REVIEW

In stent restenosis: bane of the stent era

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The long term outcome of stent implantation is affected by a process called in stent restenosis (ISR). Multiple contributory factors have been identified, but clear understanding of the overall underlying mechanism remains an enigma. ISR progresses through several different phases and involves numerous cellular and molecular constituents. Platelets and macrophages play a central role via vascular smooth muscle cell migration and proliferation in the intima to produce neointimal hyperplasia, which is pathognomic of ISR. Increased extracellular matrix formation appears to form the bulk of the neointimal hyperplasia tissue. Emerging evidence of the role of inflammatory cytokines and suppressors of cytokine signalling make this an exciting and novel field of antirestenosis research. Activation of Akt pathway triggered by mechanical stretch may also be a contributory factor to ISR formation. Prevention of ISR appears to be a multipronged attack as no therapeutic ''magic bullet'' exists to block all the processes in one go.

The introduction of a metallic spring into the popliteal artery of an experimental animal by Charles Dotter[1] signalled the beginning of the stent era. However, the first human stent implantation, by Sigwart *et al*,[2] did not occur until 1986, and it was only in 1994 that the US Food and Drug Administration approved the use of stents following two studies[3 4] that conclusively proved the superiority of stents over balloon angioplasty with regards to their long term prognosis. On average, stents appear to have a 10% lower rate of restenosis compared with angioplasty and the favuorable results due to stent usage have been reported in several studies.[5] Unfortunately, stents have an inherent rate of restenosis of 10–60%.[6–8] The risk factors of restenosis include the method (stented or not), lesion location (the left anterior descending artery is found to be less susceptible to restenosis),[9] diabetes,[10] residual stenosis, number of stents,[11] the stent length,[12] total occlusion and late total occlusion,[13] and bifurcating or ostial lesions.[14]

Experimental studies suggest that the process of cellular proliferation starts between the first few days and up to 2–3 weeks after stent implantation, and several pharmacological approaches have been undertaken in parallel to the surgical intervention to improve the overall outcome. Thrombosis was initially responsible for the high rate of stent failure but anticoagulant (heparin) and antiplatelet therapy has to an extent succeeded in reducing thrombosis related complications.[15] For long term treatment after stent implantation, aspirin is used, and may be combined in lower doses with antithrombotic agents such as clopidogrel or warfarin.[16] Increased GPIIb/IIIa ligand binding may be associated with restenosis after coronary stenting[17] thus GPIIb/IIIa inhibitors are also used.[18] In an attempt to further reduce the degree of restenosis, numerous adjunctive strategies, such as use of high pressure stent,[19] use of specific materials and designs, prior debulking[20] and no pre-dilatation[21] have been tried. Brachytherapy represents a potentially powerful way to prevent restenosis and the delivery of local radiation to the target site after angioplasty has now been shown to help reduce restenosis.[22–24] These strategies have incrementally reduced the incidence or degree of restenosis, but total eradication has not been achieved.

Several drugs have been used systemically and locally (drug eluting stents), to prevent proliferation and migration of smooth muscle cells (SMCs), but only a few have shown any promise in either human trials or experimental animal models. Troglitazone inhibited neo-intimal hyperplasia (NIH) in a small human study,[25] while Tranilast reduced in stent restenosis (ISR) in a porcine model,[26] but could not elicit similar results in a human study.[27] Valsartan[28] and some statins[29] have also been studied without any conclusive benefits. Cilostazol, an antiplatelet agent that interferes with SMC proliferation,[30] has shown conflicting results.[31–33] Drug eluting stents have now become the medium for local drug delivery to the site of the lesion. Stents coated with any of several pharmacotherapeutic agents such as heparin, hirudin, GP IIb/IIIa inhibitors, sirolimus, and paclitaxel can be used.[34 35]

DEFINITION AND CLASSIFICATION OF IN STENT RESTENOSIS

ISR can be defined clinically or angiographically. Clinically it is defined as the presentation of recurrent angina or objective evidence of myocardial ischaemia, whereas angiographic ISR is

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Abbreviations: EC, endothelial cell; ECM, extracellular matrix; ER, endoplasmic reticulum; IAP, inhibitor of apoptosis protein; IGF, insulin-like growth factor; ISR, in stent restenosis; MAPK, mitogen activated protein kinase; MCP, monocyte chemoattractant protein; NIH, neointimal hyperplasia; PCNA, proliferating cell nuclear antigen; PTCA, percutaneous transluminal coronary angioplasty; SMC, smooth muscle cell; SOCS, suppressors of cytokine signalling; TNF, tumour necrosis factor; TNF-R, TNF receptor; TUNEL, TdT/dUTP biotin nick end labelling; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell

the presence of >50% diameter stenosis in the stented segment.[36] Traditionally, ISR has been classified based on the length of the lesion, as focal (<10 mm) or diffuse (>10 mm).

Angiographic classification appears to be more complete and classifies the ISR lesions into six groups (I–IV) according to the pattern and extent of restenosis with relation to the affected vessel. According to this classification, focal pattern I can be further subdivided into IA–ID and diffuse pattern can be divided into II–IV.[37]

CELLULAR AND MOLECULAR PATHOPHYSIOLOGY OF RESTENOSIS

Intravascular ultrasound) has demonstrated fundamental differences in the process of restenosis following angioplasty[38] and that following stent implantation.[4 5] The pathophysiology of restenosis involves accumulation of new tissue within the arterial wall (NIH). A cascade mechanism involving platelets, polymorphonuclear leucocytes, and macrophage aggregation leading to medial SMC migration and proliferation is the basis of NIH formation[39] (fig 1). Leucocyte recruitment at the site of the injury and the deposition of platelets and fibrin are hallmarks of the onset of restenosis.[40] Thrombocytopenia in experimental models has been shown to reduce restenosis,[41] and IIb/IIIa antagonists, which are antibodies to the platelet glycoprotein receptor IIb/IIIa, have been proven clinically to have similar effects.[42 43] The GPIIb/IIIa inhibitors opened the gate to a rapidly developing area of anti-integrin targeting as a therapeutic approach. The use of GPIIb/IIIa inhibitors in interventional cardiology is widespread and still increasing. Currently clinically approved for parenteral use are the Fab fragment abciximab and the small molecule GPIIb/IIIa inhibitors eptifibatide and tirofiba.[44] However, some studies refute the impact of these therapeutic agents in the clinical settings[45] Transmigration of leucocytes occur across the platelet coated surface,[46] mediated by P-selectin.[47] Neutrophil–platelet and monocyte–platelet aggregates have been found in the peripheral blood of patients with coronary artery disease, and have been proposed as predictors of disease activity.[48 49] Numerous adhesion molecules and chemoattractant agents play a vital role in the recruitment of monocytes, platelet activation, and aggregation. These include Mac-1 (CD11b/CD18), a component of leucocyte secretory granules, which promotes adhesion of polymorphonuclear leucocytes and monocytes to endothelial cells,[50] and Mac-1 expression increases following stenting.[51] Monocyte chemoattractant protein (MCP)-1 is a chemokine secreted by activated platelets[52] the expression of which rises in endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) following stenting injury.[53] Persistently elevated levels of MCP-1 have been observed in patients who developed restenosis.[54] Events occurring at the platelet surface involve CD40L, a tumour necrosis factor family transmembrane protein that translocates to the activated platelet surface where it mediates platelet EC interaction.[55] Production of CD40L and its soluble fragment sCD40L inhibits re-endothelialisation of the EC layer and predisposes to restenosis.[56] However, the role of CD40L/sCD40L in the pathogenesis of ISR is unclear.[57]

The complex mechanisms leading to ISR can be divided into an ''early'' (days to weeks) and a ''late'' (weeks to months) phase (fig 2). Each step is regulated by unique but inter-related molecular and cellular events, the overall control of which is the result of interaction among growth factors and their receptors, cytokines, secondary messengers, and proto-oncogenes involved in transcription, translation, and post-translational events.[58 59] The early phase events begin with relocation of the plaque, reorganisation of the thrombus, and an acute inflammatory reaction. Elastic recoil

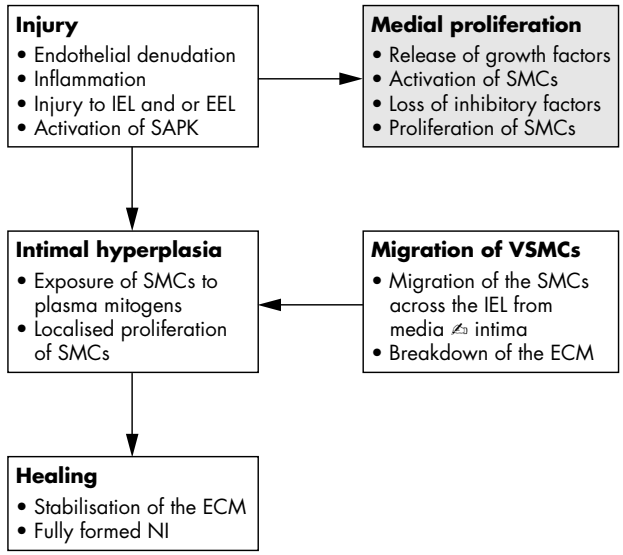

Figure 1 The ''cascade'' reaction of the vascular wall to stent injury involving several distinct steps. (A) injury to the endothelium and even the elastic lamina, triggers an inflammatory reaction, which causes (B) proliferative changes in the media. (C) There is phenotypic modulation of the medial VSMCs, which causes them to migrate into the intimal layer, where (D) increased ECM production by VSMCs adds bulk to the restenotic lesion. (E) The final healing phase results in stabilization of the fully formed lesion.

is minimal in ISR compared with restenosis secondary to percutaneous transluminal coronary angioplasty (PTCA), because of the rigid scaffolding of the stents.[60] Endothelial injury produces some element of thrombus formation,[61] and fibrin and platelet deposition at the site of injury provides the foundation for the inflammatory aggregate. There is increased leucocyte trafficking to the stent site and subsequent migration into the vessel wall,[62] the predominant cells being monocyte derived macrophages.[63] Sustained production of adhesion molecules, cytokines, chemoattractants, and growth factors by the platelets, monocytes, and SMCs leads to further leucocyte recruitment and infiltration. The weeks following injury lead into the late phase. The main event of the late phase is the phenotypic modification of medial SMCs followed by their migration and subsequent proliferation in the intima. Coordinated extracellular matrix (ECM) synthesis by these SMCs is responsible for the increasing volume of intimal tissue (fig 3), and the bulk of the NIH is composed of ECM proteoglycans and collagens, with cellular elements making up only about 11%.[52] Thus, over the months subsequent to stent implantation, there is a shift towards greater ECM synthesis rather than SMC proliferative activity.[48 49]

The proliferation and migratory aspect of medial SMCs is important because these cells are the predominant secretors of the ECM. The pathway for SMC proliferation is an integrated mechanism involving several known and as yet unidentified cell signalling pathways coupled to the cell cycle (fig 4). Peptides binding to tyrosine kinase receptors are possibly the most potent mitogens for SMCs,[64] and they modulate a variety of signalling pathways, including ras, raf, the mitogen activated protein kinase (MAPK) cascade,[65] the phosphoinositol-3 kinase- protein kinase B pathway,[66 67] and the diacylglycerol protein kinase C pathway.[68 69] Early response genes appear to be the downstream targets and these in turn cause new protein synthesis, which commits the cell to the next phase of the cell cycle; the cyclin and cyclin dependent protein kinases appear crucial to this stage.[70 71] Passage of the cell into the mitotic phase occurs as a result of

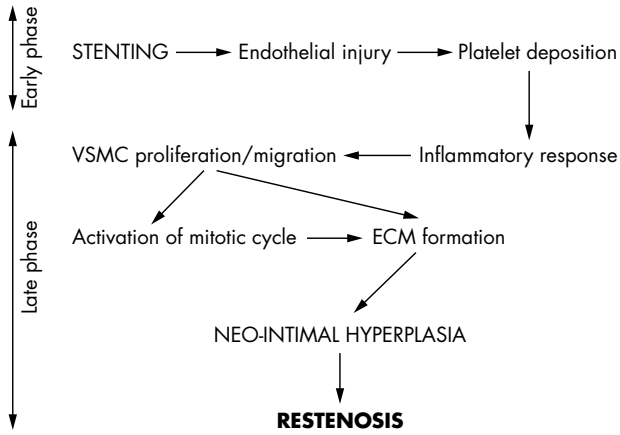

Figure 2 The time course reactions of restenosis. Chronological sequence of events leading to instent restenosis can be divided into the early and the late phases. The early phase is the initial injury followed by the inflammatory reactions and the late phase essentially consists of the various mechanisms leading to increase in lesion volume (hyperplasia).

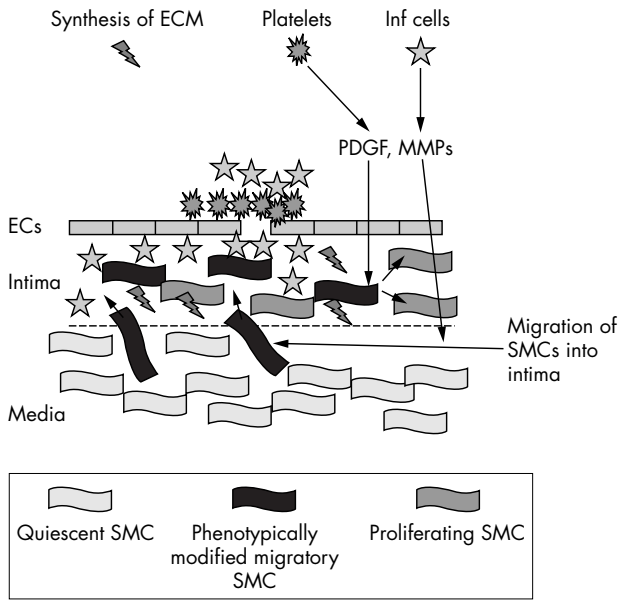

Figure 3 Schematic diagram of the cellular mechanism of ISR. Phenotypic modulation of the quiescent VSMCs and migration into the intimal layer. Continual SMC proliferation occurs in the intima with the deposition of de novo ECM.

cascade multiplying effects of cdks and the cyclins that phosphorylate the retinoblastoma proteins, causing release of transcription factor E2F, which in turn causes induction of DNA polymerase and pushes the cell beyond the critical point (R point) and into mitosis.[72]

Unlike the proliferative aspect of the SMCs, little is known about their ''motile'' activity, which allows them to migrate into the media. It is no doubt complex, involving phenotypic modulation, matrix manipulation and some form of modified or reduced cell–cell contact. Removal of focal adhesion sites responsible for cell–cell contact is possibly a mechanism to release the SMCs from their anchoring sites in the media. Cytoskeletal reorganisation modulated by the MAPK pathway and Ca^{2+} activated calmodulin kinase II[73] are believed to be involved.

What is it about the vascular cells that cause them to produce restenosis? Various concepts have emerged regarding the precise nature and role of the vascular cells in various disease states,[74–76] and numerous factors have been identified that affect the resident vascular cells,[77 78] leading to changes in the cellular composition of the vessel wall.[79 80] SMCs are multifunctional cells of the vascular system (fig 5), and it is accepted that these cells undergo morphological changes leading to loss of their contractile properties and causing them to become ''synthetic'' cells.[81] A second paradigm suggests heterogeneity of the SMC population, with only a fraction of cells capable of a rapid response to injury stimuli. These ''stem'' SMCs differ in morphology, gene expression and behaviour compared with their genetically different counterparts, as observed in cell cultures in vitro.[82 83] The third paradigm is the role of the non-muscle adventitial fibroblasts. It has been suggested that these cells are able to react, migrate, proliferate, and synthesise ECM, thereby functioning in a similar fashion to the SMCs.[84–86] Experimental injury to a porcine model produced migration and proliferation of non-muscle cells of adventitial origin leading to neo-intima formation.[87 88] Certain functional differences in the cellular constituents of coronary and non-coronary vascular beds may influence the mechanisms of vascular repair and intima formation.[89]

ROLE OF APOPTOSIS IN ISR

Apoptosis was first recognised almost 30 years ago as a genetically encoded cell death process.[90] Apoptosis comes from a Greek word meaning ''the dropping of leaves from a tree''. Subsequent studies found the occurrence of this

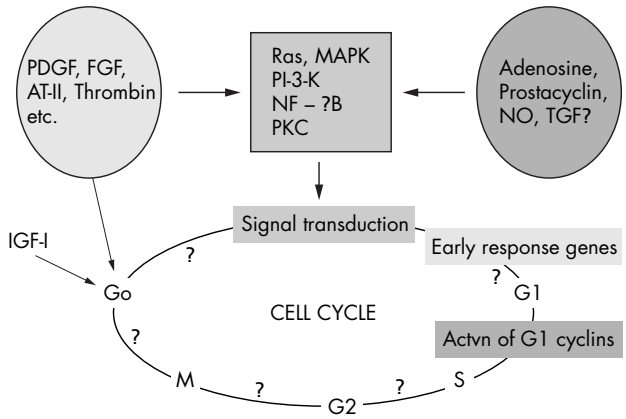

Figure 4 Cell signalling–cell cycle coupling in ISR. Under the proliferative influence of numerous cytokines and growth factors, which act via intracellular cyclins and cyclin dependent kinases, the VSMCs are driven from the resting (G0) phase to through the various stages of G1 phase before going onto S, G2, M, and subsequent cell division.

process in a number of normal and pathological tissues.[91] The recognition of apoptosis in normal as well as rapidly proliferating tissues suggested a role for it in the maintenance of stable cell numbers in tissues with varying proliferative activities. Persistently high levels of proliferative activity were observed in SMCs of a rat carotid model,[92] but calculated values based on kinetic studies indicated that the increase should have been much greater than that observed experimentally. This led the researchers to remark that ''cell death must account for our findings''.[72]

Apoptosis is best characterised by the cleavage of genomic DNA into multiple smaller fragments of ~180 bp or multiples of this number. These are then detected by gel electrophoresis of the lysate from cells grown in culture and appear as a DNA ladder.[93] However, this approach is somewhat limited to cell culture studies. Apoptosis in tissue sections is normally performed by the TdT/dUTP biotin nick end labelling

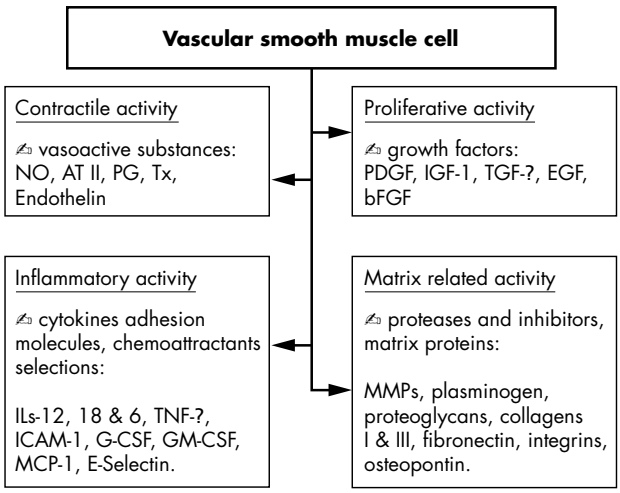

Figure 5 Multifunctional role of SMCs. Numerous substances synthesized and secreted by the VSMCs regulate several processes that contribute to restenosis. These include inflammation, proliferation, and apoptosis, all of which play a significant role in the overall restenosis process.

(TUNEL) method, which involves specific immunolabelling of DNA fragments with terminal deoxynucleotidyl transferase.[94]

Apoptosis in cardiovascular tissues has been a focus of interest for a long time, but there is little documented evidence. The possible role of apoptosis in various cardiac disorders including atherosclerosis and restenosis have been studied using immunostaining, gel electrophoresis, TUNEL, and nucleosomal DNA ladders.[95 96] Numerous studies have been performed to establish the relationship of apoptosis to atherosclerosis. Necropsy studies[97–101] and directional atherectomy specimens[102–105] have shown a paucity of apoptotic cells in primary atherosclerotic plaques, which was supported by the Coronary Angioplasty Versus Excisional Atherectomy Trial study.[106] Using proliferating cell nuclear antigen (PCNA) it was seen that some atherosclerotic lesions exhibit some proliferation, but the overall population of PCNA positive cells was low (mean 0.85%).[107] Other studies using atherectomy samples from symptomatic/asymptomatic patients and from coronary and peripheral arteries also gave low values of around 3.6%.[108] This was attributed to the low turnover of the cell population in some tissues and hence the low visualisation of apoptosis in such tissues.[109]

Restenotic lesions, however, appear to be more proliferative than primary atherosclerotic lesions. This is supported by evidence from necropsy and atherectomy samples.[110 111] Foci of hypercellularity observed in such cases were interpreted as antecedents to proliferative activity, and experimental results from various animal models reinforced this assumption.[112–115] Isner *et al*[116] observed the occurrence of apoptosis most consistently in the hypercellular tissue specimens typical of restenosis.

Modulators of apoptosis

Four major groups of molecules are involved. They are the caspases, the adaptor proteins that control the activation of initiator caspases, members of the TNF group and their associated receptors (TNF-R), and members of the Bcl-2 family of proteins.[117]

Caspases are a group of cysteine proteases essential for the process of apoptosis.[118] At least 14 have been identified to date. Caspases are synthesised as low activity zymogen molecules and the activated enzyme is a heterotetramer composed of two identical subunits.[119 120] The process of apoptosis is a cascade mechanism triggered by the initiator caspases-8, 9, 10 and 12, which are closely coupled with some pro apoptotic signals. Pro apoptotic stimuli include FasL, TNF-α, DNA damage, and endoplasmic reticulum (ER) stress.[121] These caspases then proceed to cleave and activate the downstream effector caspases 3, 6, and 7. The effector caspases in turn cleave and inactivate certain vital cellular proteins including poly (ADP-ribose) polymerase, α-fodrin, lamin, gelsolin, mouse double minute 2 (which is an inhibitor of p53), and protein kinase C-δ.[122] There is release of cytochrome c from the mitochondria, which is coupled to the activation of caspase-9 a key initiator caspase.[123] Caspase-8 and 10 are activated by Fas and TNF-R, and DNA damage produces activation of caspase-9; calcium mediated activation of caspase-12 occurs secondary to ER stress. Inhibitor of apoptosis protein (IAP) promotes survival by binding and inhibiting several caspases.[124 125] Mitochondrial stress leads to the release of Smac/Diablo,[126] a mitochondrial protein that acts as a competitive inhibitor of IAPs and removes their inhibitory effect on the caspases.

Adaptor proteins act as bridges between the caspases and the death receptors and Bcl-2 family members. Association between the adaptor proteins and the caspases or TNF-R molecules occurs typically through the death domains, the death effector domain, and the caspase recruitment domain.[127 128] The TNF-R has multiple actions and, depending on the signal it receives, can initiate apoptosis, proliferation, differentiation, or survival. The death domain essential for the induction of apoptosis is located on the cytoplasmic region of TNF-R1 and CD-95 (also known as Fas or APO-1).[129 130]

Bcl-2 is a potent inhibitor of apoptosis and, several molecules bearing structural homology to Bcl-2 have been identified in the past 5 years. Bcl-2 proteins regulate apoptosis by controlling mitochondrial permeability. It exerts its anti-apoptotic effect by blocking mitochondrial release of cytochrome-c.[131] There is also evidence of modulation of Ca^{2+} homeostasis and proton flux by the Bcl-2 family.[132] Bcl-xL dimerises with certain apoptotic molecules, thereby neutralising their apoptotic effect,[133 134] and also stabilises the mitochondrial membrane under conditions of stress.[135] By far the most potent activators of apoptosis are a group of proteins that include Bad, Bid, and Bim, among others. Bad promotes cell death by displacing Bax from Bcl-2 and Bcl-xL.[136 137] Serine phosphorylation of Bad inhibits the apoptotic effect of Bad by binding to 14-3-3 proteins and thereby preventing the displacement of Bax. Akt is able to phosphorylate Bad at serine −136.[138 139] Bid resides in the cytosolic fraction[140] as an inactive precursor,[141 142] which, under apoptosis inducing conditions, is cleaved by caspase-8 as a step in the Fas signalling pathway. The t-BID formed by this cleavage translocates to the mitochondrial membrane and induces cytochrome-c release[143 144]

Restenosis has been implicated with apoptosis.[145 146] Stretch injury as in barotrauma (PTCA) and stenting initiate apoptosis in the medial SMCs of the arterial wall[147] and it was found that early SMC apoptosis was greater in stented vessels than in vessels that had undergone PTCA.[148] The SMCc lying closest to the region of injury undergo maximum apoptosis,[149] and over a period of time it is seen that some surviving SMCs migrate towards the arterial lumen, thereby leading to intimal formation.[150] Using a rabbit model, it was found that the degree of apoptosis and proliferation of the SMCs reached its maximum at 7 days after injury.[151] Injury causes the medial SMC in the region of trauma to undergo phenotypic modulation[152 153] and subsequently to migrate and proliferate in the intima.[154] Trauma is also thought to induce apoptosis by stimulating MAPKs, which phosphorylate transcription factors involved in expression of genes for

SMC proliferation,[155–157] and MAPK levels have been found to be elevated shortly after experimental injury to arteries.[158] ZVAD-fmk, a synthetic broad spectrum caspase inhibitor,[159 160] was found to reduce restenosis when delivered locally to the site of stretch injury in rabbit iliac artery.[161]

ROLE OF IGF–I AND RESTENOSIS

The field of vascular biology with relation to growth hormone and insulin-like growth factor (IGF-I) has been intensively studied. There seems to be an important role of the IGF axis in atherosclerosis and restenosis; the huge volume of literature (>1000 references) found on a Medline search[162] bears testimony to its importance. There is growing evidence that IGF–I is involved in the local mechanisms leading to restenosis.[163 164] IGF-I in SMCs in early restenosis has been found to be far higher than in normal SMCs,[165] but late restenotic tissue obtained several months after intervention showed little or no IGF-I mRNA expression.[166] IGF-I also promotes vascular elastogenesis.[167 168]

POTENTIAL ROLE OF NEOVASCULARISATION IN RESTENOSIS

Angiogenesis refers to new blood vessel formation (neovascularisation) from any preexisting vasculature. Neovascularisation may contribute to chronic inflammatory disorders, tumour growth, restenosis, and atherosclerosis.[169] Recent studies, however, suggest that neovascularisation is not a simple growth of new vessels from pre-existing vessels, but also involves the contribution of bone marrow derived circulating endothelial progenitor cells.[170] Neovascularisation could be a possible biological response to vessel injury and associated with the formation of IH. Arterial medial fracture is associated with an increase in inflammatory cell and inflammation, which cause increased neoangiogenesis and an increased neointimal growth.[171] It is a time-dependent phenomenon related to the extent of injury and inflammation.[172] The remodelling of the vessel wall leads to increased angiogenesis, which is related to the degree of neointimal hyperplasia.[172] The process involves both positive and negative regulators. Positive regulators, including growth factor receptors, matrix metalloproteinases and integrins, have been correlated with increased angiogenesis and these are currently under investigation as therapeutic targets.[173] The IGF-1 system exerts multiple physiological effects on the vasculature, mediated principally through the IGF-1 receptor and modulated by complex interactions with IGF binding proteins. There is accumulating evidence of a role for IGF-1 in atherosclerosis, restenosis, and angiogenesis, all of which share similar pathology.[174] Vascular endothelial growth factor (VEGF), an important modulator in restenosis, is involved not only through its angiogenic properties, but also via a synergistic effect with platelet derived growth factor.[175] In advanced stages of restenosis, extensive neovascularisation was located in close proximity to stent struts. The neovessels were found to be colocalised with VEGF-A mRNA.[176] T-cadherin levels correlate with the progression of atherosclerosis, restenosis and tumour neovascularisation. It is regulated during the cell cycle and its overexpression has been seen to promote proliferation.[177] Perlecan, a heparan sulphate proteoglycan found in abundance in the vessel wall, has been shown to be a potent inhibitor of SMC activity. Animal models of arterial injury have shown that perlecan may inhibit thrombosis and intimal hyperplasia, but can have an opposite effect on endothelial cells, where it promotes angiogenesis.[178] Recent studies have implicated the cell cycle regulatory protein p27Kip1 as a key modulator of vascular cell growth and locomotion in vitro, and during vascular remodelling and angiogenesis in vivo.[179] Mammalian target of rapamycin signalling plays a key role in smooth muscle and endothelial proliferation and angiogenesis in vitro.[180] Recently, the role of plasminogen activators in vascular remodelling of atherosclerosis, restenosis, and angiogenesis have been examined as a possible therapeutic avenue.[181] Local delivery of the antiangiogenic agent, angiostatin, significantly reduced neovascularisation and subsequent IH formation in a rabbit model.[182] There are therefore prospects of angiostatin eluting stents reducing IH by limiting neovascularity. Numerous biomolecules have been studied and their role in neovascularisation has been investigated in detail, but the overall mechanism still remains unclear.

TAKE HOME MESSAGES

- The long term outcome of stent implantation is affected by a process called in stent restenosis (ISR).
- Although stents reduce the risk of restenosis compared with percutaneous transluminal coronary angioplasty, the prevailing rates of ISR are still unacceptably high.
- Increased extracellular matrix formation appears to form the bulk of the neointimal hyperplasia tissue.
- Prevention of ISR appears to be a multipronged attack as no therapeutic ''magic bullet'' exists to block all the processes in one go.

CONCLUSION

Although stents reduce the risk of restenosis compared with PTCA, the prevailing rates of ISR are still unacceptably high. The cellular and molecular mechanisms are yet to be fully understood even though many pieces of the jigsaw have been put in place. Damage to the endothelium caused by stent implantation initiates an initial inflammatory response followed by a healing process that culminates in increased cell and matrix turnover, producing an NIH somewhat analogous to scar formation in the wound healing process. Study of SMC—matrix interactions, attachments of cells to matrix via the cell surface integrins (matrix receptors), and matrix degradation could yield substantial insight into the process of NIH. Specific matrix molecules, cell signalling pathways, and their coupling to the cell cycle could be the focus of future research. Identifying the ''gateway'' to NIH formation could be the key to reducing the incidence of ISR.

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