**Smooth muscle cells and vascular diseases**

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Vascular smooth muscle cells (VSMCs) are the stromal cells of the vascular wall, and, due to their myosin/actin interactions, they are also responsible for arterial contractile tone and regulating blood pressure and flow in relation to specific metabolic demands. VSMCs show considerable differences depending on their position in the arterial tree (large conduit vs. small resistance vessels), their embryologic origin, and their organ-dependent microenvironment; the heart, brain, kidney, etc. As the stromal cells of the arterial wall, VSMCs synthesize and secrete insoluble extracellular matrix (ECM) molecules that assume the function of withstanding the high pressure of the circulating blood in the arterial system. For example, totally decellularized aortic grafts, created using sodium dodecyl sulphate detergent, are experimentally able to resist arterial blood pressure in the aorta in vivo, without dilating. This mechanical function predominates in large vessels, since pressure-dependent stress of the wall is also dependent on the diameter. Therefore, cell–ECM interactions are of particular importance in these large arteries. The contractile tonus of VSMCs, dependent on sympathetic innervation, is responsible for the peripheral resistance to blood flow generated by the beating heart, leading to the genesis of blood pressure. This function is mainly the characteristic of resistance arteries and arterioles and involves cell–cell interactions.

Due to pressure-dependent radial hydraulic conductance, the arterial wall is constantly submitted to outward convection of circulating plasma molecules. This physiological outward convection of plasma peptides or macromolecules is the main source of extrinsic stimuli, which, with time, cause damage to arterial VSMCs (pressure-dependent strain, lipid overload, hyperglycaemia, zymogens). In response to changes in their plasma-dependent microenvironment, VSMCs may either die or adapt, modifying their phenotype through acute, ligand/receptor-dependent signalling pathways or chronic nuclear signalling involving epigenetic molecular remodelling of their nuclear chromatin. VSMCs can also be the target of intrinsic defects, mainly due to monogenic diseases, such as Marfan syndrome, which is responsible for aneurysms and dissections of the ascending aorta, via defects in fibrillin or other molecules, or cerebral microangiopathy, via an intercellular molecular defect in Notch. In these contexts, intrinsic molecular defects targeting VSMCs promote extrinsic injury generated by blood-borne components. These pathophysiological concepts illustrate the important role of VSMC plasticity in response to numerous stimuli, and the ability of these cells to switch from their quiescent contractile phenotype to more migratory, proliferative, synthetic, endocytic, phagocytic, or osteoblastic ones (Figure 1).

One of the reviews in this Spotlight on Smooth Muscle Cells and Vascular Diseases by Tsao’s group develops the question of VSMC plasticity and the importance of chromatin remodelling, underlining the predominant role of acetylation/deacetylation and methylation of histones in the differentiation of VSMCs during development. This epigenetic modification of histones leads to changes in DNA accessibility to repressor or enhancer transcription factors. These transcription factors predominantly involve Kruppel-like factor 4, P300, myocardin, and serum responsive factor.

In parallel, Gomez and Owens raise the question of why immunohistochemistry of functional proteins is insufficient to characterize cell lineage, and particularly to differentiate between VSMCs and blood-borne macrophages in human atheroma. Due to their high plasticity, in parallel with the synthetic/proliferative phenotype, VSMCs can also acquire a macrophage-like phenotype, including CD68 positivity, which is associated with endocytic/phagocytic activity, particularly of lipids in the context of atheroma. The authors claim the necessity to use epigenetic markers, rather than functional proteins, for identifying cell origin within the arterial wall.

The question of macrophages vs. VSMCs is also raised by Francis and colleagues. They suggest that the role of VSMCs in foam cell genesis and in cholesterol crystal formation and accumulation is probably underestimated in human early atheroma. Furthermore, there are probably major differences in this field between the mouse and human. They emphasize that VSMCs possess the complete molecular equipment for the endocytosis of modified LDL, including numerous scavenger receptors. On the other hand, VSMCs also possess the ATP-binding cassette transporter A1 (ABCA1), which controls cholesterol efflux, and particularly the ability to transfer excess cholesterol to newly formed HDL particles. The expression ABCA1 is dependent on the nuclear liver X receptor and differs in VSMCs and macrophages. In particular, ABCA1 is poorly expressed by intimal VSMCs, suggesting an increased sensitivity of these cells to foam cell formation. This review also points out the limits of mouse models of atheroma for studying human disease.

Since oxidative stress and signalling play an important role in vascular diseases, the review by Bennett’s group explores the...
predominant role of mitochondria in the genesis of oxidative stress and how mitochondrial damage influences cell death, senescence, and pro-inflammatory phenotype of the vascular wall. Oxidative stress can induce non-specific post-translational modifications of proteins and largely contribute to protein aggregation. Oxidative stress is inseparably linked to mitochondrial dysfunction, as mitochondria are both generators of and targets for reactive oxygen species. Autophagy is a lysosome-mediated degradation process for damaged cell constituents, including protein aggregates. Oxidative stress, accumulation of protein aggregates, and autophagic stress in VSMCs are probably the main consequences of extrinsic injury, including, but not limited to, atherosclerosis. That oxidative stress contributes to deleterious effects of S-adenosyl-homocysteine (SAH) is supported by the demonstration that high plasma SAH levels in apolipoprotein E-deficient mice are associated with larger atherosclerotic plaques, VSMC proliferation, and higher levels of aortic reactive oxygen species. This oxidative stress-dependent proliferative effect involves predominantly the ERK1/2 pathway.

The turnover of intracellular proteins governing VSMC survival and response to hypoxia is regulated by the ubiquitin proteasome system (UPS). Indeed, acceleration of hypoxia-inducible factor-α subunit (HIF-1α) proteasome-dependent degradation contributes to inhibition of HIF-1-induced ET-1 gene expression by statins. Demasi and Laurindo detail the involvement of the proteasome system in VSMCs, with emphasis on transcription control and inflammation. There is now growing evidence for a strong effector role of the proteasome in the transition from the contractile to the synthetic phenotype. The UPS down-regulates NADPH oxidase activity in parallel with the degradation of NOS isoforms. NFκB activation and its migration to the nucleus for transcriptional regulation of inflammatory cytokines are dependent on proteasome-mediated IkB degradation. This review points out the complexity of the opposing and context-specific effects of proteasome activation/inhibition in pathology and pharmacology.

VSMCs are the main cellular determinants of arterial wall pathology. Mechanical signals can directly (blood pressure) or indirectly (shear rate mediated by endothelium) influence the VSMC phenotype. VSMCs directly participate in the genesis of hypertension and are also targets for hypertension in large arteries via VSMC/ECM interactions. Hypertension increases contractile protein synthesis (hypertrophy) and ECM protein secretion, contributing to the increase in wall rigidity. Similar changes are observed in ageing. In early atheroma, VSMCs are first in line to support lipid retention via glycosaminoglycan synthesis, lipid overload via foam cell formation and death, and healing via intimal migration and fibrous cap synthesis. The VSMC is also the organizer of the adventitial response, particularly of the inwardly directed angiogenic response to lipid overload.

Cell therapy-based approaches, using smooth muscle progenitor cells (SMPCs) along with endothelial progenitor cells (EPCs), have emerged as promising therapeutic tools for regenerative medicine. Levy’s group summarizes the current knowledge on different origins of circulating or resident SMPCs. Several putative earlier markers of SMPCs have been suggested, but immature SMPCs exhibit a flexible phenotype, partially overlapping with that of several other progenitor cell types, including EPCs. Although no correlation between in vitro differentiation of SMPCs and their functional properties has yet been established, their therapeutic use is moving towards co-implantation of SMPCs and EPCs in post-stroke ischaemia and angiogenesis. On the other hand, adult and embryonic stem cells could provide an abundant source of VSMCs and endothelial cells for therapeutic use. In their review, Liu describes how physical and mechanical cues, like cell shape and the rigidity of the matrix microenvironment, regulate not only the stem cell expansion and commitment to different lineages, but also cell behaviour, such as switching of
VSMCs between proliferative and contractile phenotypes. Integrins play an important role in the transmission of biochemical signalling to genomic programme expression via the formation of focal adhesions, which recruit diverse scaffold and signalling proteins, regulating the dynamics of adhesion and the actin cytoskeleton.

In contrast, as described above, in small arteries the cell–cell interactions are predominant. In their review, the Joutel group\(^5\) describes the role of the Notch system in these VSMC interactions. Notch signalling plays an important role in the development of small arteries, and Notch mutations are directly involved in CADASIL disease (a pathology of small cerebral arteries leading to vascular dementia).

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They hypothesize that the contribution of GPCRs/mediators in the control of myogenic tone may depend on both the receptor level and the local generation of appropriate agonists.

Wnt signalling is conserved in mammals and exists as two intracellular pathways, i.e. canonical (ß-catenin-dependent) and non-canonical (ß-catenin-independent) Wnt signalling. Wnt ligands trigger signalling pathways via their interaction with Frizzled receptors as well as with a specific co-receptor. In their review, Mill and George\(^25\) present data indicating that the mutation or altered expression of genes encoding Wnt signalling components is associated with increased incidence of early coronary artery disease, hypertension, and type-2 diabetes. They hypothesize that Wnt signalling is likely to play an important role in atherosclerosis, aneurysm formation and intimal thickening, given its involvement in SMC proliferation, migration, and survival. They also discuss the exploitation of small molecule Wnt inhibitors, which act at different steps in the Wnt/ß-catenin signal transduction pathway, as potential therapeutic reagents.

In conclusion, this special issue on VSMCs presents new experimental and conceptual progress in the comprehension of mechanisms driving the diversity of VSMC functions and phenotypes. This progress covers both the cell pharmacology of intracellular signalling and the response to changes in the VSMC microenvironment. These spotlight reviews shed new light on the plasticity of VSMCs, the stromal cells of the arterial wall, which are able to remodel their pattern of genomic expression in different ways, including constitutive epigenetic switching of gene expression. Although some aspects of this molecular genomic remodelling have already been explored, e.g. the switch from contractile to synthetic phenotype, other important responses remain to be further investigated in the near future in relation to other changes in the VSMC microenvironment, including lipid overload and endocytosis, in the context of vascular diseases.

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References