NR4A nuclear receptors in vascular disease
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General Introduction on Atherosclerosis and Restenosis
Atherosclerosis

The underlying cause of cardiovascular diseases, like coronary artery disease (CAD) and stroke, is atherosclerosis. Well-known risk factors for atherosclerosis are described and include amongst others age, hypertension, diabetes, dyslipidemia, smoking and chronic inflammatory diseases. Beyond these systemic risk factors, local artery-defined factors are of importance, which is reflected by the tendency of atherosclerotic plaques to arise at locations in the vascular tree prone to turbulent blood flow such as bifurcations and curvatures. Formation of atherosclerotic plaques is characterized by an accumulation of oxidized lipids and cellular debris accompanied by a chronic inflammatory response leading to increased inflammatory cell and smooth muscle cell (SMC) content and extracellular matrix deposition in the arterial vessel wall. Atherosclerotic plaques can grow in size over decades without clinical symptoms since arteries can preserve their luminal diameter and thus maintain arterial blood flow to distal organs by expansive, outward arterial remodeling. However, when atherosclerotic plaque growth exceeds this compensatory, outward remodeling the organ involved can become ischaemic especially in situations of increased oxygen demand, which results in clinical symptoms like angina pectoris (heart), angina abdominale (intestine) or claudicatio intermittens (leg). In case of plaque rupture, acute obstruction of blood flow can occur by thrombus formation, which results in infarction of the distal organ, for example myocardial infarction or stroke.

The healthy arterial vessel wall consists of three layers: the intima, media and adventitia. The innermost intima is composed of a single-cell layer denoted as the endothelium, which separates the blood from other components of the vessel wall and is supported by the internal elastic lamina that separates the endothelium from the arterial media. The endothelium is crucially involved in regulation of vascular tone and permeability and prevents blood coagulation. The normal arterial media consists of SMCs and extracellular matrix components, which stabilize the arterial wall and generates vascular tone. The most outer layer of the artery is called the adventitia and consists of extracellular matrix components, (myo)fibroblasts and vasa vasorum.

Early in atherogenesis, endothelial cells become dysfunctional, which results in leakage and accumulation of low-density lipoprotein (LDL) in the subendothelial space that become oxidized by resident reactive-oxygen species (ROS). These dysfunctional endothelial cells express enhanced levels of adhesion molecules that provoke increased monocyte recruitment. Recruited monocytes differentiate into macrophages that express scavenger receptors, including scavenger receptor-A (SR-A) and CD36, enabling these cells to internalize oxidized LDL that are stored in lipid droplets. When these cells become loaded with lipid droplets they
get a foamy appearance when seen through the microscope and become so called ‘foam cells’. These foam cells are the main constituent of an early atherosclerotic lesion or ‘fatty streak’ and produce cytokines and chemokines that further propagate the inflammatory response. When such an early atherosclerotic lesion progresses to an advanced lesion, these ‘foam cells’ can become necrotic and contribute to necrotic core formation. SMCs dedifferentiate from a contractile to a synthetic phenotype and proliferate and migrate to the intima, where they form a substantial part of the lesion and contribute to fibrous cap formation. This fibrous cap, covered by endothelium prevents contact of thrombogenic plaque constituents with the blood stream. Due to the release of matrix-degrading enzymes like matrix metalloproteinases (MMP) by macrophages such a fibrous cap can become unstable or vulnerable, which may result in plaque rupture, thrombus formation and infarction of tissue distal of the artery involved.

**Atherosclerosis-related pathologies: restenosis and vein graft disease**

A close relation exists between atherosclerosis and vascular pathologies that occur after invasive atherosclerosis treatment modalities, including coronary artery bypass grafting (CABG) or percutaneous (transluminal) coronary angioplasty or intervention (PTCA or PCI). During the latter procedure, the culprit lesion that obstructs blood flow to a distal segment of the myocardium is treated by catheter-delivered intra-coronary high pressure balloon dilatation followed by stent placement. The main complication of this procedure is so-called ‘in-stent restenosis’, which is the result of a response-to-injury of the artery involved. The injury response is evoked by de-endothelialization, crush of the plaque and stretch of the artery segment. The denudated arterial vessel wall recruits and activates platelets and leucocytes, which produce cytokines and growth factors that stimulate SMC proliferation, migration and extracellular matrix deposition. As opposed to atherosclerotic lesions, these lesions arise in weeks to months after the procedure and are mainly composed of SMCs and fibrous material. The discovery of pathophysiological mechanisms involved has resulted in the application of drug-eluting stents (DES) that target cellular proliferation and inflammatory responses. Nowadays, sirolimus and paclitaxel-coated stents are frequently used, which has resulted in a significant reduction of in-stent restenosis incidence. However, the use of DES is associated with a higher incidence of in-stent thrombosis, a potentially fatal condition.

The surgical procedure of coronary artery bypass grafting (CABG) is an alternative treatment for coronary atherosclerosis. During CABG, culprit lesion(s) are bypassed by one or more grafts most frequently derived from a native saphenous vein or mammary or radial arteries. It is well-known that native arterial grafts have a better patency than saphenous vein grafts. The failure of venous grafts is caused by a vascular pathology called ‘vein graft disease’, which
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is considered an accelerated form of atherosclerosis that is characterized by excessive SMC proliferation. Amongst others the high, pulsatile arterial blood pressure to which the vein grafts are exposed has been put forward as an important etiological factor in this disease.\(^9\)

References