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Vascular Smooth Muscle Cell Apoptosis – a Dangerous Phenomenon in Vascular Disease?

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Vascular smooth muscle cell (VSMC) apoptosis has been identified in atherosclerosis and after arterial injury, including angioplasty restenosis. The induction of apoptosis has therefore been suggested to be of therapeutic benefit, reducing neointimal size. In contrast, most available evidence suggests that VSMC apoptosis may predispose to plaque rupture and aneurysm formation. In addition, VSMC apoptosis induces a local and systemic pro-coagulant state, and may directly promote inflammation in the vessel wall. This review summarises the concerns that VSMC apoptosis may be detrimental to vascular structure and function. *J Clin Basic Cardiol 2000; 3: 63–5.*

Key words: apoptosis, vascular smooth muscle, atherosclerosis, restenosis

Apoptosis (programmed cell death) of vascular smooth muscle cells (VSMCs) has been recognised recently in the vessel wall in disease states such as atherosclerosis and restenosis after angioplasty, and also in physiological arterial remodelling. Although apoptosis has been observed, the role and importance of VSMC apoptosis has not been determined. Although VSMC apoptosis is undoubtedly one mechanism employed for changing VSMC mass in vessel remodelling, VSMC apoptosis appears to be almost entirely a detrimental phenomenon in vascular disease.

VSMC apoptosis – dangerous in atherosclerosis?

The orthodox view holds that VSMC accumulation by cell division and migration is a major contributor to disease states such as atherosclerosis or restenosis after angioplasty. This view argues that deregulated cell proliferation and abnormalities in VSMC phenotype generate the disease, analogous to the deregulated cell division seen in cancer. As a consequence, major efforts have been made to inhibit VSMC proliferation in vascular disease, which have been universally unsuccessful in inhibiting clinical events in either atherosclerosis or restenosis.

In contrast, the complications associated with advanced atherosclerotic plaques are mostly due to plaque rupture. Rupture of plaques is associated with a thinning of the VSMC-rich fibrous cap overlying the core. Rupture occurs particularly at the shoulder regions of plaques, which are noted for their lack of VSMCs and the presence of macrophages and other inflammatory cells. Recently, it has been recognised that VSMCs and their products, extracellular matrix and collagen, comprise the major structural components of the atherosclerotic plaque, and a reduction in cell numbers, either by inhibition of cell proliferation or increased cell death by apoptosis, may be detrimental. Indeed, VSMC accumulation in atherosclerosis is now viewed as a beneficial repair process, and failure of repair may lead to plaque rupture. Unsurprisingly then, apoptotic VSMC are evident in advanced human plaques [1–3], including the shoulder regions, prompting the suggestion that VSMC apoptosis may hasten plaque rupture. Indeed, there is evidence of increased VSMC apoptosis in unstable versus stable angina lesions [4].

Increased apoptosis is just one feature of plaque VSMCs that impair their ability to repair plaques. VSMCs from ad-

vanced human plaques show poor proliferation, early senescence and increased apoptosis [5]. These cells are of a 'senescent' phenotype, incapable of effective repair, and do not resemble cancer cells. Indeed, plaque VSMCs show intrinsic defects in both proliferation and survival signalling, and activation of cell cycle machinery to induce cell division in plaque VSMCs induces apoptosis, not cell proliferation [5]. This emphasises that VSMCs lost through apoptosis are unlikely to be efficiently replaced.

Plaque VSMCs show increased sensitivity to agents that induce DNA damage such as oxidised lipids/cholesterol and nitric oxide [6] released from endothelial cells lining the blood vessel. These agents specifically kill plaque VSMCs, leaving normal VSMCs in the artery unaffected, further weakening the plaque and predisposing to plaque rupture [6]. Plaque VSMCs are also killed by inflammatory cells which are adjacent in the plaque [7], and a major effect of drugs that reduce cholesterol may be due also to reducing the numbers of inflammatory cells in the plaque, preventing VSMC death and plaque rupture.

Although the hypothesis that VSMC apoptosis promotes plaque rupture is attractive in concept, there is no direct evidence of the effect of apoptosis *per se* in the advanced human lesion. Most apoptotic cells in histological sections are found in advanced lesions next to the lipid core [8] and it is still not clear how many of these apoptotic cells are macrophages or VSMCs. Loss of macrophages from atherosclerotic lesions is likely to promote plaque stability rather than rupture, since macrophages can promote VSMC apoptosis by both direct interactions [9] and by release of cytokines [10]. Of interest, apoptosis also occurs in early stages of atherosclerosis induced by cholesterol feeding in animals, at the fatty streak stage before morphological evidence of lesion formation [11]. Again, the effect of apoptosis at this early stage of lesion development is unknown.

VSMC apoptosis – dangerous in angioplasty restenosis?

Experimental evidence from animal models of arterial injury has shown that medial VSMC apoptosis occurs early after injury [12]. Intimal apoptosis also occurs at later time points [13], and therapeutic manipulation of VSMC apoptosis can reduce neointimal size at early times after injury [14, 15]. These studies have suggested that induction of intimal cell

apoptosis may be of therapeutic benefit in humans. However, the role of VSMC apoptosis in either the initial injury or the remodelling process in restenosis is still unclear in human vessels. In humans, restenosis after angioplasty has been reported to be associated with either an increase [3], or decrease [4] in VSMC apoptosis. Of major concern, human vessels that undergo angioplasty are diseased, not the normal vessels used in animal studies. If VSMC apoptosis does promote plaque rupture, then induction of intimal apoptosis in human vessels may convert the stable lesions seen after angioplasty into unstable plaques.

VSMC apoptosis – dangerous in arterial aneurysms?

The commonest form of arterial aneurysm in humans is associated with advanced atherosclerosis, and is characterised by a loss of VSMCs from the vessel media, with fragmentation of elastin and matrix degradation, leading to progressive dilatation and eventually rupture. Apoptosis of VSMCs is increased in aortic aneurysms [16–18] compared with normal aorta and is associated with an increase in expression of a number of pro-apoptotic molecules, such as death receptors and p53 [16, 18]. Macrophages and T-lymphocytes are found in aneurysmal lesions, suggesting that inflammatory mediators released by these cells may increase the loss of cells from these areas. Moreover, the production of tissue metalloproteinases by macrophages may accelerate cell death by degrading the extracellular matrix from which VSMCs derive survival signals. All of these studies suggest that VSMC apoptosis has a direct, causative role in the generation of arterial aneurysms. Clearly, this is also of relevance if therapeutic induction of VSMC apoptosis is considered.

VSMC apoptosis – important sequelae

Therapeutic induction of apoptosis in the vessel wall may also be limited by important sequelae. In contrast to the prevailing notion that apoptotic deaths are effectively silent (that is, they do not elicit an immune response) a number of deleterious effects of apoptotic cells have emerged within the vasculature. First, the exposure of phosphatidylserine on the surface of apoptotic cells provides a potent substrate for the generation of thrombin and activation of the coagulation cascade [19, 20]. Apoptotic cells release membrane-bound microparticles into the circulation which remain pro-coagulant and are increased in patients with unstable versus stable coronary syndromes [21, 22]. Although apoptotic cells are not the only source of circulating microparticles, such microparticles may contribute to the increased pro-coagulant state in these syndromes.

Apoptotic VSMCs can also release both mitogens (bFGF) and pro-inflammatory cytokines such as MCP-1 resulting in recruitment of monocytes [23], both of which may abrogate any direct reduction in neointima formation. Indeed, in some studies massive induction of apoptosis in intimal VSMCs may reduce cell density but not overall neointimal size or increase lumen dimensions [23]. The demonstration that apoptosis releases active molecules rather negates the idea of apoptosis as a 'silent' mechanism of deleting cells. However, apoptotic cells that are not rapidly phagocytosed will begin to release inflammatory cytokines as they undergo secondary necrosis. This release of inflammatory cytokines will result in the recruitment of monocytes and macrophages to the surrounding area. This may well occur to allow phagocytosis of a large number of apoptotic cells that cannot be efficiently disposed of by surrounding healthy smooth muscle cells [24]. In

atherosclerosis, inefficient phagocytosis of dead cells may occur due to the presence of modified LDL, which hampers phagocytosis of apoptotic cells [25]. Thus, it may be that death is initially silent in atherosclerotic lesions but as corpses mount up and professional phagocytes are impeded by modified LDL, more inflammatory cells may be recruited. Moreover, soluble death ligands such as Fas-L are released from the surface of monocyte / macrophages as they phagocytose, resulting in bystander death of adjacent neutrophils or monocytes [26], enhancing the deficit of professional phagocytic cells. Therefore, the potential for the death and subsequent phagocytosis of apoptotic cells exists in atherosclerotic plaques to trigger further apoptosis, setting up a positive feedback loop.

Summary

The effect of VSMC apoptosis is clearly context-dependent. Thus, VSMC apoptosis in advanced atherosclerotic plaques would be expected to promote plaque rupture (although there is as yet no direct evidence that it does so), and medial atrophy in aneurysm formation (where there is more evidence of such). In neointima formation post injury, VSMC apoptosis of both the intima and media can limit neointimal formation [12, 14, 15] at a defined time point (although long term studies have not been performed to ensure that the neointima is not simply delayed). It is not yet known whether such inhibition of neointimal formation in an animal model can translate into suppression of restenosis following angioplasty or stenting. However, the evidence suggesting that most of angioplasty restenosis occurs through remodelling [27] and the near total failure of anti-proliferative therapy to inhibit restenosis does not augur well.

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