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(54) Title: MODULATION OF AKT-DEPENDENT RESPONSE TO PREVENT RESTENOSIS

(57) Abstract: Restenosis of vessels after angioplasty, and narrowing of implanted blood vessels, such as arteries, veins, vascular grafts, and conduits, following implantation, is prevented or alleviated by inhibiting or modifying Akt activity in the cells of the vessel. The inhibition of Akt activity is achieved by administering to the blood vessel wall an effective amount of an agent capable of inhibiting Akt activity. The Akt inhibitor may be coated on a stent that is positioned within the blood vessel.

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PATENT APPLICATION

TITLE: MODULATION OF AKT-DEPENDENT RESPONSE TO PREVENT RESTENOSIS

RELATIONSHIP TO OTHER APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 60/328,803, filed October 15, 2001, the entire disclosure of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention:

[0002] This invention relates to the prevention of restenosis of arteries or veins after percutaneous coronary intervention. This invention also relates to the prevention of stenosis of conduits, and to stabilize cells deployed on stents, on vascular grafts, or on conduits, that are to be used as platforms to deliver therapeutic factors to tissues. More particularly to the use of pharmacological or molecular approaches able to modulate cellular Akt functions and aimed to prevent restenosis.

Brief Description of the Prior Art:

[0003] Coronary angioplasty has become an important method of treating narrowed (stenotic) arteries supplying the heart or the legs. Although the initial success rate of coronary angioplasty for opening obstructed coronary arteries exceeds 95%, restenosis occurs at the site of angioplasty in 25-50% of patients within six months, regardless of the type of angioplasty procedure used. Although the use of stents has appreciably reduced the rate of stenosis, even with this treatment strategy restenosis occurs in 5 to 20% of patients. Importantly, when restenosis occurs within a stent, the chance that restenosis will recur is very high. Thus, the problem of restenosis is still formidable, despite recent advances in reducing its incidence.

[0004] Two primary mechanisms appear to be involved in the development of restenosis. First, recoil of the vessel wall (negative remodeling) leads to gradual narrowing of the vessel lumen. Second, an exaggerated healing response of medial and/or adventitial smooth muscle

cells (SMCs) to vascular injury occurs, which involves the excessive proliferation of SMCs and the migration of SMCs to the sub-intima, where they continue to proliferate and begin to secrete extracellular matrix. These processes involving SMCs cause the neointimal mass to expand and gradually encroach upon the lumen of the vessel. Ultimately the expanding lesion narrows the vessel, increases the resistance to blood flow, and causes ischemic symptoms. In the absence of stenting, both remodeling and an expanding neointima contribute to restenosis. When stents are deployed, negative vascular remodeling is prevented and restenosis occurs only as a result of the expanding neointimal mass. Given these pathophysiologic mechanisms, the problem of controlling restenosis occurring with stent deployment becomes largely the problem of controlling the development of the neointimal mass. Similar mechanisms relate to the development of stenosis of vascular grafts and conduits.

[0005] Many attempts have been made and reported to be successful in inhibiting neointima development in various experimental models. However, with the notable exception of brachytherapy (and, more recently, two agents delivered via stents-see below), almost invariably their translation to clinical interventions has been without success. These strategies have included the oral administration of drugs, their systemic administration, and their local delivery. Therapeutic strategies began to focus on local delivery as it became apparent that high concentrations of active agent were needed at the target site. It would be very unlikely that such high concentrations could be achieved by any other approach than local delivery. Unfortunately, despite years of development and testing, the consensus is that catheter delivery systems are too inefficient to provide a high probability of success. Only one percent or less of the delivered product appears to persist for any period of time in the vessel wall.

[0006] The concept that drugs could be incorporated into stent coatings has become popularized, with mixed results. Preliminary very encouraging results using stents having a coating impregnated with either taxol or its derivatives, or rapamycin, have been reported at several international meetings.

[0007] The success of these drugs is based on the cellular and molecular effects on modulation of the response of cells to mitogens and cytokines, and proteins controlling progress of cells through the cell-cycle.

Proteins controlling progress of cells through the cell-cycle:

[0008] SMCs within the vessel wall are normally in a quiescent state. Immediately after injury, however, early response genes are expressed and the cells enter the cell cycle, wherein

their replication is tightly regulated by an array of cell cycle regulatory proteins acting conjointly and in sequence at various points of the cycle. These regulatory proteins include cyclin-dependent kinases, which phosphorylate critical regulatory proteins, and the interaction of such kinases with cyclin-dependent kinase inhibitors, such as p16, p21, $p27^{K1}p'$, $p57^{K1}pz$. Changes in the levels of these inhibitors exert marked effects on cell cycle progression through inhibition of critical phosphorylation reactions.

[0009] One of the proteins involved in cell cycle progression that is regulated by phosphorylation is the tumor suppressor protein retinoblastoma protein (Rb). In the hypophosphorylated state Rb complexes with DNA binding and gene activating proteins, such as E2F thereby exerting an inhibiting effect on cell cycle progression in Go/mid G1. Upon phosphorylation, the Rb/E2F complex dissociates, freeing E2Fto bind to its DNA binding sites and consequently stimulate the transcription of genes inducing progression to the S phase of the cell cycle.

[0010] Akt (Akt/PKB), the cellular homolog (c-Akt) of a viral oncogene (v-Akt) of an avian transforming retrovirus AKT, is a protein kinase with similarities to both protein kinase C (PKC) and protein kinase A (PKA) (hence the name PKB). The lipid products of PI3K bind with high affinity and specificity to the Akt/PKB PH domain, with a preference of Ptdlns-3,4-P2 over Ptdlns-3,4,5-P3 both in vitro and in vivo. In addition to lipid binding, phosphorylation of a number of key residues in the catalytic kinase core serves to potently activate the enzyme. In the case of Akt/PKB, phosphorylation of Thr-308 in the activation loop and Ser-473 in the C-terminal hydrophobic motif is required for catalytic activity. Phosphorylation of both sites is mitogen- and PI3K-dependent, whereas an additional third site, Thr-450, appears to be constitutively phosphorylated in resting cells.

[0011] The phosphoinositide-dependent kinase-I (PDK-l) specifically phosphorylates Thr-308 in vivo. Phosphorylation of Ser-473 is also required for Akt/PKB activity, and a putative enzyme named PDK-2 was predicted to exist and be responsible for catalyzing this reaction. Negative regulation of Akt/PKB also appears to play an important role in signaling. Inactivation of Akt/PKB also occurs by removal of the Ptdlns-3,4,5-P3 signal, and this occurs by the action of the tumor suppressor PTEN, a Ptdlns-3,4,5-P3 phosphatase.

[0012] Once activated, Akt/PKB leaves the plasma membrane to phosphorylate intracellular substrates. Consistent with this, translocation of Akt/PKB to the nucleus has been reported, and this undoubtedly links Akt/PKB to phosphorylation of transcription factors such as cAMP-responsive element-binding protein (CREB), E2F, NF-B, and forkhead transcription

factors. The phosphorylation of the repressor of transcription, 4E-BP protein (eucaryotic initiation factor-4Ebinding protein), is also Akt/PKB-dependent, leading to mRNA translation. Other components of the translational machinery, including p70S6K, and the target of rapamycin (TOR) are Akt/PKB targets, although the precise role of Akt/PKB in these pathways is presently unclear.

[0013] Little is known about the involvement of Akt in proliferation. Very recently, Akt activation was shown to be an essential step by which growth factors trigger cellular proliferation. The 70-kDa S6 protein kinases, referred to collectively as p70S6k, is the principal kinase that exerts translational control of mRNA transcripts and is required for growth factor-induced G1 progression. In some cell types, p70S6k appears to be an essential downstream effector of Akt. Mitogen-induced activation of p70S6k is necessary for expression of early-immediate genes such as c-fos, c-jun, and c-myc. Activation of p70S6k is required to control the levels of cell growth-associated proteins as c-myc, cyclin DI, cyclin A, p21 and PCNA; this effect determines duration of the G1 phase of the cell cycle.

[0014] One of the major functions of Akt/PKB is as a cell survival factor, and a number of proteins have been shown to mediate its anti-apoptotic function. The pro-apoptotic Bcl-2 family member BAD is phosphorylated and inactivated by Akt/PKB, leading to protection from apoptosis. Both the pro-apoptotic cysteine protease, caspase-9, as well as forkhead transcription factors such as FKHRL1, are potent at inducing apoptosis, an event that can be inhibited by Akt/PKB-mediated phosphorylation of both proteins.

[0015] Data has also emerged demonstrating that Akt/PKB has an important role in cellular migration.

[0016] In view of the above-described state of the art in prevention of restenosis in blood vessels after angioplasty or grafting, a need has continued to exist for methods of preventing stenosis in blood vessels after surgical intervention such as angioplasty or bypass grafting.

SUMMARY OF THE INVENTION

[0017] Advances in the treatment of restenosis after angioplasty, and in the patency of vascular grafts and conduits, have been achieved by this invention which generally comprises administering to the wall of a blood vessel in association with or after angioplasty or grafting of a substance capable of inhibiting or modifying the activity of Akt. The invention encompasses the direct administration of an inhibitory substance as well as the use of a cell-based platform to deliver an agent to a vessel or conduit, such as an artery or vein, in order to

modify and/or inhibit Akt activity.

[0018] Accordingly, it is an object of the invention to provide a method for preventing or alleviating restenosis of an artery or vein after angioplasty or grafting.

[0019] A further object is to provide a method for preventing or alleviating restenosis of an artery or a vein after angioplasty, wherein a stent implanted in the treated artery is coated with a composition incorporating a pharmacological or a molecular compound (or DNA or other vector containing DNA encoding a molecule that inhibits Akt activity) that is able to inhibit extracellular and intracellular Akt-dependent functions.

[0020] It is another object of the invention to provide a method using a cell-based platform for delivering agents for preventing or alleviating the development of restenosis of an artery or a vein after angioplasty, wherein a stent implanted in the treated artery is coated with a composition incorporating cells (either progenitor endothelial cells or stem cells, or other cells found to be able to deliver therapeutic substances) that have been genetically engineered so they now contain genes whose protein products inhibit extracellular and/or intracellular Akt-dependent functions.

[0021] It is a further object of the invention to provide a method that stabilizes cells used for a cell-based platform for delivering agents for preventing or alleviating the development of restenosis of an artery or a vein after angioplasty, wherein a stent implanted in the treated artery is coated with a composition incorporating cells (either progenitor endothelial cells or stem cells, or other cells found to be able to deliver therapeutic substances) that have been genetically engineered so they now contain genes whose protein products inhibit Akt-dependent functions, which therefore prevents such cells from excessively proliferating and migrating, and thereby preventing such cells from contributing to the restenosis process.

[0022] It is yet another object of the invention to provide a method for preventing or alleviating stenosis of the vessel or conduit after implantation, wherein a vessel or conduit is implanted in a patient and the vessel or conduit is coated with a composition incorporating a pharmacological or a molecular compound (or DNA or other vector containing DNA encoding a molecule that inhibits Akt activity), that is able to inhibit extracellular and intracellular Akt-dependent functions.

[0023] A still further object of the invention is to provide a method using a cell-based platform for delivering agents for preventing or alleviating the development of stenosis of the vessel or conduit after implantation, wherein a vessel or conduit is implanted in a patient and the vessel or conduit is coated with a composition incorporating cells (either progenitor endothelial cells

or stem cells, or other cells found to be able to deliver therapeutic substances) that have been genetically engineered so they now contain genes whose protein products inhibit extracellular and/or intracellular Akt-dependent functions.

[0024] Another object of the invention is to provide a method that stabilizes cells used for a cell-based platform for delivering agents for preventing or alleviating the development stenosis of the vessel or conduit after implantation, wherein a vessel or conduit is implanted in a patient and the vessel or conduit is coated with a composition incorporating cells (either progenitor endothelial cells or stem cells, or other cells found to be able to deliver therapeutic substances) that have been genetically engineered so they now contain genes whose protein products inhibit Akt-dependent functions, which therefore prevents such cells from excessively proliferating and migrating, and thereby preventing such cells from contributing to narrowing of the vessel or conduit.

[0025] Further objects, and a greater understanding of this invention, will be achieved from the description of the invention which follows.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

[0026] Due to its pivotal role in controlling cell proliferation, apoptosis, and cell migration, Akt can be considered a master regulator of the proliferative/migratory response of vessel wall cells to arterial injury.

[0027] Accordingly, the invention comprises 1) any pharmacological, or molecular (DNA, RNA, protein, peptide or non-peptide), or cell-based delivery platform (cells genetically engineered so they contain relevant transgenes) that is able to modify Akt functions in the arterial wall, venous wall, vascular graft, or conduit wall and, correspondingly, 2) prevents restenosis of an artery or vein, or stenosis of a vascular graft or conduit by modifying Akt functions in the arterial wall, venous wall, vascular graft, or conduit wall. The strategy described herein has the benefits of substantially reducing the incidence of restenosis or of graft or conduit narrowing, with minimal incidence of untoward complications, a result that has not been achieved by other anti-restenosis strategies whose results have been limited or, as with radiation therapy, carry unknown future risks.

[0028] According to the invention, the delivery systems utilized to affect Akt functions in the arterial wall, venous wall, vascular graft, or conduit wall may take several forms.

[0029] In a first embodiment, a pharmacologically effective amount of a compound which modifies and inhibits Akt cellular functions is delivered to the injured arterial wall, venous

wall, vascular graft, or conduit wall in order to inhibit cell migration or proliferation, and/or enhance apoptosis, and thereby prevent vascular or conduit narrowing. Any agent that is able to modify the Akt cellular functions can be administered to achieve this effect. The agent with anti-Akt function can be in the form of any pharmacological agent, molecular agent (DNA, RNA, protein, peptide or non-peptide), or cell-based delivery platform (cells genetically engineered so they contain relevant transgenes). In this regard, reference may be made to U.S. Patents numbers 6,187,586 and 6,291,220, whose disclosure is incorporated herein by reference. For example, the procedure of supplying antisense compounds, as disclosed in U.S. Patent 6,187,586 can be used to inhibit the expression of Akt, thereby reducing its effect. In another embodiment, the vessel wall may be contacted with a virus capable of transfecting the SMCs, e.g., adenovirus capable of transfection of dominant negative AKT mutant (Ad-dnAKT) into SMCs to inhibit p70S6K phosphorylation.

[0030] The material used to modify the activity of Akt may completely or partially inhibit the expression or action of Akt. In the discussion and claims herein, the term "inhibit" includes both the elimination of the effect of Akt or a reduction of its usual and customary effect in cells involved in restenosis. The agent that produces this effect may be referred to as an "anti-Akt agent".

[0031] The anti-Akt agent can be delivered to the arterial wall, venous wall, vascular graft, or conduit wall either through a catheter, or by impregnation into the coating of a stent, or by adhering to the stent struts. The anti-Akt agent may also be delivered by means of a stent carrying genetically engineered cells, or by impregnation directly into a vascular graft or conduit, or by impregnation into a matrix that is then applied (or is) the vascular graft or conduit. The impregnation can occur either in vivo or, in the case of a stent, vascular graft, or conduit, ex vivo.

[0032] The invention also comprises a method wherein cells (either progenitor endothelial cells or stem cells, or other cells found to be able to deliver therapeutic substances) that have been genetically engineered to contain genes whose protein products inhibit Akt-dependent functions are placed in association with the walls of an artery, venous graft, or conduit in order to deliver such protein Akt inhibitors to the cells, e.g., SMCs in such vessel walls (cell-based platform). The Akt inhibitors so supplied to the cells in the vessel walls prevent such cells from excessively proliferating and migrating, and thereby prevent such cells from contributing to narrowing of the vessel or conduit. The cells may be applied by coating them onto a stent

(stent platform), which is placed within the vessel or by suspending them in a vehicle that is coated onto the artery before or after angioplasty or coated onto a venous graft or conduit, or the like, either before or after implantation.

[0033] In another embodiment, the invention comprises a method for preventing or alleviating stenosis of a vessel or conduit after implantation, wherein the vessel or conduit is coated, before or after implantation, with a composition incorporating a pharmacological or a molecular compound (or DNA or other vector containing DNA encoding a molecule that inhibits Akt activity) that is able to inhibit extracellular and intracellular Akt-dependent functions.

[0034] In another embodiment, the invention comprises a method delivering agents capable of transfecting the cells of the artery, venous graft, conduit, or the like, with a gene or genes that cause the cells of the wall themselves to produce one or more cellular products that inhibit the activity of Akt, and thereby prevent or reduce cell proliferation and/or migration. Such agents can be, e.g., conventional viral vectors. They can be administered by coating onto a stent that is subsequently positioned within the vessel, or by suspension in an appropriate vehicle that is coated on the vessel wall (preferably a vehicle that adheres to the wall for a period of time to permit effective transfection), or by impregnation into the wall of the artery, venous graft, conduit, or the like, before or after implantation.

[0035] Those skilled in the art will recognize that many different routes of administration of an anti-Akt material can be utilized to achieve the prevention or alleviation of restenosis. Accordingly, any possible route of administration of any compound able to affect Akt function in the cells of the arterial wall, venous wall, vascular graft, or conduit wall in order to prevent restenosis following angioplasty, or lumenal narrowing in the context of a vascular graft or conduit, is embraced by this invention.

[0036] Thus, the active Akt-inhibiting ingredient or cell, or the like, capable of supplying the Akt-inhibiting ingredient or inducing the local production of the Akt-inhibitor can be performed in any artery or interposed vein (such as, but not limited to, a saphenous vein graft to a coronary artery) that is obstructed or stenosed and thereby impairs blood flow to the target tissue (whether it be heart or leg). It can also be applied to any new vascular graft or conduit that is to be implanted in the patient.

[0037] The prevention of vessel restenosis and prevention of graft or conduit narrowing, are clinical endpoints that comprise but are not limited to, inhibition of smooth muscle cell (SMC) proliferation or migration and induction of SMC apoptosis, by inhibiting Akt dependent

signaling.

[0038] Effects observed in vitro have in vivo parallels. Blocking Akt functions in vitro has antiproliferative effects on SMCs. Blocking Akt functions in acute vascular injury, in rats, reduces neointimal formation. For example, adenovirus mediated transfection in vitro of dominant negative AKT mutant (Ad-dnAKT) inhibited p70S6K phosphorylation in rat SMCs. Cell proliferation, assessed over 5 days, was also inhibited, and thymidine incorporation at 48 h was reduced compared to control (Ad.bgal).

[0039] In a parallel in vivo experiment, in the balloon-injured rat common carotid artery model in vivo transfection of Ad-dnAKT significantly inhibited neointimal hyperplasia, assessed at 14 days, compared to control. Similarly, the neointima/media ratio was reduced. These results indicate a new target for preventing neointima formation after angioplasty, and for preventing lumenal narrowing following graft or conduit implantation.

[0040] The invention, having now been fully described, it should be understood that it may be embodied in other specific forms or variations without departing from its spirit or essential characteristics. Accordingly, the embodiments described above are to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims rather than the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are intended to be embraced therein.

WE CLAIM:

1. A method for inhibiting stenosis of a mammalian blood vessel which is susceptible to stenosis comprising, administering to said blood vessel a substance capable of inhibiting Akt activity therein, in an amount which effectively inhibits, at least partially, said Akt activity.

2. The method of Claim 1, wherein said mammalian blood vessel is a human blood vessel.

3. The method of Claim 1, comprising administering said Akt-inhibiting substance to a wall of said blood vessel.

4. The method of Claim 3, comprising administering said Akt-inhibiting substance to said blood vessel through a catheter.

5. The method of Claim 3, comprising impregnating the wall of said blood vessel with said Akt-inhibiting substance.

6. The method of Claim 3, comprising coating said Akt-inhibiting substance onto a stent and implanting said stent within said blood vessel.

7. The method of Claim 3, comprising administering said Akt-inhibiting substance in suspension in a vehicle so as to coat it onto the wall of said blood vessel.

8. The method of Claim 3, comprising administering said substance capable of inhibiting activity of Akt by contacting said blood vessel with a cell genetically engineered to produce said Akt-inhibiting substance.

9. The method of Claim 8, wherein said cell is supported on a stent and said stent is implanted within said blood vessel.

10. The method of Claim 3, wherein said Akt-inhibiting substance is an antisense compound.

11. The method of Claim 3 wherein said Akt-inhibiting substance is an agent capable of transfecting cells in said wall of said blood vessel with a gene capable of producing a cellular product capable of inhibiting the activity of Akt.

12. The method of Claim 3, comprising

providing a stent comprising a lattice of interconnected struts with openings between said struts,

coating at least a portion of said struts with a composition containing a source of an Akt-inhibiting compound, so as to produce a stent capable of supplying said Akt-inhibiting compound to cells within a blood vessel, and

positioning said coated stent within a blood vessel adjacent to a wall of said vessel in conjunction with an angioplasty procedure.

13. The method of Claim 12, wherein said composition comprises a coating containing said Akt-inhibiting compound.

14. The method of Claim 12, wherein said composition is a coating containing cells capable of supplying said Akt-inhibiting compound to said wall of said blood vessel.

15. The method of Claim 12, wherein said composition is a coating containing a nucleic acid vector capable of transfecting cells of said wall of said blood vessel.

16. The method of Claim 15, wherein said nucleic acid is DNA.

17. The method of Claim 15, wherein said vector is a viral vector.

18. A stent comprising, a lattice of interconnected struts with openings between said struts, at least a portion of said struts being coated with a composition containing a source of a substance capable of inhibiting Akt activity.

19. The stent of Claim 16, wherein said composition comprises a coating containing said Akt-inhibiting compound.

20. The stent of Claim 16, wherein said composition is a coating containing cells capable of supplying said Akt-inhibiting compound to said wall of said blood vessel.

21. The stent of Claim 16, wherein said composition containing a source of an Akt-inhibiting compound is a coating containing a nucleic acid vector capable of transfecting cells of said wall of said blood vessel.

22. The method of Claim 19, wherein said nucleic acid is DNA.

23. The method of Claim 19, wherein said vector is a viral vector.