ROLE OF ADVENTITIA IN VASCULAR REMODELING IN HYPERTENSION:
A TROPHOBIOLOGICAL VIEW

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- The vascular wall has the capacity to undergo remodeling in response to long-term changes or injuries. This is a process of structural rearrangement that involves cell growth, cell death, cell migration, cell modulation and secretion/degradation of extracellular matrix molecules (1). Vascular remodeling is an adaptive phenomenon, e.g. Glagov's compensatory enlargement in atherosclerosis (2), but it may grow into vascular diseases (1), such as hypertension (3), atherosclerosis (4,5), and coronary restenosis after angioplasty (2,6,7). Nowadays paradigms defining the cell biology of vascular diseases are the following: (/) the hypertensive vessel is characterized by hyperinnervation-associated medial thickening due to smooth muscle cell (SMC) hypertrophy/hyperplasia and increased extracellular matrix content, (2/) the atherosclerotic plaque is characterized by SMC/immune cells/increased extracellular matrix-containing intimal thickening, and (3/) the restenotic coronary artery is characterized by SMC/immune cells-containing neointimal thickening. The spontaneously hypertensive rats (SHR), the stroke-prone SHR (SHRSP), the genetically hypertensive (GH) rats, and other genetically hypertensive strains are widely used as a model of human essential hypertension. In this volume of Biomedical Reviews, Bell (8) updates the knowledge about vascular wall neurotrophobiology in relation to the pathogenesis of hypertension in SHR and GH rats. Also, Kondo et al (9) systematize the perivascular nerve-related SMC structural changes in the development of hypertension in SHR and SHRSP. The data presented in these reviews are evaluated mainly in terms of Levi-Montalcini's neurotrophic theory (10).

See Reviews on pages 43 and 57

In this context, the role of immune cells in neural-effector interactions should also be considered (see 8 and Refs 23,113-120 therein). The neurobiology of immune cells is one of the expanding fields of neuroscience research, largely due to the involvement of cytokines and neurotrophins in neuroimmune interactions (11). Besides the neurotrophic support of specific populations of neurons, there is an increasing evidence that nerve growth factor (NGF) is "not just for neurons" (12), e.g. it also exerts immunotrophic effects on mast cells and lymphocytes (13, 14). Conversely, stem cell factor (mast cell growth factor, c-kit ligand) and leukemia inhibitory factor are not just for immune cells, they also possess neurotrophic effects (11, 15). This Editorial will attempt to apply lessons learned from the study of vascular diseases and ageing to the trophobiology of vascular remodeling in hypertension.

- Lesson from atherosclerosis: do not Ignore adventitial immune cells and perivascular nerves

In 1962 Schwartz (cited by 16) wrote with respect to the presence of adventitial mononuclear cell infiltration of atheroscle-
rotic vessels: "It is perhaps surprising that such prominent cellular accumulation should have received so little attention... Nevertheless, since cellular infiltration of the adventitia shows such a constant relationship to the presence and degree of plaque formation, it should not be disregarded". This and other related works have been largely ignored (16 and Refs therein), and the atherosclerosis research for a long time has been focused on the intimal changes, appreciating extravasation of immune cells through the arterial lumen, SMC proliferation and hypersecretion of extracellular matrix molecules by SMC (reviewed in 4, 5, 17, in which the word "adventitia" is conceptually absent). However, the observation that adventitial injury alone can lead to intimal thickening is an evidence for the dynamic interaction between the adventitia and intima. Examples of such adventitial injuries include (/) chronic application of lipopolysaccharide (18) and interleukin-1p (19) to the vascular adventitia, (/') placement of a cuff around the adventitial surface (20), and (HI) removal of the adventitia (21-23).

Together these studies suggest a potential role of adventitial immune cells and perivascular nerves in atherosclerosis (Fig. 1). Studies aiming at further evaluation of a neural-immune relationship in atherosclerotic adventitia (29-32) are needed.

**Lesson from coronary restenosis: do not ignore adventitial fibroblasts**

In 1983 at the seminar organized by Dr George Pappas (Department of Anatomy, Medical School, University of Illinois, Chicago, IL), one of us (GNC) delivered a lecture entitled "The fine structure of secretory-state SMC and their possible role in occlusive arterial diseases". During the discussion, the question whether some adventitial fibroblasts may migrate to the intima was raised. The answer of the author was "I do not know. It seems impossible." However, what seemed "impossible" in 1983 was proven possible in 1996 when Shi et al (6) and Wilcox and Scott (16) summarized their results indicating that the adventitial fibroblasts proliferate and modulate their phenotype to myofibroblasts migrating to the luminal surface of the balloon-injured coronary arteries, thus contributing to the neointimal formation. Also, it was recently suggested that neoadventitial formation, consisted of fibrotic tissue and mononuclears, could play an important role in coronary restenosis by circumferential neoadventitial, scar-like contraction, which may cause luminal narrowing (7). Collagen type I involvement in cerebral vasospasm (33) may also be at work for adventitial myofibroblast contraction in restenosis. Altogether these data

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**Figure 1.** A scheme summarizing data about the role of perivascular nerves in the pathogenesis of hypertension and atherosclerosis, including denervation-associated transplant coronary arteriosclerosis (3, 8, 9, 21-24). Question marks are depicted because of missing data about the role of perivascular nerves for vascular immune cell biology. In other tissues, the denervation results in monocyte invasion into superior cervical ganglion (25), mast cell proliferation in spleen (26), lung (26) and gut (27), and mast cell activation in dura mater (28). SMC - smooth muscle cell.
suggest an important role of adventitial fibroblasts in, and bring into question the sole contribution of SMC to neointimal thickening in coronary restenosis. Moreover, they may bring us back in 1886 to Langhans' description of stellate-shaped cells in atherosclerotic plaques (see 34), thus prompting us to reappreciate Virchow's original opinion about the fibroblast nature of these cells. It should also be noted that a large proportion of the intimal foam cells may be derived from foam cells of the media and adventitia rather than from the lumen, after balloon angioplasty of cholesterol-fed rabbits (35).

• Lesson from ageing: adventitial immune cells and fibroblasts may also provide a neurotrophic support to perivascular nerves

Ultrastructurally, perivascular nerve-immune cell (36, 37) and adventitial fibroblast-mast cell (38, 39) links are found in cerebral arteries. Furthermore, there is a correlation between (/) degeneration of SMC, (º) decreased number of adventitial mast cells (see also 40 for human coronary arteries), and (///) atrophy of adventitial fibroblasts (37-39), suggesting that a reduction in the availability of neurotrophins derived from SMC (8, 14), mast cells and/or fibroblasts probably contributes to the decreased density of perivascular nerves during ageing of cerebral arteries (38, 39). These data bring into question the sole contribution of effector SMC to neurotrophic support of perivascular nerves as currently believed.

• Implication of the lessons: appreciate the adventitia in hypertension

In hypertension research, in contrast to atherosclerosis and restenosis, a considerable attention has been paid to the perivascular nerves and their trophic interactions with the medial SMC (3, 8, 9), leaving adventitial immunocytes and fibroblasts ignored. Hence, the morphometry of hypertensive vascular wall traditionally includes measurements of (ie cross-sectional area of intima and media and calculation of media/lumen ratio, the adventitial area being commonly neglected, with an exception of Lee et al (42, 43). These authors showed that neonatal sympathetic alone and its combination with bilateral adrenergic denervation cause adventitial thickening in mesenteric arteries both in SHR and Wistar-Kyoto (WKY) rats. Also, Lee et al (43) found a significant increase in the adventitial thickness in SHR compared to that in WKY rats. The importance of the adventitial thickening in SHR arteries and in arteries from sympathectomized animals is unclear. It is known that sympathetic hyperactivity (3, 8, 9) as well as sympathectomy (24) results in collagen overproduction (see Fig. 1). Recent findings show that angiotensin II-induced medial hypertrophy occurs in densely but not sparsely innervated rat arteries (44). These authors suggest a perivascular nerve-mediated hypertrophic effect of angiotensin II. Such a mechanism may also operate in antinecrotic (9) and/or antiapoptotic (45) action of angiotensin II in vascular SMC. Note that cardiac mast cell-derived chymase possesses angiotensin I-converting enzyme activity and thus contributes to cardiovascular fibrosis (46). Hence, immune cells in cooperation with medial SMC and with adventitial fibroblasts may be involved in the fibrogenesis of hypertension (see Solomon and Levi-Schaffer [47] in this volume of Biomedical Reviews for mast cell-fibroblast interactions in fibrotic diseases, and 48, 49 for immune cells and hypertensive heart fibrosis).

Moreover, evidence is accumulating that bidirectional trophic interactions exist between perivascular nerves and endothelium (50, see also 18-24 mentioned in Lesson from atherosclerosis). “It is thus intriguing that loss of substance P (SP) in nerves at the adventitia results in increase in SP at the intima” in the rat pulmonary artery (51). However, results from the same research group “indicate that endothelial substrate P is unrelated to the substance P content of sensory nerves since there was no difference in endothelial substance P after capsaicin treatment” in rat mesenteric arteries (52). This could represent a form of intervascular heterogeneity (3). Furthermore, endothelial injury enhances the density of SP-positive perivascular nerves (50). The mechanism by which such an adventitia-endothelium cross-talk operates remains unknown. Possibly, the easily diffusable nitric oxide (53) and carbon monoxide (54), the nexuses between medial SMC, and the adventitial immune cell-derived cytokines carried into the vessel wall by the vasa vasorum could mediate the adventitia-endothelium bidirectional interaction. Until such mediators are not discovered, we suggest they be named burnstockines, to appreciate the contribution of Burnstock and coworkers (50, 51).

• Conclusion

The presented data bring into question the sole contribution of vascular SMC to neurotrophic support and, eventually, to medial hypertrophy in hypertensive blood vessels. They raise the significant possibility that a concerted action of different neurotrophins and cytokines derived from multiple cellular sources, i.e. medial SMC, adventitial immune cells and adventitial fibroblasts, is involved in the neurotrophobiology and fibrogenicity of hypertension. This is a substantial part of the hypothesis of neural-immune-effector trophic interactions (38, 39), which application to hypertension research may provide new insights into the pathogenesis and therapy of essential hypertension (Fig.2). In effect, we should recognize that we have paid less attention to the neurotrophic and fibrogenic potentials of the adventitia in vascular remodeling in hypertension. Perhaps it is time to change that.

ACKNOWLEDGEMENTS

• The authors thank Anton B. Tonchev, BSc, Olawale A.R. Sulaiman, BSc and Ruzha Pancheva, BSc for their collaboration.
Figure 2. Suggested role of adventitia-based trophic interactions in vascular remodeling in hypertension. Note that three cell types may provide multifactorial neurotrophic support (arrows in bold).

Abbreviations and the respective references: IL-1 - interleukin-1 (19, 55), TNF-a-tumor necrosis factor-a (11, 47, 55), NGF-nerve growth factor (11-14), NO - nitric oxide (50), E - endothelins (50), ATP - adenosine S'-triphosphate (56), A - adenosine (56), CT-1 - cardiotrophin-1 (57), AngII - angiotensin II (3, 44, 46), NT - neurotransmitters (3, 8, 9, 11), Bk - burnstocksines (50, 51), LIF- leukemia inhibitory factor (11), SCF - stem cell factor (mast cell growth factor) (15), H - histamine (47), FGF-fibroblast growth factor (47). Additional mediator molecules may also be involved but are not shown.

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Biomed Rev 6, 1996