phe Gln Gln Gln Tyr Tyr Pro Gly Leu Ser Asn Glu Ser Glu Ser Glu		
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[0637]	65	70 75 80
[0638]	Gly	Val Ser Val Val Arg Arg Val Ile Glu Pro Arg Gly Leu Leu Leu
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[0700]	Ser Gln Trp Gln Ser Ser Arg Arg Gly Ser Pro Arg Gly Cys Arg Phe		
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[0716]	Gly	Asp	Val	Ile	Ala	Leu	Pro	Ala	Gly	Val	Ala	His	Trp	Cys	Tyr	Asn
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[0829]	Pro Ser His Ala Asp Thr Tyr Asn Pro Arg Ala Gly Arg Ile Thr Arg
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[0831]	Leu Asn Ser Gln Lys Phe Pro Ile Leu Asn Leu Val Gln Leu Ser Ala
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[0926]	Lys Arg Ala Ile Lys Val Val Gly Thr Pro Ala Tyr Glu Glu Met Val			
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[1225]	Gly Lys Asn Ser Val Phe Arg Ala Leu Pro Val Asp Val Val Ala Asn
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[1364]	20 25 30

[1365]	Ala Tyr Arg Ile Ser Arg Glu Glu Ala Gln Arg Leu Lys His Asn Arg
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[1463]	Ser Asn Leu Gly Lys Thr Val Phe Asn Gly	
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[1496]	Ser Gly Phe Asn Asn Glu Leu Leu Ser Glu Ala Leu Gly Val Asn Ala
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[1500]	Ile Arg Val Lys Asn Gly Leu Lys Leu Leu Arg Pro Ala Phe Ala Gln
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[1525]	Leu Tyr Val Phe Asp Leu Asn
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[1536]	Gly Lys Asn Ser Ile Phe Arg Ala Met Pro Val Asp Val Ile Ala Asn
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[1538]	Ala Tyr Arg Ile Ser Arg Glu Gln
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[1549]	Ala Gly Ser Ala Pro Gly Ile Glu Gly Asp Glu Ile Ala Pro Leu Ala
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[1654] 1 5 10
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[1672] 1 5 10
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 [1691] Val Lys
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 [1709] 1 5 10 15
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[1731]	1 5 10 15
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[1785]	1 5 10 15
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[1787]	20
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[1836]	<210> 91
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[1857]	20 25
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[2032]	Phe Asp Leu Ala Lys
[2033]	20
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[2041]	Lys Asn Pro Gln Leu Gln Asp Leu Asp Ile Phe Val Asn Tyr Val Glu
[2042]	1 5 10 15
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[2365] 1 5 10 15
[2366] Gln Arg Asp
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[2474]	1	5 10 15
[2475]		Asp Glu Phe
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[2485]		Asp Glu
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[2530]	1 5 10
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[2539]	1 5 10
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[2548]	1 5 10
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[2557]	1 5 10
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[2595] 1 5 10 15
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[2604] 1 5 10 15
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[3129]	Ser Arg Ala Ile Val Ile Val Thr Val Asn Glu Gly Lys Gly Asp Phe			
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[3137]	Ala Gly Tyr Pro Val Ala Ile Lys Ala Ser Ser Asn Leu Asn Leu Val			
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[3174]	Gly Asn Glu Asn Gln Gln Ser Tyr Phe Gln Gly Phe Ser Lys Lys Ile		
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[3176]	Leu Glu Ala Ser Phe Asn Ser Asp Tyr Glu Glu Ile Glu Arg Val Leu		
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[3180]	Arg Gln Gln Ser Gln Glu Thr Asp Val Ile Val Lys Ile Ser Arg Glu		
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[3182]	Gln Ile Glu Glu Leu Ser Lys Asn Ala Lys Ser Asn Cys Lys Lys Ser		
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[4060]	Pro His Tyr Asn Ser Arg Ala Ile Val Thr Val Leu Val Asn Glu Gly
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[4438]	Arg Gln Gly Asp Val Ile Ala Val Pro Pro Gly Val Ala His Trp Leu
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[4440]	Tyr Asn Asn Gly Asp Ser Pro Val Val Ala Phe Ser Val Ile Asp Phe
[4441]	180 185 190
[4442]	Gly Asn Asn Ala Asn Gln Leu Asp Pro Lys Pro Arg Glu Phe Phe Leu
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[5414]	Ala Phe Glu Pro Ile Arg Thr Val Arg Ser Gln Ala Gly Val Thr Glu
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[5418]	Val Arg Arg Val Ile Glu Pro Arg Gly Leu Leu Leu Pro His Tyr Ser
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[5515]	Thr Arg Leu Asn Gly Gln Asn Phe Pro Ile Leu Asn Leu Val Gln Met		
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[5554]	Gly	His Gly Ala Pro Gly Gly Ala Val Asp Glu Gln Leu Arg Gln Asp
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[5556]	Cys	Cys Arg Gln Leu Ala Ala Val Asp Asp Ser Trp Cys Arg Cys Ser
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[5558]	Ala	Leu Asn His Met Val Gly Gly Ile Tyr Arg Glu Leu Gly Ala Thr
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[5560]	Asp	Val Gly His Pro Met Ala Xaa Val Phe Pro Gly Cys Arg Arg Gly
[5561]		115 120 125
[5562]	Asp	Leu Glu Arg Ala Ala Ala Ser Leu Pro Ala Phe Cys Asn Val Asp
[5563]		130 135 140
[5564]	Ile	Pro Asn Gly Thr Gly Gly Val Cys Tyr Trp Leu Gly Tyr Pro Arg
[5565]	145	150 155 160
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[5584]					85					90					95	
[5585]	Leu	Asn	His	Met	Val	Gly	Gly	Ile	Tyr	Arg	Glu	Leu	Gly	Ala	Thr	Asp
[5586]				100					105					110		
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[5589]	Leu	Glu	Arg	Ala	Ala	Ala	Ser	Leu	Pro	Ala	Phe	Cys	Asn	Val	Asp	Ile
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[5591]	Pro	Asn	Gly	Thr	Gly	Gly	Val	Cys	Tyr	Trp	Leu	Gly	Tyr	Pro	Arg	Thr
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[5597]	<212> PRT															
[5598]	<213> 水稻															
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[5604]	Val	Val	Tyr	Thr	Pro	Gly	Gln	Leu	Cys	Gln	Pro	Gly	Ile	Gly	Tyr	Pro
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[5606]	Thr	Tyr	Pro	Leu	Pro	Arg	Cys	Arg	Ala	Phe	Val	Lys	Arg	Gln	Cys	Val
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[5608]	Ala	Pro	Gly	Thr	Val	Asp	Glu	Gln	Val	Arg	Arg	Gly	Cys	Cys	Arg	Gln
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[5612]	Met	Leu	Arg	Ile	Ile	Tyr	Arg	Glu	Ser	Gly	Ala	Ala	Asp	Ala	Gly	His
[5613]			100						105				110			
[5614]	Pro	Met	Ala	Glu	Val	Phe	Arg	Gly	Cys	Arg	Arg	Gly	Asp	Ile	Glu	Arg
[5615]			115					120					125			

[5616]	Ala Ala Ala Ser Leu Pro Ala Phe Cys Asn Val Asp Ile Pro Asn Gly
[5617]	130 135 140
[5618]	Val Gly Gly Val Cys Tyr Trp Leu Pro Gly Thr Gly Tyr
[5619]	145 150 155
[5620]	<210> 261
[5621]	<211> 495
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[5627]	Leu Leu Cys Asn Gly Ser Met Ala Gln Leu Phe Asp Pro Ala Thr Asn
[5628]	20 25 30
[5629]	Gln Trp Gln Thr His Arg Gln Gly Ser Phe Arg Glu Cys Arg Phe Glu
[5630]	35 40 45
[5631]	Arg Leu Gln Ala Phe Glu Pro Leu Gln Asn Val Arg Ser Glu Ala Gly
[5632]	50 55 60
[5633]	Val Thr Glu Tyr Phe Asp Glu Thr Asn Glu Leu Phe Gln Cys Thr Gly
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[5635]	Thr Phe Val Ile Arg Arg Val Ile Gln Pro Gln Gly Leu Leu Ile Pro
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[5637]	Arg Tyr Ala Asn Thr Pro Gly Met Val Tyr Ile Ile Gln Gly Arg Gly
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[5639]	Ser Met Gly Leu Thr Phe Pro Gly Cys Pro Ala Thr Tyr Gln Gln Gln
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[5641]	Ser Gln Gln Phe Leu Phe Gln Gly Glu Ser Gln Ser Gln Lys Phe Ile
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[5643]	Asp Glu His Gln Lys Ile His Gln Phe Arg Gln Gly Asp Ile Val Val
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[5645]	Leu Pro Thr Gly Val Ala His Trp Phe Tyr Asn Asp Gly Asp Thr Pro
[5646]	165 170 175
[5647]	Val Val Ala Leu Tyr Val Tyr Asp Ile Asn Asn Ser Ala Asn Gln Leu
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[5649]	Glu Pro Arg His Arg Glu Phe Leu Leu Ala Gly Lys Asn Asn Arg Val
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[5651]	Gln Gln Val Tyr Gly Arg Ser Ile Gln Gln His Ser Gly Gln Asn Ile
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[5655]	Thr Val Thr Thr Lys Arg Leu Gln Ser Gln Asn Asp Gln Arg Gly Glu		
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[5659]	Gln Arg Gln Glu Gln Glu Gln Ala Gln Tyr Gln Glu Val Gln Tyr Ser		
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[5661]	Glu Lys Pro Gln Thr Ser Ser Arg Trp Asn Gly Leu Glu Glu Asn Leu		
[5662]		290	300
[5663]	Cys Thr Ile Lys Thr Arg Leu Asn Ile Glu Asn Pro Ser Arg Ala Asp		
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[5665]	Ser Tyr Asp Pro Arg Ala Gly Arg Ile Thr Ser Leu Asp Ser Gln Lys		
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[5667]	Phe Pro Ile Leu Asn Ile Ile Gln Met Ser Ala Thr Arg Val Asn Leu		
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[5669]	Tyr Gln Asn Ala Ile Leu Thr Pro Phe Trp Asn Val Asn Ala His Ser		
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[5671]	Leu Met Tyr Val Ile Arg Gly Arg Ala Arg Val Gln Val Val Ser Asn		
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[5673]	Phe Gly Lys Thr Val Phe Asp Gly Val Leu Arg Pro Glu Gln Leu Leu		
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[5675]	Ile Ile Pro Gln Asn Tyr Val Val Leu Lys Lys Ala Gln His Glu Gly		
[5676]		405	410
[5677]	Cys Gln Tyr Ile Ala Ile Asn Thr Asn Ala Asn Ala Phe Val Ser His		
[5678]		420	425
[5679]	Leu Ala Gly Val Asp Ser Val Phe His Ala Leu Pro Val Asp Val Ile		
[5680]		435	440
[5681]	Ala Asn Ala Tyr Cys Ile Ser Arg Glu Glu Ala Arg Arg Leu Lys Asn		
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[5683]	Asn Arg Gly Asp Glu Tyr Gly Pro Phe Pro Pro Arg Leu Gln Gln Gln		
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[5697]			35					40					45			
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[5702]	Arg	Tyr	Ser	Asn	Thr	Pro	Gly	Leu	Val	Tyr	Ile	Ile	Gln	Gly	Thr	Gly
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[5708]	Leu	Arg	Asp	Glu	Asn	Gln	Lys	Ile	His	Gln	Phe	Arg	Gln	Gly	Asp	Val
[5709]		130					135					140				
[5710]	Val	Ala	Leu	Pro	Ser	Gly	Ile	Pro	His	Trp	Phe	Tyr	Asn	Glu	Gly	Asp
[5711]	145					150					155					160
[5712]	Thr	Pro	Val	Val	Ala	Leu	Phe	Val	Phe	Asp	Val	Asn	Asn	Asn	Ala	Asn
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[5714]	Gln	Leu	Glu	Pro	Arg	Gln	Lys	Glu	Phe	Leu	Leu	Ala	Gly	Asn	Asn	Ile
[5715]				180					185					190		
[5716]	Glu	Gln	Gln	Val	Ser	Asn	Pro	Ser	Ile	Asn	Lys	His	Ser	Gly	Gln	Asn
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[5718]	Ile	Phe	Asn	Gly	Phe	Asn	Thr	Lys	Leu	Leu	Ser	Glu	Ala	Leu	Gly	Val
[5719]		210					215					220				
[5720]	Asn	Ile	Glu	Val	Thr	Arg	Arg	Leu	Gln	Ser	Gln	Asn	Asp	Arg	Arg	Gly
[5721]	225					230					235					240
[5722]	Asp	Ile	Ile	Arg	Val	Lys	Asn	Gly	Leu	Arg	Leu	Ile	Lys	Pro	Thr	Ile
[5723]				245					250					255		
[5724]	Thr	Gln	Gln	Gln	Glu	Gln	Thr	Gln	Asp	Gln	Tyr	Gln	Gln	Ile	Gln	Tyr
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[5729]		290					295					300				
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[5731]	305					310					315					320
[5732]	Lys	Phe	Ser	Ile	Leu	Asn	Leu	Val	Gln	Met	Ser	Ala	Thr	Arg	Val	Asn

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[5735]		340		345		350
[5736]	Ser Leu Val Tyr Thr Ile Gln Gly Arg Ala Arg Val Gln Val Val Ser					
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[5738]	Asn His Gly Lys Ala Val Phe Asn Gly Val Leu Arg Pro Gly Gln Leu					
[5739]		370		375		380
[5740]	Leu Ile Ile Pro Gln Asn Tyr Val Val Met Lys Lys Ala Glu Leu Glu					
[5741]		385		390		395
[5742]	Gly Phe Gln Phe Ile Ala Phe Lys Thr Asn Pro Asn Ala Met Val Asn					
[5743]		405		410		415
[5744]	His Ile Ala Gly Lys Asn Ser Val Leu Arg Ala Met Pro Val Asp Val					
[5745]		420		425		430
[5746]	Ile Ala Asn Ala Tyr Arg Ile Ser Arg Gln Glu Ala Arg Ser Leu Lys					
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[5748]	Asn Asn Arg Gly Glu Glu Ile Gly Ala Phe Thr Pro Arg Tyr Gln Gln					
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[5750]	Gln Lys Ile His Gln Glu Tyr Ser Asn Pro Asn Glu Ser Glu Thr Gln					
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[5761]	Pro Trp Gln Ser Ser Arg Gln Gly Gly Leu Arg Gly Cys Arg Phe Asp					
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[5763]	Arg Leu Gln Ala Phe Glu Pro Leu Arg Gln Val Arg Ser Gln Ala Gly					
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[5765]	Ile Thr Glu Tyr Phe Asp Glu Gln Asn Glu Gln Phe Arg Cys Ala Gly					
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[5767]	Val Ser Val Ile Arg Arg Val Ile Glu Pro Gln Gly Leu Leu Leu Pro					
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[5769]	Gln Tyr His Asn Ala Pro Gly Leu Val Tyr Ile Leu Gln Gly Arg Gly					
[5770]		100		105		110
[5771]	Phe Thr Gly Leu Thr Phe Pro Gly Cys Pro Ala Thr Phe Gln Gln Gln					

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[5773]	Phe Gln Pro Phe Asp Gln Ala Arg Phe Ala Gln Gly Gln Ser Lys Ser		
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[5775]	Gln Asn Leu Lys Asp Glu His Gln Arg Val His His Ile Lys Gln Gly		
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[5777]	Asp Val Val Ala Leu Pro Ala Gly Ile Val His Trp Cys Tyr Asn Asp		
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[5779]	Gly Asp Ala Pro Ile Val Ala Val Tyr Val Phe Asp Val Asn Asn Asn		
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[5781]	Ala Asn Gln Leu Glu Pro Arg Gln Lys Glu Phe Leu Leu Ala Gly Asn		
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[5783]	Asn Lys Arg Glu Gln Gln Phe Gly Gln Asn Ile Phe Ser Gly Phe Ser		
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[5785]	Val Gln Leu Leu Ser Glu Ala Leu Gly Ile Ser Gln Gln Ala Ala Gln		
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[5787]	Lys Ile Gln Ser Gln Asn Asp Gln Arg Gly Glu Ile Ile Arg Val Ser		
[5788]	245	250	255
[5789]	Gln Gly Leu Gln Phe Leu Lys Pro Phe Val Ser Gln Gln Gly Pro Val		
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[5791]	Glu His Gln Ala Tyr Gln Pro Ile Gln Ser Gln Gln Glu Gln Ser Thr		
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[5793]	Gln Tyr Gln Val Gly Gln Ser Pro Gln Tyr Gln Glu Gly Gln Ser Thr		
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[5795]	Gln Tyr Gln Ser Gly Gln Ser Trp Asp Gln Ser Phe Asn Gly Leu Glu		
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[5797]	Glu Asn Phe Cys Ser Leu Glu Ala Arg Gln Asn Ile Glu Asn Pro Lys		
[5798]	325	330	335
[5799]	Arg Ala Asp Thr Tyr Asn Pro Arg Ala Gly Arg Ile Thr His Leu Asn		
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[5801]	Ser Lys Asn Phe Pro Thr Leu Asn Leu Val Gln Met Ser Ala Thr Arg		
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[5803]	Val Asn Leu Tyr Gln Asn Ala Ile Leu Ser Pro Tyr Trp Asn Ile Asn		
[5804]	370	375	380
[5805]	Ala His Ser Val Met His Met Ile Gln Gly Arg Ala Arg Val Gln Val		
[5806]	385	390	395
[5807]	Val Asn Asn His Gly Gln Thr Val Phe Asn Asp Ile Leu Arg Arg Gly		
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[5809]	Gln Leu Leu Ile Ile Pro Gln His Tyr Val Val Leu Lys Lys Ala Glu		
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[5815]	Asp	Val	Leu	Ala	Asn	Ala	Tyr	Arg	Ile	Ser	Arg	Gln	Glu	Ser	Gln	Asn
[5816]	465						470				475					480
[5817]	Leu	Lys	Asn	Asn	Arg	Gly	Glu	Glu	Phe	Gly	Ala	Phe	Thr	Pro	Lys	Phe
[5818]					485					490					495	
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[5821]	Thr	Glu	Lys	Ala	Ser	Glu										
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[5834]	Ser	Val	Thr	Thr	Ser	Ala	Arg	Ala	Thr	Pro	Lys	Gln	Gln	Arg	Ser	Val
[5835]		50					55				60					
[5836]	Gln	Arg	Gly	Ser	Arg	Arg	Phe	Pro	Ser	Val	Val	Val	Tyr	Ala	Thr	Gly
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[5838]	Ala	Gly	Met	Asn	Val	Val	Phe	Val	Gly	Ala	Glu	Met	Ala	Pro	Trp	Ser
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[5840]	Lys	Thr	Gly	Gly	Leu	Gly	Asp	Val	Leu	Gly	Gly	Leu	Pro	Pro	Ala	Met
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[5842]	Ala	Ala	Asn	Gly	His	Arg	Val	Met	Val	Ile	Ser	Pro	Arg	Tyr	Asp	Gln
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[5845]			130					135					140			
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[5847]	145					150					155					160
[5848]	Asp	Arg	Val	Phe	Val	Asp	His	Pro	Ser	Phe	Leu	Glu	Lys	Val	Trp	Gly
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[5852]	Asp Asn Gln Met Arg Phe Ser Leu Leu Cys Gln Ala Pro Arg Ile Leu		190
[5853]		195	200
[5854]	Asn Leu Asn Asn Asn Pro Tyr Phe Lys Gly Thr Tyr Gly Glu Asp Val		205
[5855]		210	215
[5856]	Val Phe Val Cys Asn Asp Trp His Thr Gly Pro Leu Ala Ser Tyr Leu		220
[5857]		225	230
[5858]	Lys Asn Asn Tyr Gln Pro Asn Gly Ile Tyr Arg Asn Ala Lys Val Ala		235
[5859]		245	250
[5860]	Phe Cys Ile His Asn Ile Ser Tyr Gln Gly Arg Phe Ala Phe Glu Asp		240
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[5862]	Tyr Pro Glu Leu Asn Leu Ser Glu Arg Phe Arg Ser Ser Phe Asp Phe		270
[5863]		275	280
[5864]	Ile Asp Gly Tyr Asp Thr Pro Val Glu Gly Arg Lys Ile Asn Trp Met		285
[5865]		290	295
[5866]	Lys Ala Gly Ile Leu Glu Ala Asp Arg Val Leu Thr Val Ser Pro Tyr		300
[5867]		305	310
[5868]	Tyr Ala Glu Glu Leu Ile Ser Gly Ile Ala Arg Gly Cys Glu Leu Asp		315
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[5870]	Asn Ile Met Arg Leu Thr Gly Ile Thr Gly Ile Val Asn Gly Met Asp		335
[5871]		340	345
[5872]	Val Ser Glu Trp Asp Pro Ser Lys Asp Lys Tyr Ile Thr Ala Lys Tyr		350
[5873]		355	360
[5874]	Asp Ala Thr Thr Ala Ile Glu Ala Lys Ala Leu Asn Lys Glu Ala Leu		365
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[5876]	Gln Ala Glu Ala Gly Leu Pro Val Asp Arg Lys Ile Pro Leu Ile Ala		380
[5877]		385	390
[5878]	Phe Ile Gly Arg Leu Glu Glu Gln Lys Gly Pro Asp Val Met Ala Ala		395
[5879]		405	410
[5880]	Ala Ile Pro Glu Leu Met Gln Glu Asp Val Gln Ile Val Leu Leu Gly		415
[5881]		420	425
[5882]	Thr Gly Lys Lys Lys Phe Glu Lys Leu Leu Lys Ser Met Glu Glu Lys		430
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[5884]	Tyr Pro Gly Lys Val Arg Ala Val Val Lys Phe Asn Ala Pro Leu Ala		445
[5885]		450	455
[5886]	His Leu Ile Met Ala Gly Ala Asp Val Leu Ala Val Pro Ser Arg Phe		460
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[5888]	Glu Pro Cys Gly Leu Ile Gln Leu Gln Gly Met Arg Tyr Gly Thr Pro		475
			480

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[5893]	515				520				525							
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[5895]	530				535				540							
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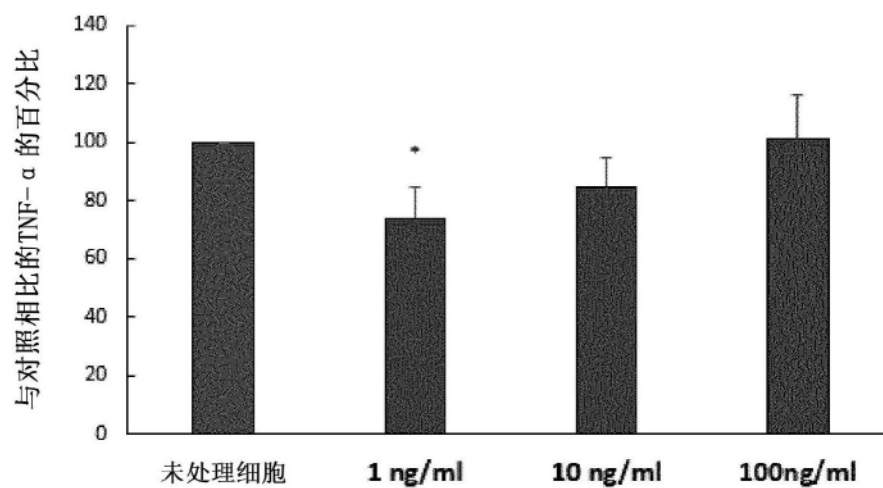


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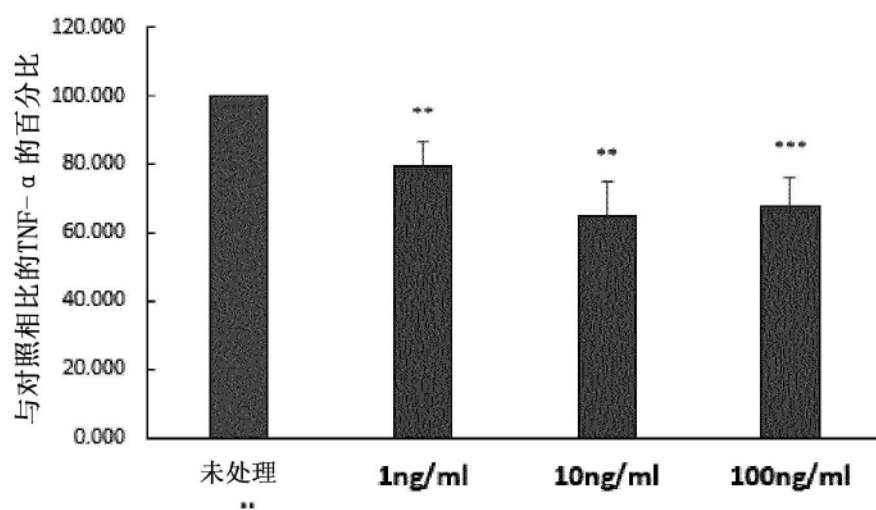


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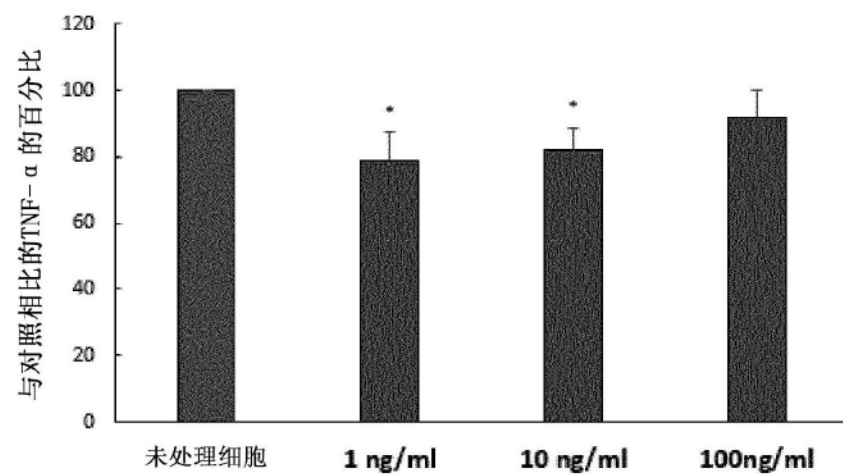


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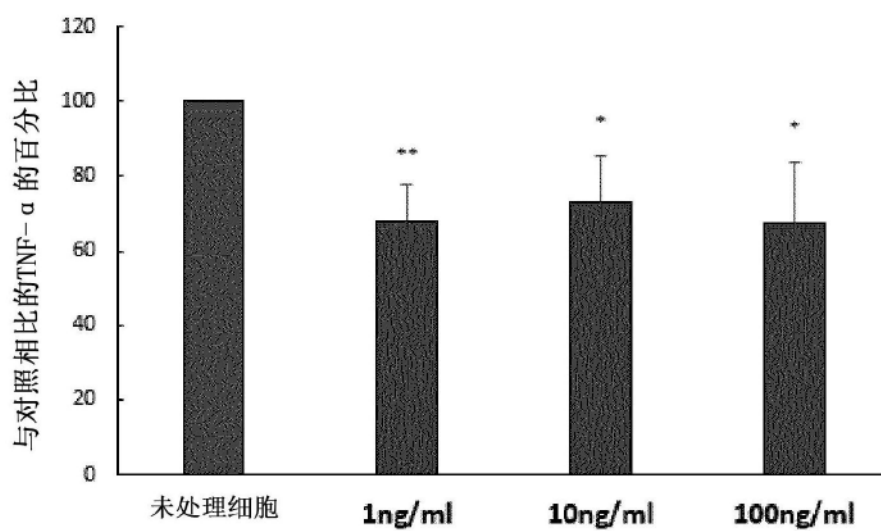


图4

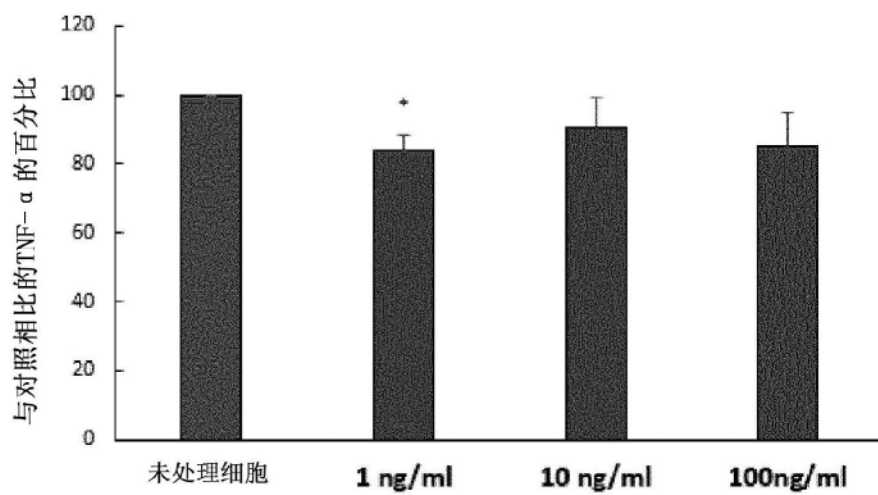


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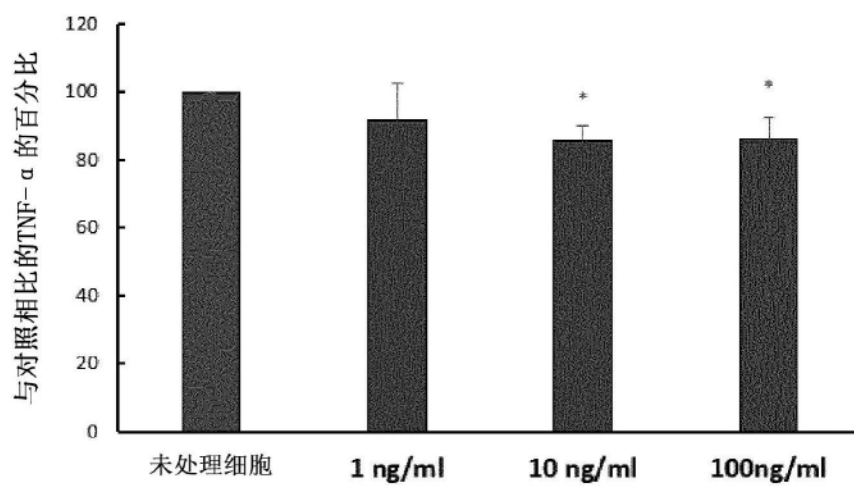


图6

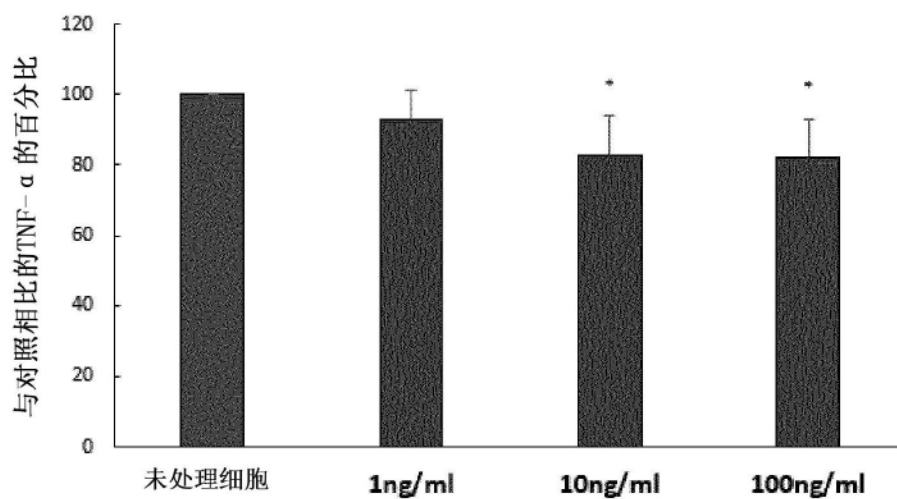


图7

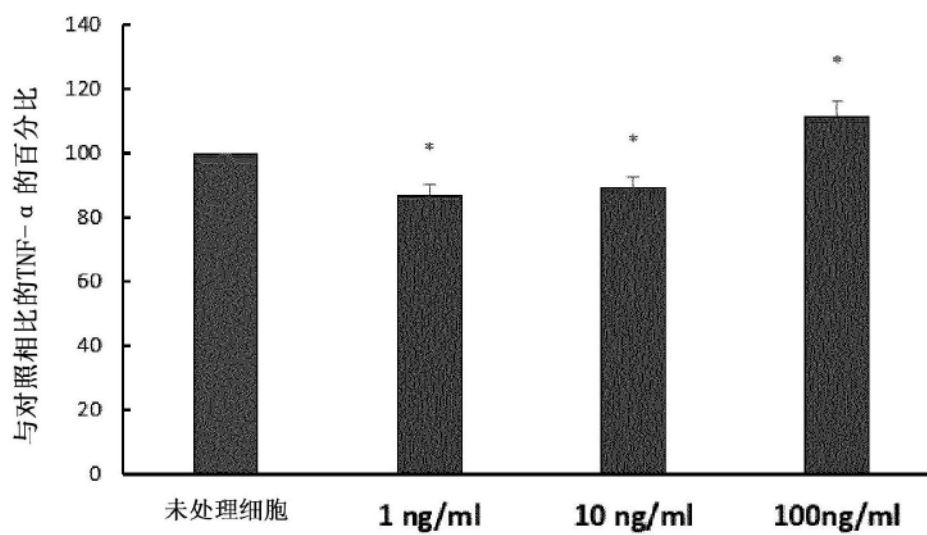


图8

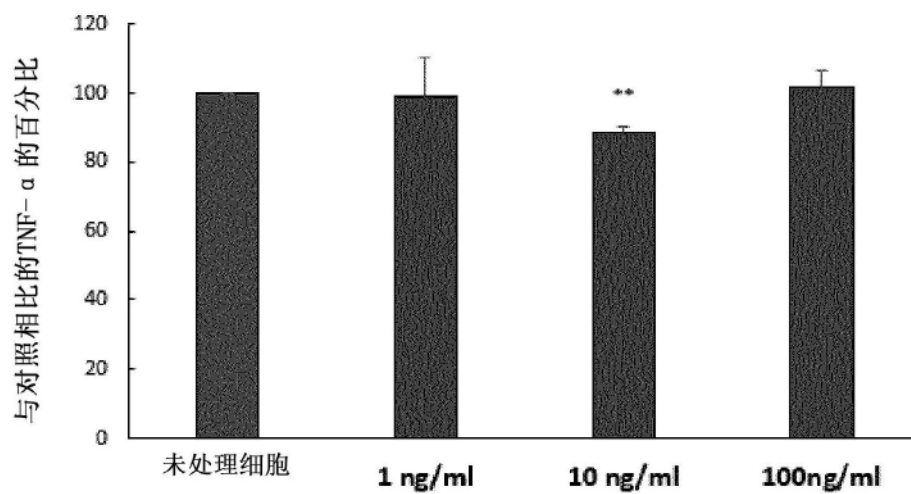


图9

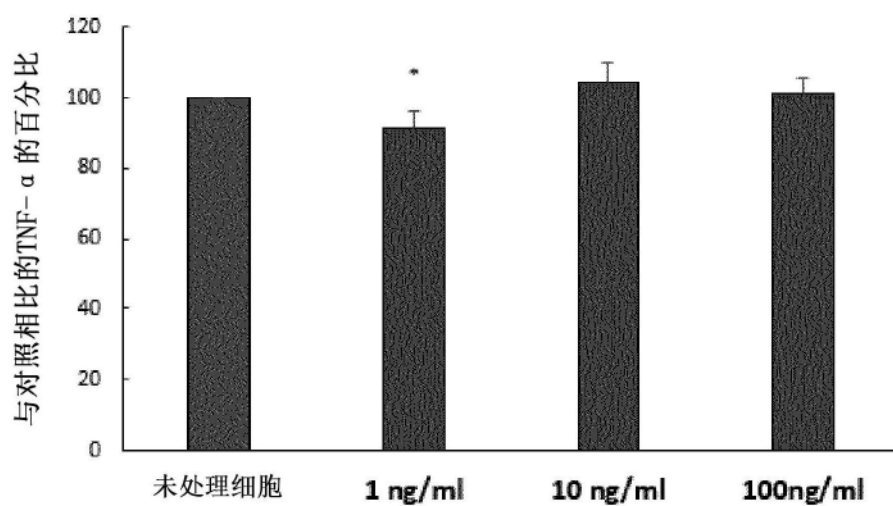


图10

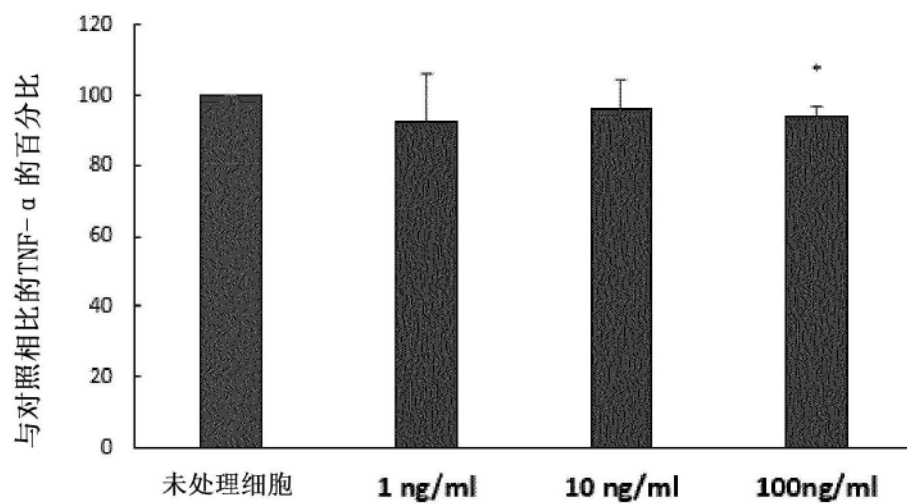


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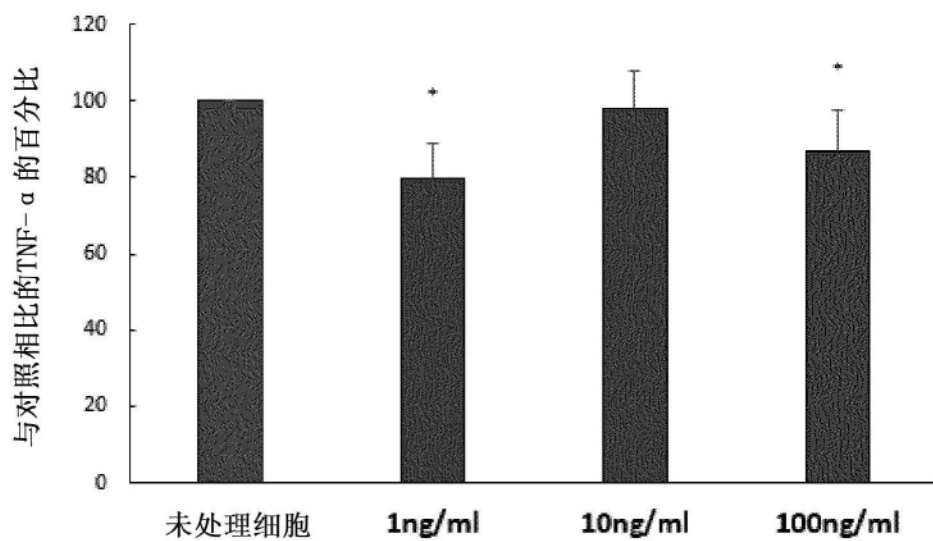


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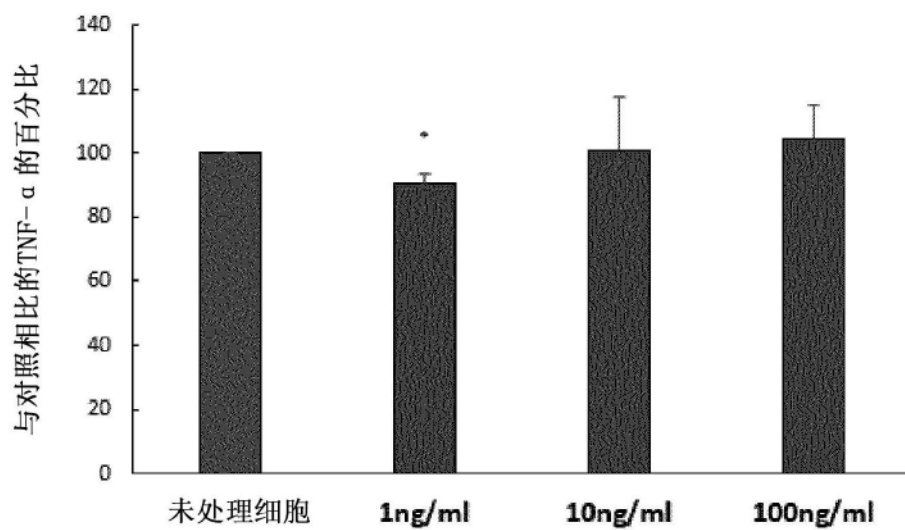


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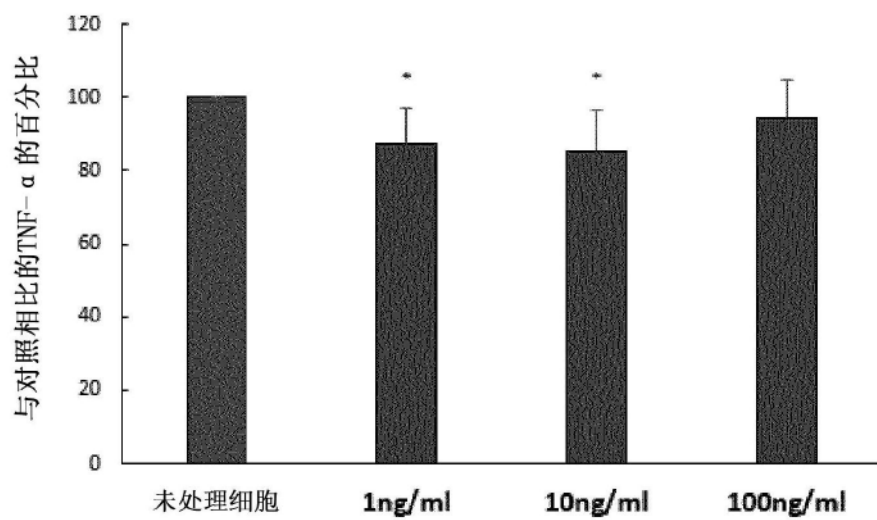


图14

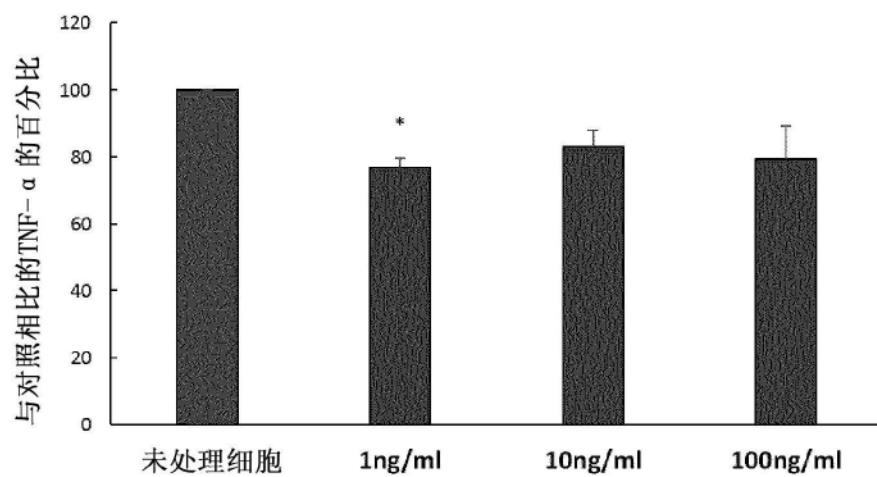


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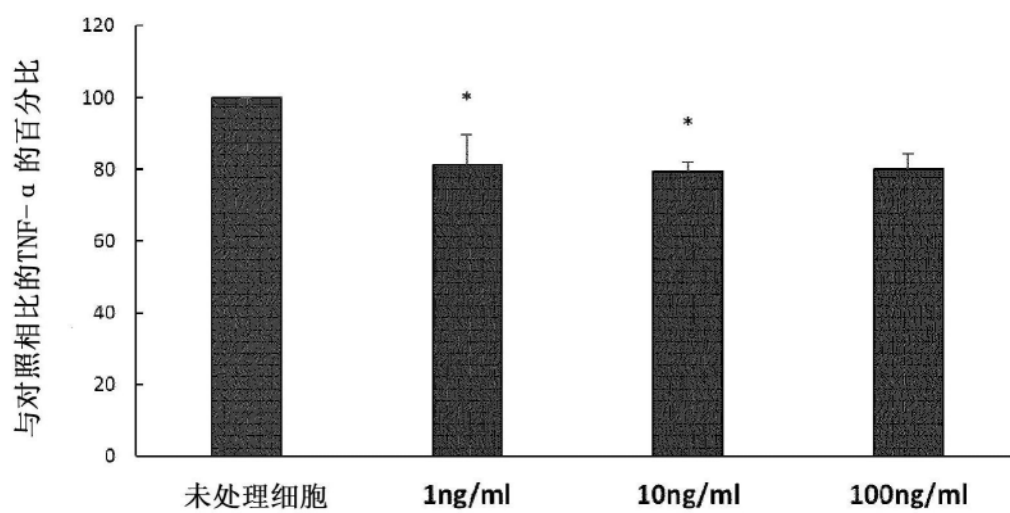


图16

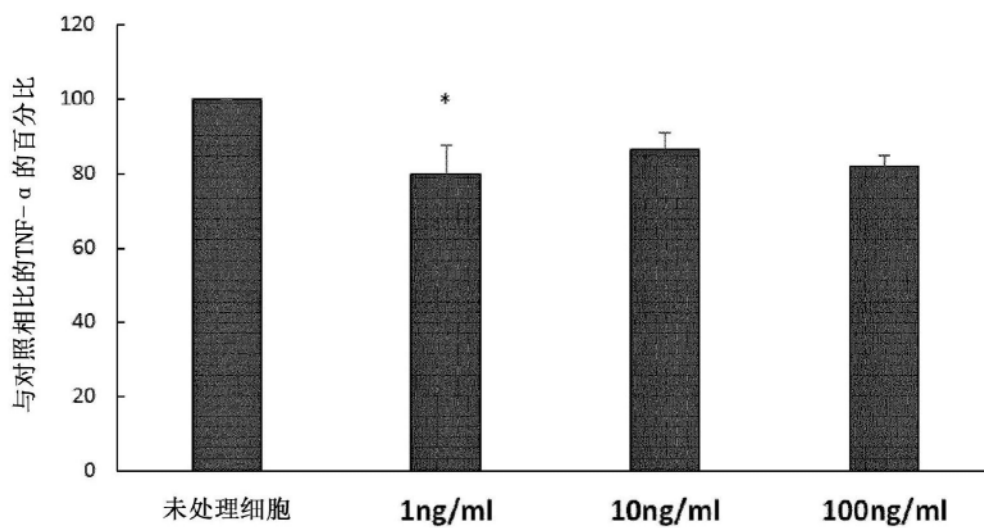


图17

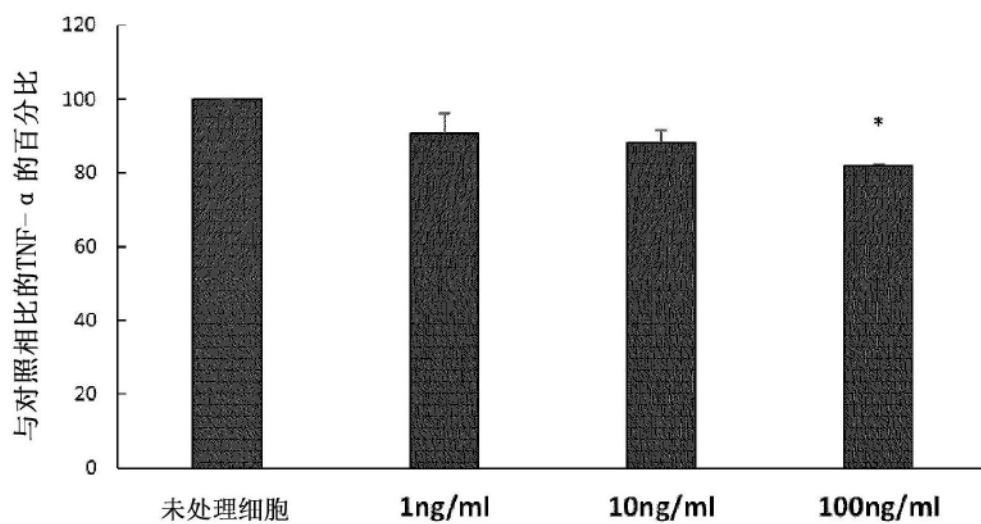


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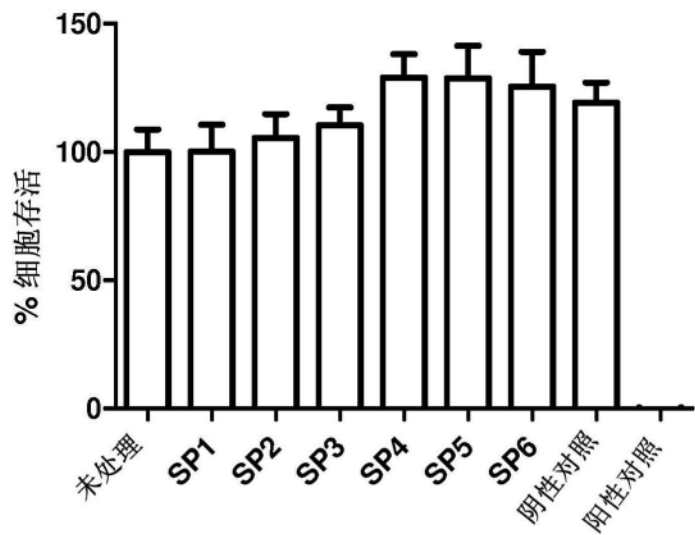
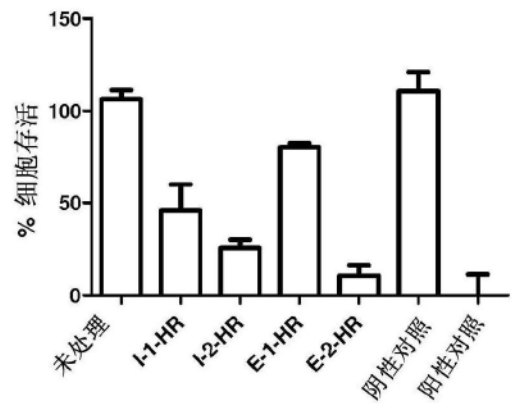


图19

(A)



(B)

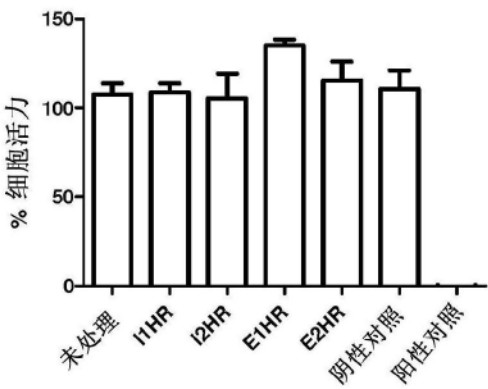


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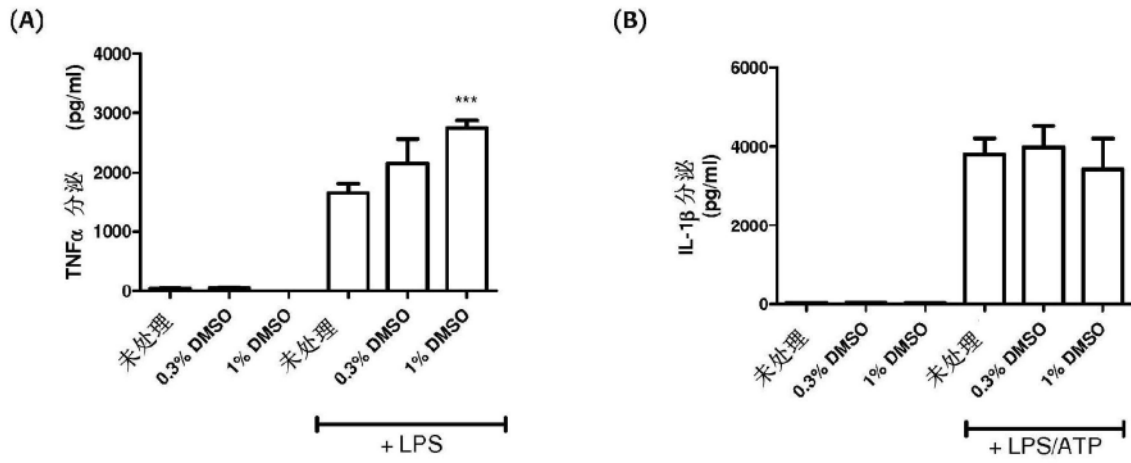


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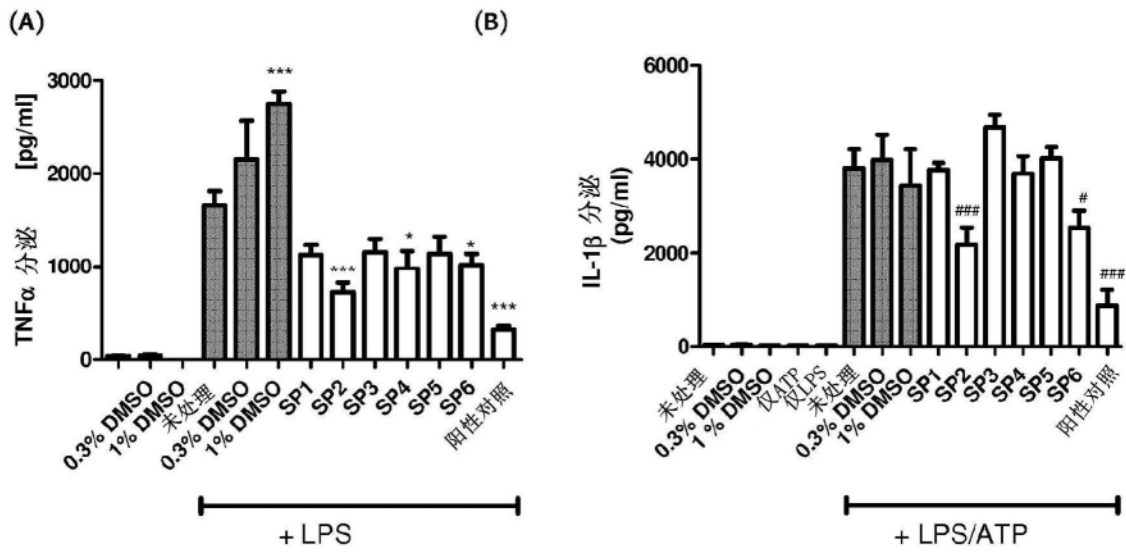


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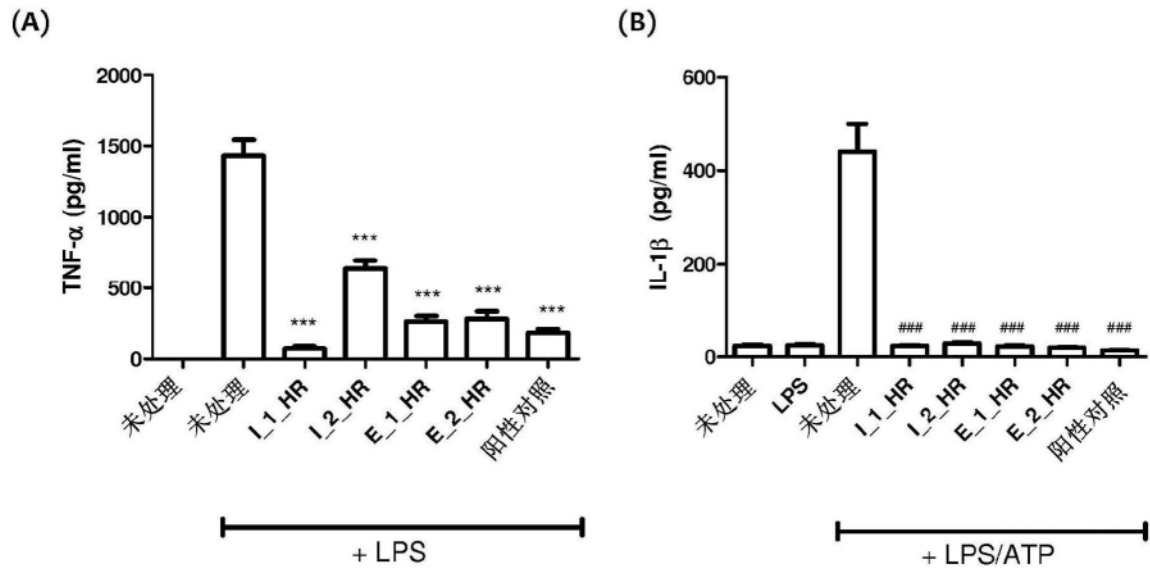


图23

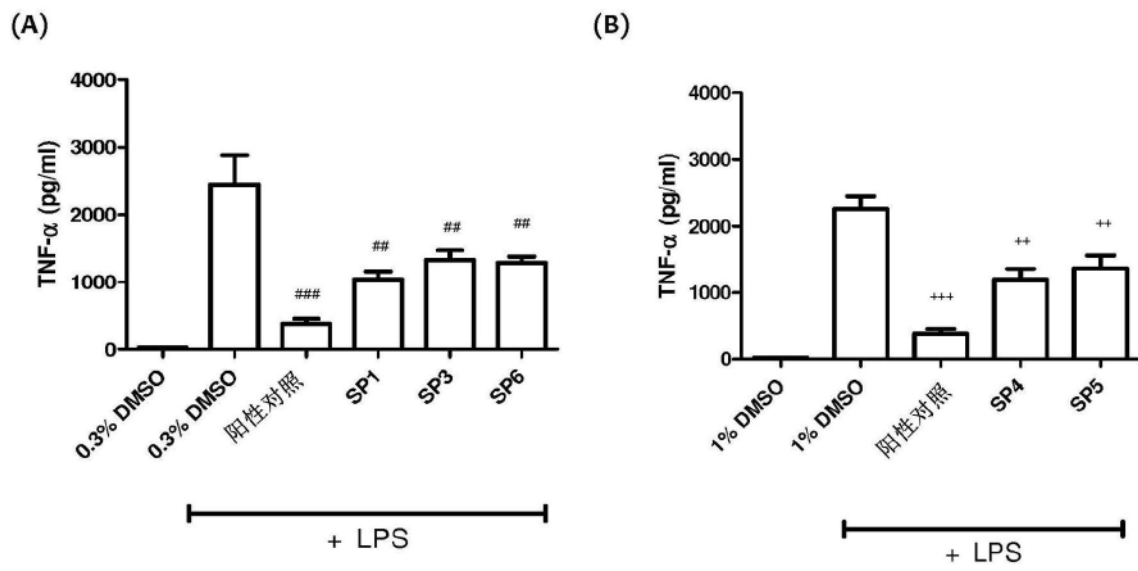


图24

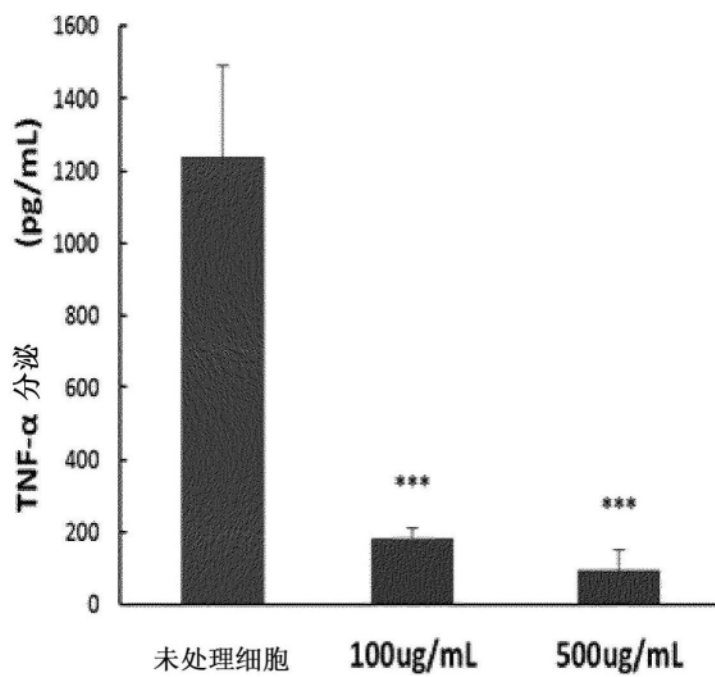


图25

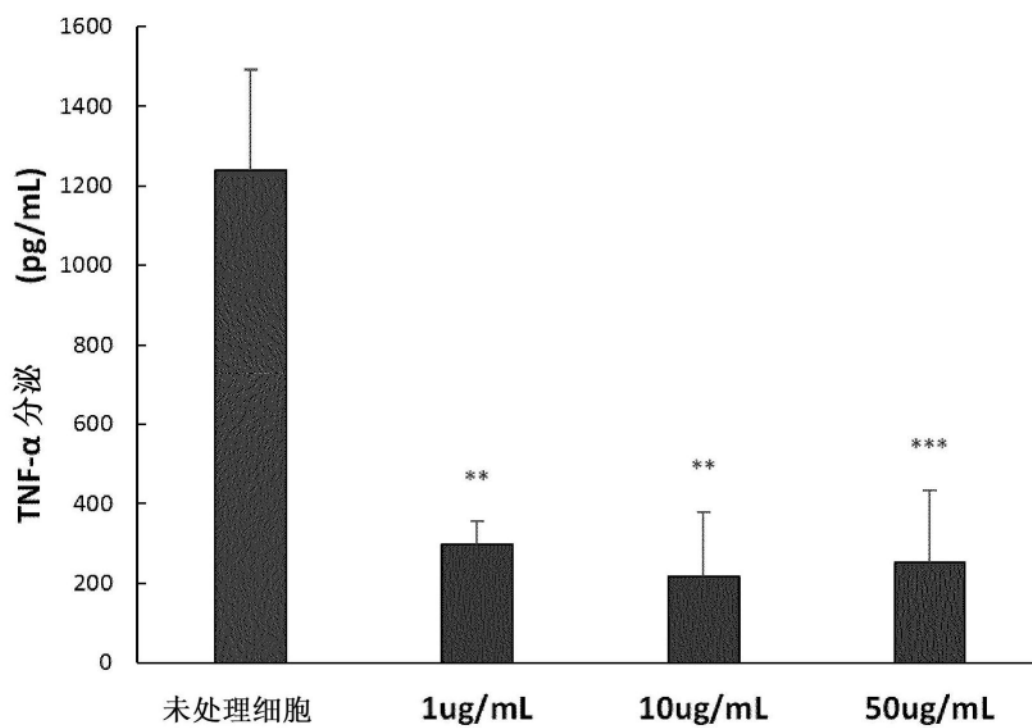


图26

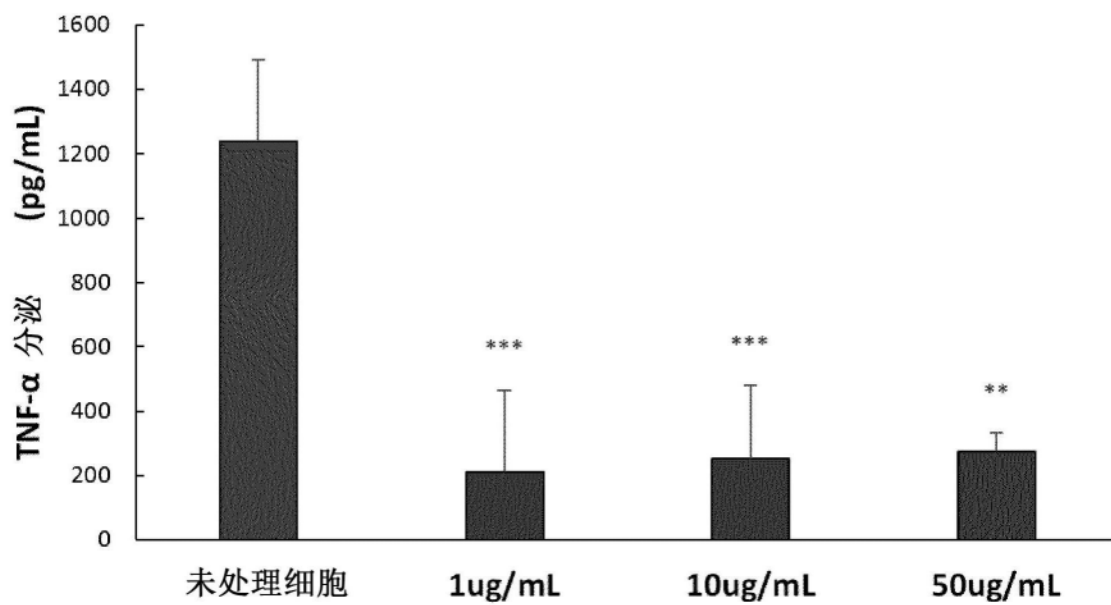


图27

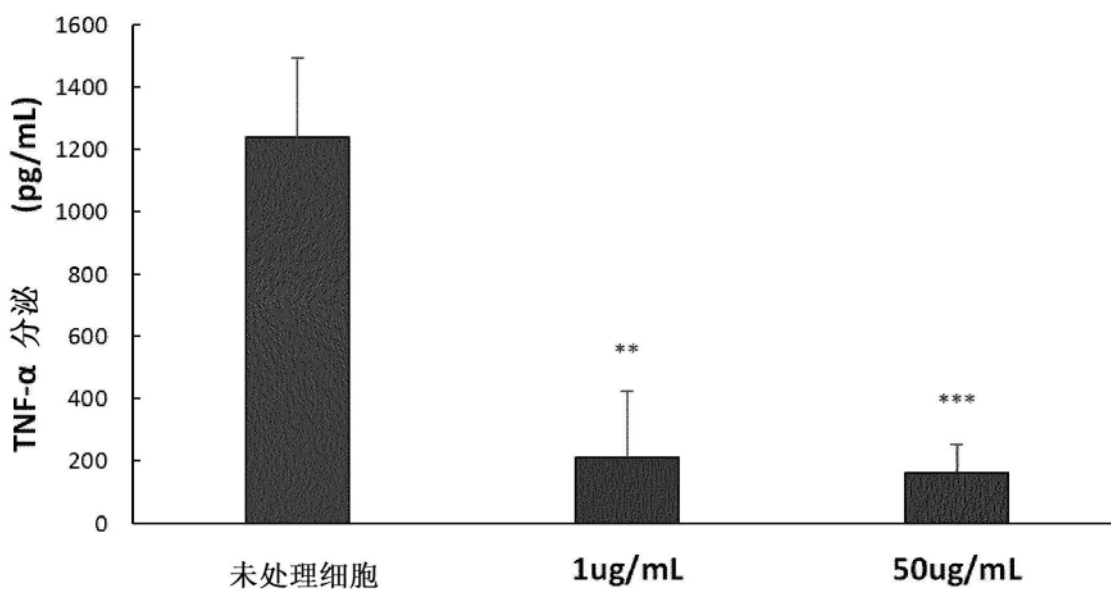


图28