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(54) Title: COSMETIC USE OF DERMCIDIN, OR ANALOGUES OR FRAGMENTS THEREOF, FOR PREVENTING AND/OR TREATING BODY ODOUR AND ALSO FOR DIAGNOSING ODOROUS SWEAT

(57) Abstract: Cosmetic use of dermcidin, or analogues or fragments thereof, for preventing and/or treating body odour and also for diagnosing odorous sweat The present invention relates to the cosmetic use of dermcidin, or analogues or fragments thereof or of a composition containing the same, for preventing and/or treating body odour, particularly from the armpits and the feet, and also for diagnosing odorous sweat. The invention also relates to a process for applying the abovementioned cosmetic composition for preventing and/or treating body odour. The present invention also relates to the use of a biomarker for diagnosing odorous sweat.

Cosmetic use of dermcidin, or analogues or fragments thereof, for preventing and/or treating body odour and also for diagnosing odorous sweat

The present invention relates to the cosmetic use of dermcidin, or analogues or fragments thereof or of a composition containing the same, for preventing and/or treating body odour, particularly from the armpits and the feet, and also for diagnosing odorous sweat.

The invention also relates to a process for applying the abovementioned cosmetic composition for preventing and/or treating body odour.

The present invention also relates to the use of a biomarker for diagnosing odorous sweat.

The invention also relates to a process for screening active agents that are capable of preventing or treating body odour.

For the purposes of the invention, the term "skin" means the entire epidermis of the human body. More particularly, the skin under consideration in the present invention is preferably the skin of the armpits, the scalp and the feet, and preferably the skin of the armpits.

For the purposes of the invention, the definition of "body odour" is given in the publication *Cosmetic Science and Technology Series* - 1988/Volume 7 chap. 10 – IIIc. For the purposes of the invention, "body odour" is caused by odorous sweat.

The anatomy and physiology of the skin vary from one part of the body to another. However, irrespective of the anatomical region, the skin contains sebaceous and sweat

glands whose excretions consist, inter alia, of water, amino acids, urea, electrolytes and/or specific fatty acids. Besides the fact that these excretions constitute an excellent nutritive medium for all of the flora, mainly the bacterial flora, which colonizes the skin, the components thereof, once in contact with the air, undergo chemical reactions, for instance oxidation, which degrade them and give rise to products responsible for body odour that may occasionally prove to be disagreeable.

In the cosmetic field, it is well known to use, in topical application, deodorant products containing active substances of antiperspirant type for reducing or even preventing body odour, in particular the generally unpleasant underarm odour.

However, cutaneous excretions are not the only factors responsible for body odour caused by odorous sweat. The cutaneous flora itself is partly responsible therefor.

The underarm microflora is mainly composed of gram-positive bacteria, such as staphylococci (e.g. *S. epidermidis*, *S. hominis*, etc.), coryneforms (more particularly *C. xerosis*), micrococci (e.g. *M. luteus*), Brevibacteria and Propionibacteria.

The bactericides conventionally used for obtaining good deodorant efficacy lead to the indiscriminate destruction of all the cutaneous flora. In order to obtain deodorant efficacy without impairing the equilibrium of the microbial flora, it is necessary to use novel active agents that do not have the drawbacks of the active substances previously employed in deodorant compositions.

Now, the Applicant has discovered, surprisingly, that dermcidin, a natural antimicrobial peptide, and particularly the isoforms 1 (DCD-1) and 2 (DCD-2), and preferably peptides derived from the cleavage of the isoforms DCD1 and DCD2, makes it possible to achieve this objective.

Its use or the use of active agents that increase its synthesis may thus be used in a cosmetic or dermatological composition, in particular as an anti-odour active agent.

One subject of the invention is thus the use of a cosmetic composition containing at least one amino acid sequence of dermcidin, and more particularly of the isoforms 1 and 2 thereof (DCD-1 and DCD-2), or of a peptide derived from this protein, an analogue or fragment thereof or a nucleic acid sequence coding for a peptide in accordance with the invention, for preventing and/or treating body odour, particularly from the armpits, the scalp and the feet, and also for diagnosing odorous skin.

The invention also relates to a cosmetic treatment process in which a cosmetic composition comprising an amino acid sequence of dermcidin, and more particularly of the isoform 1 or 2 thereof, an analogue or fragment thereof and/or preferably at least one peptide in accordance with the invention, at least one nucleic acid sequence coding for a peptide in accordance with the invention, or at least one modulator of the expression or activity, especially biological, of said peptide, is applied to the skin.

Another aspect of the invention is the use of dermcidin, and more particularly of the isoform 1 or 2 thereof, an analogue or a fragment thereof and/or preferably at least one peptide in accordance with the invention, at least one nucleic acid sequence coding for a peptide in accordance with the invention, especially as a biomarker for diagnosing odorous skin and/or odorous sweat.

Preferably, the invention relates to the use of dermcidin, and more particularly of the isoform 1 or 2 thereof, an analogue or a fragment thereof and/or preferably at least one peptide in accordance with the invention, at least one nucleic acid sequence coding for a peptide in accordance with the invention, as a biomarker for evaluating the level of odour of the skin and/or of sweat.

The invention also relates to a process for screening active agents that are capable of modulating the expression or activity, especially biological, of said peptide.

Dermcidin

Dermcidin/Protease Inducing Factor (DCD/PIF) is a 110-aa protein comprising a 19-aa signal peptide and whose gene is located on chromosome 12, locus 12q13.1 and which is constitutively expressed in the sweat glands (Rieg, Garbe *et al.,* 2004). Furthermore,

two isoforms are listed in the UniProt base, a shorter one, isoform 1 (DCD-1), and a longer one, isoform 2 (DCD-2). It is secreted in sweat (Schittek, Hipfel *et al.,* 2001). After proteolytic post-translational processing (essentially by cathepsin D) which takes place in sweat (Baechle, Flad *et al.,* 2006), the protein precursor gives rise to numerous peptides whose length ranges from 25 to 48 aa (Flad, Bogumil *et al.,* 2002). Some of these peptides show antimicrobial activity against microorganisms such as *S. aureus*, *E. coli*, *Enterococcus faecalis*, *Candida albicans*, etc. The antimicrobial peptides are derived from the C-terminal part of the protein. The activity of these peptides is independent of their charge (Steffen, Rieg *et al.,* 2006) and is thought to proceed via a step of interaction with bacterial phospholipids (Li, Rigby *et al.,* 2009). The N-terminal part of the protein consists of a biologically active factor that promotes cell survival (Cunningham, Hodge *et al.,* 1998). The decrease in DCD observed in the sweat of atopic skin types may partly explain the microbial susceptibilities of this skin type (Rieg, Steffen *et al.,* 2005). Some of its antimicrobial fragments and also of its N-terminal part are capable of stimulating the production of cytokines/chemokines via keratinocytes or other cell types involving it even more in the regulation of cutaneous immunity (Watchorn, Dowidar *et al.,* 2005; Niyonsaba, Suzuki *et al.,* 2009). A recent publication mentions the use of DCD as a particularly sensitive specific marker of the presence of traces of sweat by RT-PCR or by ELISA that can be used in the medico-legal field (Sakurada, Akutsu *et al.,* 2009).

Amino acid and nucleic acid sequences

dermcidin or preproteolysin (DCD) is a 110-amino acid protein (SEQ ID NO: 1) comprising a 19-amino acid signal peptide (SEQ ID NO: 3) whose gene is located on chromosome 12, locus 12q13.1. Two isoforms of this protein are listed, one being the shorter one, isoform 1 (SEQ ID NO: 4), the other being the longer one, isoform 2 (SEQ ID NO: 5).

After cleavage of the signal peptide, dermcidin (DCD) is a 90-amino acid protein having the sequence SEQ ID NO: 2.

After proteolytic post-translational maturation, essentially with cathepsin D, which takes place in sweat (Baechle, Flad *et al.*, 2006), this protein precursor gives rise to numerous peptides whose length ranges from 25 to 48 aa (Flad, Bogumil *et al.*, 2002).

Among these peptides, the inventors have discovered that some of them are greatly under-expressed in odorous sweat.

Dermcidin 1 (DCD1)	SEQ ID NO 4
SSLLEKGLDGAKKAVGGLGKLGKDAVEDLESVGKGAVHDVKDVLDSVL	SEQ ID NO 6
AVEDLESVGKGAVH	SEQ ID NO 7
AVHDVKDVLDS	SEQ ID NO 8
DVKDVLDS	SEQ ID NO 9
ESVGkGAVHDVKDVLDSV	SEQ ID NO 10
VEDLESVGkGAVHDVKDVL	SEQ ID NO 11
VHDVKDVLD	SEQ ID NO 12
AVHDVkDVLDS	SEQ ID NO 13
GAVHDVkDVLDS	SEQ ID NO 14
GkDAVEDLESVGkGA	SEQ ID NO 15
GKGAVHDVKDVLDS	SEQ ID NO 16
lESVGkGAVHDVkD	SEQ ID NO 17
SVGkGAVHDVkDVLDSV	SEQ ID NO 18
VEDLESVGkGAVHDV	SEQ ID NO 19
Dermcidin 2 (DCD2)	SEQ ID NO 5
SSLLEKGLDGAKKAVGGLGKLGKDAVEDLESVGKGGEERLVFGAPVNLTSIPLTSVSRP	SEQ ID NO 20
APVNLTSIPLTSVSRP	SEQ ID NO 21
ESVGkGGEER	SEQ ID NO 22
FGAPVNLTSIPLTSVSRP	SEQ ID NO 23
VFGAPVNLTSIPLTSVSRP	SEQ ID NO 24
LESVGKGGEER	SEQ ID NO 25
GAPVNLTSIPLTSVSRP	SEQ ID NO 26

Among the peptides derived from dermcidin maturation, as described in US 2008/020 976, some show antimicrobial activity against various microorganisms, such as *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis* or *Candida albicans*. The antimicrobial peptides are derived from the C-terminal part of the protein and do not correspond to all of the identified peptides represented by SEQ ID NO 6 to SEQ ID NO 26.

In accordance with the invention, the expression "analogue of an amino acid sequence" is intended to denote any amino acid sequence having at least 85%, preferably at least 90%, more preferentially at least 95% and even more preferably at least 99% sequence identity with said sequence, and biological activity of the same nature.

The expression "biological activity of the same nature" with regard to an amino acid sequence according to the invention means the antimicrobial properties or the properties of stimulation of cell survival and/or proliferation usually attributed to dermcidin.

The sequence identity may be determined by visual comparison or by means of any information technology tool generally used in the field, such as the Blast programs available on www.ncbi.nlm.nih.gov and used with the default parameters.

An analogue in accordance with the invention may be a peptidomimetic agent.

An analogue of an amino acid sequence of the invention may result from modifications derived from mutation or variation in the peptide sequences according to the invention originating either from the deletion or insertion of one or more amino acids, or from the substitution of one or more amino acids, or alternatively from alternative splicing. Several of these modifications may be combined.

Advantageously, an analogue of an amino acid sequence of the invention may comprise conservative substitutions relative to this amino acid sequence.

As examples of mutations that may be considered in the present invention, mention may be made, in a non-exhaustive manner, of the replacement of one or more amino acid residues with amino acid residues having a similar hydropathic index, without, however, substantially affecting the biological properties of the polypeptide. The hydropathic index is an index assigned to amino acids according to their hydrophobicity and their charge (Kyte *et al.* (1982), J. Mol. Biol., 157: 105).

An amino acid sequence or an analogue thereof targeted by the present invention may be an amino acid sequence that has undergone one or more post-translational maturations.

The term "post-translational maturation(s)" is intended to encompass all the modifications that an amino acid sequence is liable to undergo after its synthesis in a cell, for instance one or more phosphorylations, deamidation, one or more thiolations, one or more acetylations, one or more glycosylations, one or more lipidations, such as a farnesylation or a palmitoylation, a structural rearrangement such as disulfide bridge formation and/or cleavage within the peptide sequence.

An analogue of an amino acid sequence moreover has substantially the same biological activity as this amino acid sequence.

It is moreover known that a primary amino acid sequence may comprise sites specifically recognized by enzymes of protease type, such as trypsin, which, once the recognition of these sites is effective, will induce cleavage of the sequence by proteolysis. This proteolysis results in the generation of various peptides, or fragments of amino acid sequences of the invention.

Consequently, the invention also covers fragments of dermcidin or of the isoforms 1 and 2 thereof or peptides thereof, derived, where appropriate, from its proteolysis.

For the purposes of the invention, the term "fragment of an amino acid sequence" means any portion of the amino acid sequence in accordance with the invention comprising from 3 to 48 consecutive amino acids of said sequence.

According to one embodiment, an amino acid sequence that is suitable for use in the invention may be an amino acid sequence represented by a sequence chosen from SEQ ID NO: 4 to 26, especially from SEQ ID NO: 6 to SEQ ID NO: 26, or an analogue or fragment thereof.

According to another embodiment, a peptide that is suitable for use in the invention may also be a natural or synthetic amino acid sequence, which may be obtained, where appropriate, after enzymatic or chemical hydrolysis of dermcidin or by chemical or biological synthesis, or alternatively any natural or synthetic amino acid sequence whose sequence totally or partially comprises an abovementioned amino acid sequence.

A person skilled in the art can obtain an amino acid sequence in accordance with the invention by means of processes based on recombinant DNA, for instance those described in the manual *Molecular Cloning - A Laboratory Manual* (2nd edition), Sambrook *et al.*, 1989, Vol. I-III, Coldspring Harbor Laboratory, Coldspring Harbor Press, NY, (Sambrook).

According to one subject, the present invention relates, per se, to an isolated peptide represented by an amino acid sequence chosen from SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25 and/or SEQ ID NO: 26, or an analogue or fragment thereof.

The present invention also relates to cosmetic compositions comprising in a cosmetically acceptable medium an effective amount of at least one amino acid sequence of the invention.

More particularly, the invention relates to a cosmetic composition comprising a peptide represented by an amino acid sequence chosen from SEQ ID NO: 6 to SEQ ID NO: 26, or an analogue or fragment thereof.

The amounts of the various constituents of the compositions according to the invention are those conventionally used in the fields under consideration.

The amount of amino acid sequence, or of nucleic acid sequence of the invention, or of active agent in accordance with the invention contained in a composition of the invention, also known as the "effective amount", depends, of course, on the nature of the active agent and of the desired effect and may thus vary within a wide range.

To give an order of magnitude, a composition may contain an amino acid sequence, or an active agent in accordance with the invention, in an amount representing from 0.00001% to 5% of the total weight of the composition, in particular in an amount representing from 0.001% to 2% of the total weight of the composition and more particularly in an amount representing from 0.1% to 1% of the total weight of the composition.

For the purposes of the present invention, the term "effective amount" of a compound of the invention means an amount of this compound that is sufficient and necessary to obtain a desired effect, and more particularly to prevent and/or treat body odour.

For the purposes of the invention, the term "prevent" means reducing the risk of manifestation of a given phenomenon, i.e. in the present invention, body odour.

The cosmetic composition according to the invention may comprise, besides SEQ ID NO 4 or SEQ ID NO 5 or a peptide derived from these proteins, an analogue or a fragment thereof in accordance with the invention, deodorant or antiperspirant active agents conventionally used in deodorant or antiperspirant compositions.

Among the deodorant active agents, examples that may be mentioned include water-soluble zinc salts, such as zinc pyrrolidonecarboxylate (more commonly known as zinc pidolate), zinc sulfate, zinc chloride, zinc lactate, zinc gluconate and zinc phenolsulfonate,

and bactericides such as 2,4,4'-trichloro-2'-hydroxydiphenyl ether (Triclosan) or 3,7,11-trimethyldodeca-2,5,10-trienol (Farnesol).

Among the antiperspirant active agents, examples that may be mentioned include aluminium salts, such as aluminium chloride and aluminium hydroxyhalides, aluminium/zirconium hydroxyhalides, for instance hydroxyzirconyl salts, complexes of metals (such as aluminium or zirconium) with an amino acid (for instance glycine) and as described in patent US-3 792 068.

The cosmetic composition according to the invention is conventionally formulated according to the presentation form for which it is intended.

It is more particularly formulated in a cosmetically acceptable vehicle which may especially be essentially aqueous, or contain organic solvents and especially C_1-C_4 monoalcohols, preferably ethanol, to accelerate the evaporation of the product, or propylene glycol, dipropylene glycol or ethers thereof.
The cosmetic composition according to the invention may also be formulated as a water-in-oil or oil-in-water emulsion or as a water-in-oil-in-water triple emulsion (such emulsions are known and described, for example, by C. Fox in "Cosmetics and Toiletries" - November 1986 - Vol. 101 - pages 101-112).

The cosmetic composition according to the invention may also comprise cosmetic adjuvants chosen from fatty substances, gelling agents, emollients, softeners, antioxidants, opacifiers, stabilizers, antifoams, moisturizers, vitamins, fragrances, preserving agents, surfactants, fillers, sequestrants, polymers, propellants, acidifying or basifying agents, dyes, pigments, thickeners, or any other ingredient usually used in cosmetics for this type of application.

Needless to say, a person skilled in the art will take care to select this or these optional additional compounds such that the advantageous properties intrinsically associated with the cosmetic composition in accordance with the invention are not, or are not substantially, adversely affected by the envisaged addition(s).

The surfactants are preferably chosen from anionic, amphoteric and nonionic surfactants. The fatty substances may consist of an oil or a wax or a mixture thereof, petroleum jelly, paraffin, lanolin, hydrogenated lanolin or acetylated lanolin.

The cosmetic composition according to the invention may thus be in the form of a lotion, a cream or a fluid gel dispensed as an aerosol spray, in a pump-dispenser bottle or as a roll-on, in the form of a thick cream dispensed in a tube and in the form of a stick or a powder, and, in this regard, may contain ingredients and propellants generally used in products of this type that are well known to those skilled in the art.

Cosmetic use

The present invention relates to the cosmetic use of an effective amount of at least one amino acid sequence as an active agent for preventing and/or treating body odour.

According to another aspect, the present invention relates to a cosmetic, or non-therapeutic, process for preventing and/or treating body odour in an individual in need thereof, the process comprising at least one step consisting in administering to said individual at least one composition comprising as an active agent at least one amino acid sequence of the invention, especially as defined above.

A process or a use of the invention make it possible to prevent and/or treat body odour.

Preferably, a process of the invention may comprise the topical application to at least a part of the skin of an individual in need thereof, in particular to the skin of the armpits, the scalp and/or the feet, of at least one coat of a topical composition of the invention.

A cosmetic process according to the invention may be performed daily, for example at a rate of a single application per day or of an administration split into two or three times per day, for example once in the morning and once in the evening.

A cosmetic process according to the invention may be performed over a time period ranging from one week to several weeks, or even several months, this period moreover possibly being repeated after periods without treatment, for several months or even several years.

By way of example of a cosmetic process according to the invention, it is possible to envision application of a cosmetic composition of the invention, for example, at a rate of 1, 2 or 3 times per day, or more, and generally over an extended period of at least 4 weeks, or even 4 to 15 weeks, with, where appropriate, one or more periods of stoppage.

Biomarker

Unexpectedly, in the course of a differential proteomic study via the iTRAQ technique, the inventors observed, using liquid sweat collected from 24 healthy male individuals after 45 minutes in a sauna, that dermcidin (or DCD) and more particularly the isoform 1 thereof (DCD-1) proved to be a sensitive and specific biomarker of the level of body odour of the skin and/or of sweat.

More specifically, the inventors observed that the level of expression of peptides derived from SEQ ID NO 4 and SEQ ID NO 5 and identified by the sequences SEQ ID NO: 6 to SEQ ID NO: 26 were systematically reduced in the odorous sweat when compared with the non-odorous sweat.

To the inventors' knowledge, this antimicrobial skin surface protein and more particularly the isoforms thereof characterized by the sequence SEQ ID NO 4 and SEQ ID NO 5 and even more particularly the peptides identified by SEQ ID NO 6 to SEQ ID NO 26 have never been classified as a variant of odorous sweat and even less so as one of the most pertinent biomarkers emerging from studies of this type. To the inventors' knowledge, the isoform 2 has itself never been described in sweat.

It is known that sweating decreases with age (Anderson and Kenney 1987; Kenney and Fowler 1988) and that dermcidin is a sweat protein (Schittek, Hipfel *et al.*, 2001). However, the experimental data obtained by the inventors show, unexpectedly, that

there is a specific deficit in the expression and/or maturation of the peptides identified by SEQ ID NO 6 to SEQ ID NO 26 in odorous sweat, since they are under-represented in the studied samples.

The present invention relates to the use of at least one amino acid sequence of the invention as a biomarker of the level of body odour of the skin.

Preferably, a use in accordance with the invention makes it possible to characterize the level of body odour.

For the purposes of the invention, the term "biomarker" means a molecule or the activity of a molecule whose presence, content or degree of activity is characteristic of a biological, physiological or pathological process, or of the impact or effect induced by the administration of an active agent or of a physical treatment on such a process.

According to one embodiment, a decrease in the activity, expression or maturation of said biomarker may be indicative of odorous skin and/or of odorous sweat.

In a use in accordance with the invention, a decrease or an increase in the activity, expression or maturation of said biomarker may be determined by comparison with a reference measurement obtained according to any method known to those skilled in the art.

A "reference measurement" with regard to a given parameter is a qualitative or quantitative measurement of this parameter performed under "control" or "normal" conditions, for example determined in a reference sample, or determined in a sample in the absence of a treatment presumed to have an effect on the parameter.

For example, a reference measurement for an amino acid sequence or a nucleic acid sequence in accordance with the invention may be a quantitative or qualitative value relative to the expression, maturation or activity of said sequences determined in a sample of non-odorous or odorous skin or sweat before a cosmetic treatment.

Preferably, a reference measurement is a statistical measurement, i.e. a measurement that has been repeated on various samples so as to obtain an average.

The reference measurement may be taken in parallel with or sequentially to the test measurement.

It may also be a "historical" measurement, i.e. a measurement taken prior to the test measurement, and stored, for example, in a database, for the purpose of subsequent use.

A comparison of the test measurement with a reference measurement, and an observation of a deviation or an absence of deviation between the two measurements makes it possible to draw information regarding the measured parameter for example the decrease or increase in the expression, maturation or activity of an amino acid sequence in accordance with the invention.

Such information may be subsequently used to determine the odorous nature of a skin and/or sweat and to identify the specific disequilibria thereof.

According to one embodiment, the invention relates to a process, in particular an *in vitro* or *ex vivo* process, for characterizing the level of body odour of the skin and/or of sweat.

The qualitative or quantitative measurement of the expression, maturation or activity of an amino acid sequence of the invention may be performed using any method known to those skilled in the art.

By way of methods for detecting the expression, maturation or activity of an amino acid sequence, mention may be made of Western blotting, slot blotting, dot blotting, ELISA (Enzyme Linked Immuno-Sorbent Assay) methods of singleplex or multiplex type, proteomic or glycomic methods, methods for staining polypeptides in a polyacrylamide gel with a silver-based stain, with Coomassie blue or with SYPRO, immunofluorescence methods, UV absorption methods, immunohistochemical methods by conventional, electron or confocal microscopy, FRET (fluorescence resonance energy transfer) methods, TR-FRET (time resolved FRET) methods, FLIM (fluorescence lifetime imaging microscopy) methods, FSPIM (fluorescence spectral imaging microscopy) methods, FRAP (fluorescence recovery after photobleaching) methods, reporter gene methods, AFM (atomic force microscopy) methods, surface plasmon resonance methods, microcalorimetry methods, flow cytometry methods, biosensor methods, radioimmunoassay (RIA) methods, isoelectric focusing methods, and enzymatic tests, methods using peptide chips, sugar chips, antibody chips, mass spectrometry methods, of iTRAQ, MRM or SWATH type, and spectrometry methods of MALDI-TOF type.

More generally, immunoenzymatic assay methods using protein solutions, which are more quantitative and sensitive, may in particular be used. These ELISA-type methods combine pairings of target-antigen-specific capture antibody and detection antibody. Commercial antibodies or specifically developed monoclonal, polyclonal or

recombinant antibodies may be used. High-capacity multiplex ELISA techniques may also be used. Mention may thus be made of the multiplex approach of the type such as antibodies on Luminex beads (for example Bioplex from Bio-Rad) or of the type such as antibodies on a flat surface (antibody arrays) (for example the approach proposed by the company MesoScale Discovery). In a recent approach, a novel technique based on "quench body" antibodies proposed by the Japanese company Ushio makes it possible to use only an antibody.

In particular, it may be advantageous to detect the expression of an amino acid sequence of the invention by means of an antibody, where appropriate in a marked or "tagged" form. Such an antibody may be marked with a directly detectable substance (for example with a GFP tag) or a substance that is detectable by reaction with another reagent.

The term "antibody" is intended to denote, generally, monoclonal or polyclonal antibodies, and also immunoglobulin fragments capable of binding an antigen and which can be produced by any genetic engineering technique known to those skilled in the art or by enzymatic or chemical cleavage of an intact antibody.

An antibody that may be used as a tool for evaluating the condition of an epidermis may be obtained via any process known to those skilled in the art, as described in *Antibodies: A Laboratory Manual*", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990).

According to a preferred embodiment, it may be advantageous to detect the expression of an amino acid sequence of the invention by means of an "iTRAQ" differential proteomic method.

Such a method is known to those skilled in the art and may be advantageously performed as described in the examples below.

Preferably, the determination of a state of the skin and/or of sweat, or characterization of the efficacy of a cosmetic treatment of the skin and/or of sweat may be performed by measuring the variation in the expression of an amino acid sequence of the invention, and preferably represented by a sequence chosen from SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, or an analogue or fragment thereof.

The processes of the invention are particularly advantageous since the implementation thereof does not require recourse to an invasive technique. A sample of liquid sweat may thus be directly taken and analysed via a conventional analytical technique known to those skilled in the art.

Advantageously, one of the markers of the invention may be used for the purposes of more efficient and more rigorous preclinical selection, of individuals, with a view to evaluating the efficacy of a cosmetic treatment or of a cosmetic active agent for reducing body odour.

Similarly, a biomarker of the invention may advantageously be used for evaluating the efficacy of an active agent, *in vitro*, *ex vivo* or *in vivo*.

Similarly, a biomarker of the invention may be used for establishing personalized advice for a cosmetic treatment for an individual according to said individual's skin biomarker expression profile.

According to yet another of its subjects, the present invention relates to the use (i) of at least one amino acid sequence of the invention, for screening active agents or physical treatments that are capable of modulating the activity, expression or maturation of said amino acid sequence.

For the purposes of the invention, the term "expression" with regard to an amino acid sequence, for example a protein or a peptide, means its content or the variation of its content relative to a reference.

For the purposes of the invention, the term "maturation" with regard to an amino acid sequence, for example a protein or a peptide, means the modifications that follow their synthesis in a cell environment. For example, in the case of an amino acid sequence, the term "maturation" means the post-translational modifications, such as glycosylation or farnesylation of certain amino acids, or the proteolytic steps leading to the removal of "signal" or "secretory" sequences or to the release of sequences having particular biological properties. For the purposes of the invention, the term "activity" means, with regard to an amino acid sequence, for example a protein or a peptide, the biological activity of the amino acid sequence, where appropriate after maturation, such as an enzymatic activity, an agonist or antagonist activity with respect to a receptor, an

enzyme-activating or -inhibiting activity, a "structural" activity, or an antimicrobial activity.

According to another of its subjects, the present invention relates to the use (i) of at least one amino acid sequence of the invention, for characterizing the level of body odour of the skin and/or of sweat.

Also, according to another advantage, the present invention makes it possible to propose novel active agents that are suitable for preventing and/or treating odorous skin and/or odorous sweat.

Screening

There is still a need for novel tools for screening active agents or physical treatments that are particularly useful for preventing and/or treating odorous skin and/or odorous sweat.

The aim of the present invention is to satisfy these needs.

According to one of its aspects, the present invention relates to the use of an amino acid sequence, for the screening or in a process of screening, in particular *in vitro* or *ex vivo*, of active agents that are particularly suitable for preventing and/or treating odorous skin and/or odorous sweat.

The screening active agents may especially be suitable for preventing and/or treating odorous skin and/or odorous sweat.

A use or a process of the invention may comprise the comparison of a measurement of the activity, expression or maturation of an amino acid sequence or of a nucleic acid sequence in accordance with the invention, with a reference measurement.

A reference measurement may be as previously defined.

In particular, a reference measurement may be a quantitative or qualitative value relating to the expression, maturation or activity of said sequences, determined in a sample in the absence of active agent or of physical treatment tested.

Thus, a reference measurement may be obtained by repeating the steps of a process of the invention, and especially steps a), b) and c) of a process of the invention as defined previously, in the absence of biological or chemical compounds to be tested.

A comparison of the test measurement with a reference measurement, and an observation of a deviation or an absence of deviation between the two measurements makes it possible to draw information regarding the effect of the active agent tested.

The quantitative or qualitative determination of the expression, maturation or activity of an amino acid sequence of the invention may be performed via any method known to those skilled in the art, and especially as described previously.

According to one embodiment, the screening of an active agent that is capable of modulating the activity of an amino acid sequence of the invention may be performed by measuring the activity or the expression of a target molecule belonging to the signalling or metabolic pathways in which said amino acid sequence may be involved, for instance a reporter gene system.

According to one embodiment, a process of the invention may be performed in an acellular system, i.e. in a system which does not comprise cells but which reproduces cell functions, or in an isolated cell sample.

A process in accordance with the invention may be performed on an isolated cell sample, an acellular sample, on an isolated amino acid sequence or on an isolated nucleic acid sequence of the invention, especially from a sample of liquid sweat.

Preferably, the screening of an active agent or of a physical treatment may be performed by measuring the variation of the expression, in the presence and in the absence of the screened active agent, of an amino acid sequence of the invention, and preferably represented by the sequence chosen from SEQ ID NO: 4 to SEQ ID NO: 26, or an analogue or fragment thereof.

The active agents derived from a screening according to the invention may be advantageously used for cosmetic purposes, especially for odorous skin and/or odorous sweat.

According to one embodiment, an active agent of the invention may be an agent that stimulates the activity, expression or maturation of an amino acid sequence of the invention.

For the purposes of the present invention, the term "one" should be understood, unless otherwise indicated, as meaning "at least one".

The examples and figures below are presented as non-limiting illustrations of the invention.

EXAMPLE 1: iTRAQ proteomic study of the expression profile of dermcidin in odorous and non-odorous sweat

1- Materials and methods

a- iTRAQ protocol

The detection of the expression of dermcidin (DCD), isoforms thereof and peptides thereof was performed by means of the iTRAQ (Isobaric Tagging Reagents for Quantitative Proteomic Analysis) method developed by the company Applied Biosystems. This method allows the quantification of peptides prelabelled with an isobaric tag. Four different tags exist and up to four different types of sample can be compared in the same LC/MS-MS analysis.

The principle of this method is as follows:

- Digestion of protein extracts and labelling:

In a first stage, each protein extract is digested with a proteolytic enzyme: trypsin.

In a second stage, each peptide mixture obtained is labelled with an isobaric tag having a total mass of 145, comprising a "reporter" group of mass 114, 115, 116 or 117, and a "balance" group of mass 31, 30, 29 or 28, linked together via an MS fragmentation site.

The labelling is obtained by reaction of the peptide-reactive group of each tag with the primary amines of the peptides (N-terminal end of the peptides or the side chain of lysines or tyrosines.

- LC/MS-MS analysis and quantification:

After the labelling step, the samples are pooled and analysed by mass spectrometry. A given peptide, present in several samples, will have an identical parent

mass, but its MS/MS fragmentation spectrum will generate the mass of the reporter group that is characteristic for each of the iTRAQ reagents. Comparison of the intensity of each reporter ion (114, 115, 116 or 117) then allows quantification of the peptide.

The iTRAQ method is more precisely described by Zieske (J. Exp. Bot., 2006, 57: 1501) or Wiese *et al.* (Proteomics, 2007, 7: 340).

b- Collection and treatment of the sweat samples

The liquid sweat was collected from healthy male individuals after 45 minutes in a sauna. 24 individuals were selected for this peptidomic analysis: 12 UAO- individuals (odour intensity between 1 and 3.5) and 12 UAO+ individuals (odour intensity between 6 and 9). The samples collected are stored at -20°C before the analysis.

In this study, we had to make a comparison of odorous versus non-odorous individuals, with 12 individuals/group, we made the choice of performing two iTRAQ experiments with four markers with the following four biological replicates:

Group NO

pool 1 (UAO- pool 1): individuals 6, 15 and 30
pool 2 (UAO- pool 2): individuals 28, 36 and 40
pool 3 (UAO- pool 3): individuals 12, 17 and 26
pool 4 (UAO- pool 4): individuals 25, 27 and 34

Group O

pool 1 (UAO+ pool 1): individuals 13, 33 and 35
pool 2 (UAO+ pool 2): individuals 18, 23 and 41
pool 3 (UAO+ pool 3): individuals 31, 46 and 47
pool 4 (UAO+ pool 4): individuals 32, 44 and 45

These collected sweat examples then undergo proteomic analysis by means of the "isobaric marking" technique described previously, using the iTRAQ Reagents Multiplex kit (4352135) from Applied Biosystems, in accordance with the manufacturer's instructions.

c) Results

The significant threshold was set at:

- Less than or equal to 0.8 for the peptides under-expressed in the odorous individuals compared with the non-odorous individuals.
- Greater than or equal to 1.2 for the peptides over-expressed in the odorous individuals compared with the non-odorous individuals.

Peptide sequence		**N**	**Mean ratio**
Sequences of DCD1	**SEQ ID NO 4**		
SSLLEKGLDGAKKAVGGLGKLGKDAVEDLESVGKGAVHDVKDVLDSVL	SEQ ID NO 6		
AVEDLESVGKGAVH	SEQ ID NO 7	**3**	**0.43**
AVHDVKDVLDS	SEQ ID NO 8	3	0.33
DVKDVLDS	SEQ ID NO 9	3	0.56
ESVGkGAVHDVKDVLDSV	SEQ ID NO 10	3	0.23
VEDLESVGkGAVHDVKDVL	SEQ ID NO 11	3	0.36
VHDVKDVLD	SEQ ID NO 12	3	0.6
AVHDVKDVLDS	SEQ ID NO 13	3	0.33
GAVHDVKDVLDS	SEQ ID NO 14	3	0.47
GKDAVEDLESVGKGA	SEQ ID NO 15	4	0.56
GKGAVHDVKDVLDS	SEQ ID NO 16	3	0.23
LESVGKGAVHDVKD	SEQ ID NO 17	3	0.23
SVGKGAVHDVKDVLDSV	SEQ ID NO 18	4	0.43
VEDLESVGKGAVHDV	SEQ ID NO 19	3	0.37
Sequences of DCD2	SEQ ID NO 5		
APVNLTSIPLTSVSRP	SEQ ID NO 21	3	0.43
ESVGKGGEER	SEQ ID NO 22	**3**	**0.5**
FGAPVNLTSIPLTSVSRP	SEQ ID NO 23	4	0.43
VFGAPVNLTSIPLTSVSRP	SEQ ID NO 24	4	0.46
LESVGKGGEER	SEQ ID NO 25	3	0.43
GAPVNLTSIPLTSVSRP	SEQ ID NO 26	3	0.47
N = Number of repetitions of the experiments			

An under-expression of the following sequences SEQ ID NO 7 to SEQ ID NO 19 of the isoform DCD-1 and SEQ ID NO 21 to SEQ ID NO 26 of the isoform DCD-2 is clearly observed in the samples of odorous sweat with expression ratios of less than 0.8.

This confirms their use as biomarkers for defining the level of body odour.

EXAMPLE 2: ELISA study of the expression profile of dermcidin in odorous and non-odorous sweat (Figure 1).

The samples of underarm sweat (odorous and non-odorous) were centrifuged for 8 minutes at 4°C in order to remove the corneocytes and the bacteria. The supernatants were stored at -20°C until the analysis.

ELISA Assay

The amount of dermcidin was measured in 25 µl of supernatants. The capture antibody (AbDserotec) was fixed to the bottom of the wells at a concentration of 200 µg/ml on 96-well plates (MesoScale).

The calibration curve was established with concentrations of DCD-1 ranging from 0.4 to 25 ng/ml. The wells were saturated in buffer for one hour at room temperature.

25 µl of the samples were added to each well, each measurement being performed in triplicate. The plate was agitated for one hour at room temperature and then washed five times with Tris washing buffer. The plates were then incubated for one hour at room temperature with 25 µl of primary antibody at a concentration of 1 µg/ml in each well (polyclonal goat SC27466) and then washed five times with Tris washing buffer. They were finally incubated for one hour at room temperature with 25 µl of secondary antibody at a concentration of 1 µg/ml (donkey anti-goat sulfo-tagged antibody).

The plates were washed five times with Tris washing buffer before adding to each well 150 µl of 1X READ buffer T. The plates were read with a Sector Imager 6000 machine.

The amount of DCD-1 was measured from the calibration curve in ng/ml. The inventors showed that the protein DCD-1 was significantly under-expressed in the samples of odorous sweat (Figure 1).

CLAIMS

1. Cosmetic use of at least one amino acid sequence chosen from SEQ ID NO 4 to SEQ ID NO 26, an analogue or fragment thereof, for preventing or inhibiting the development of body odour associated with human perspiration.

2. Cosmetic use according to Claim 1, in which said amino acid sequence chosen from SEQ ID NO: 4 to SEQ ID NO: 26, or an analogue or fragment thereof is chosen from SEQ ID NO: 6 to SEQ ID NO: 26, or an analogue or fragment thereof.

3. Cosmetic process for preventing and/or inhibiting the development of body odour associated with human perspiration, comprising the application to the skin of a composition comprising, in a cosmetically acceptable medium, at least one amino acid sequence or a composition containing it chosen from SEQ ID NO 6 to SEQ ID NO 26, or an analogue or fragment thereof.

4. Cosmetic use according to any one of the preceding claims, characterized in that said sequence is used as an active agent in a cosmetic composition.

5. Use (i) of at least one amino acid sequence chosen from SEQ ID NO 4 to SEQ ID NO 26 and preferably chosen from SEQ ID NO 6 to SEQ ID NO 26, or an analogue or fragment thereof, as a biomarker of non-odorous skin.

6. *in vitro* or *ex vivo* process for characterizing odorous skin of an individual, comprising at least the steps consisting in:

a) performing, in an isolated sample of skin of an individual, a qualitative or quantitative measurement of the expression, maturation or activity of the biomarker as defined in Claim 5,

b) comparing said measurement performed in step a) with a reference measurement, and

c) concluding that a reduction in the activity, expression or maturation of said biomarker relative to said reference measurement is indicative of odorous skin in this individual.

7. Process for the *in vitro* or *ex vivo* screening of active agents that are capable of preventing and/or treating odorous skin, modulating the activity, expression or maturation of an amino acid sequence as defined according to the invention, or of a nucleic acid sequence as defined according to the invention, comprising at least the steps consisting in:

a) placing said amino acid sequence or said nucleic acid sequence under conditions favourable for the activity, expression or maturation of said sequences,

b) placing said amino acid sequence or said nucleic acid sequence in contact with at least one active agent to be tested, or exposing said amino acid sequence or said nucleic acid sequence with a physical treatment to be tested,

c) performing a qualitative or quantitative measurement of the expression, maturation or activity of said amino acid sequence or of said nucleic acid sequence,

d) comparing said measurement with a reference measurement, and

e) concluding that the increase in the activity, expression or maturation of an amino acid sequence in accordance with the invention is indicative of the efficacy of said active agent for preventing or treating odorous skin and/or odorous sweat.

8. Cosmetic use according to any one of the preceding claims, characterized in that the body odour is that of the armpits and/or of the feet.

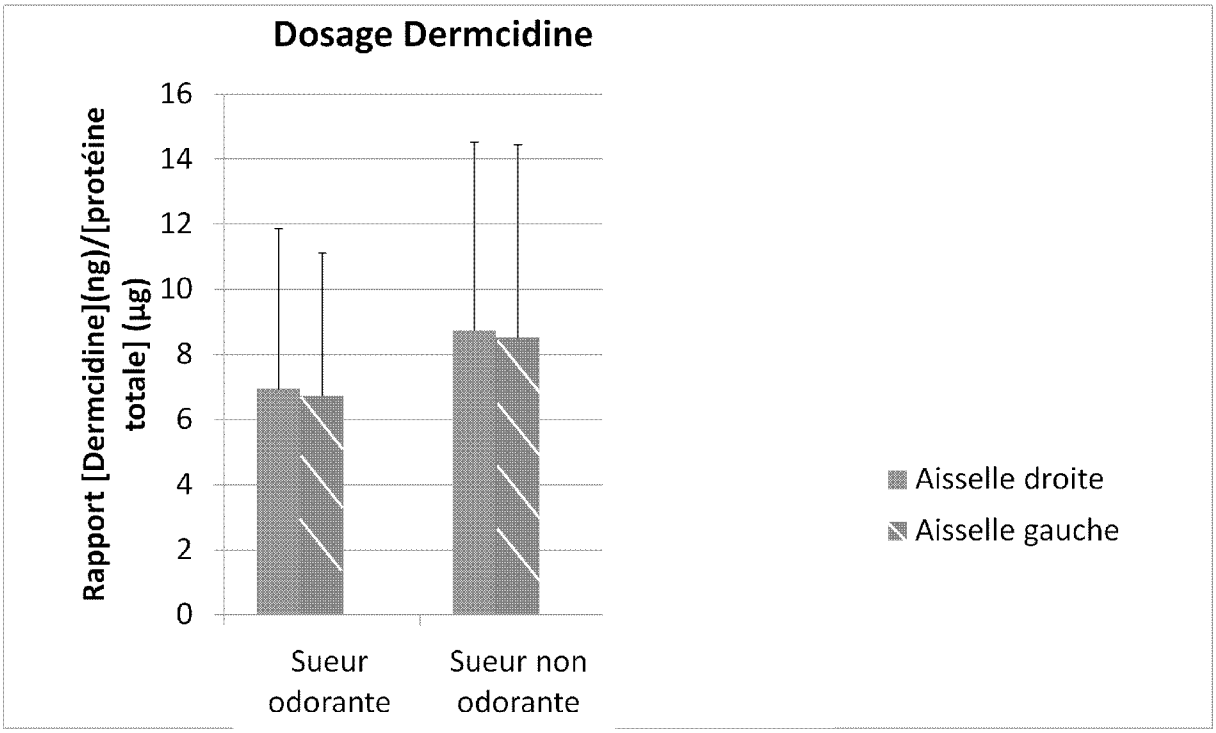
Dosage Dermcidine
Rapport [Dermcidine](ng)/[protéine totale] (µg)
16
14
12
10
8
6
4
2
0
Sueur odorante
Sueur non odorante
Aisselle droite
Aisselle gauche

Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/063655

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K8/64 A61Q15/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, Sequence Search, EMBASE, EMBL, INSPEC, CHEM ABS Data, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	pages 2-3 page 9 pages 14-18 pages 21,24; claims; figures; examples	1-8

X	FR 2 980 360 A1 (OREAL [FR]; NESTEC SA [CH]) 29 March 2013 (2013-03-29)	1,2
Y	pages 2-5; claims; examples	1-8

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2014	14/11/2014

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/063655

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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