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Mechanisms of Leukocyte Recruitment Into the Aorta During Atherosclerosis

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1. Introduction

Atherosclerosis continues to be the leading cause of cardiovascular disease. Atherosclerotic lesion progression depends on chronic inflammation in the aorta and the immune response is involved in this process (Galkina & Ley, 2009; Hansson & Hermansson, 2011). While it is now generally accepted that chronic inflammation of the arterial wall, precipitated by an immune response targeting modified low density lipoproteins, heat shock protein 60, \( \beta2 \)-glycoprotein I, and other self-antigens, underlies the pathophysiology of atherosclerosis, this notion was met with scepticism historically.

The term atherosclerosis was first introduced by the French surgeon and pathologist Jean Lobstein in 1829. Within a few years the associated cellular immune alterations in the arteries of atherosclerotic cadavers were described by two schools of pathology yielding two theories on the pathology atherosclerosis. Carl von Rokitansky proposed that initial injury of the aorta preceded the cellular inflammatory changes, suggesting a secondary role for aortic leukocytes. In contrast, Rudolf Virchow postulated an initiating role for aortic cellular conglomerates (Methe & Weis, 2007; Mayerl et al., 2006). However, despite these observations, the response-to-injury model of atherosclerosis prevailed in the literature until the early 1980s. In 1979, the presence of monocytes adhering to the endothelial layer of porcine and human atheroma was demonstrated (Gerrity & Naito, 1980). In 1980, expression of HLA-DR by vascular endothelial cells was reported (Hirschberg et al., 1980). It was also found that interferon-\( \gamma \) (IFN-\( \gamma \)) potently induced MHC-II expression on cultured endothelial cells, suggesting that T cell-derived cytokines may play an important role in the vasculature (Pober et al., 1983). In 1985 and 1986, the presence of HLA-\( \text{DR}^+ \) cells, CD4\(^+\) and CD8\(^+\) T cells in carotid endarterectomy specimens was reported, further implicating that a cellular immune response occurs in atherosclerosis (Jonasson et al., 1985; Jonasson et al., 1986). Since these initial findings a plethora of recent papers have further highlighted the presence of multiple subsets of leukocytes in aortas, and demonstrated the importance of the immune system during atherogenesis. The occurrence of inflammatory cells in the aorta depends on the dynamics of their recruitment and possibly egress, as well as the balance between proliferation, survival, and apoptosis within the aorta. To date, several adhesion molecules and chemokines, which support subset-specific leukocyte homing into the aorta, have been identified, but questions concerning the role of the adventitial vasa vasorum in leukocyte homing, kinetics and the specific mechanisms of migration of different cell subsets including B cells, T cells, mast cells, Treg and Th17 cells remain to be answered.
2. Multiple steps of the adhesion cascade

Peripheral blood leukocytes are programmed to constitutively home to secondary lymphoid organs in search of possible antigens, in order to mount an appropriate immune response against infections. It has also been recognized that a small subset of leukocytes home into non-lymphoid tissues as a part of constitutive homing in order to sample antigens in local tissues. In line with this notion, leukocytes are found within normal/non-inflamed aortas and recent studies have demonstrated that these cells constitutively migrate into the aorta. The migration of leukocytes into non-lymphoid sites where injury, infection or inflammation has occurred is also highly specific. To date, there are several examples of immune-mediated chronic diseases such as rheumatoid arthritis, Type 1 diabetes mellitus, psoriasis, and multiple sclerosis that have marked adhesion molecule-mediated homing of leukocytes into the site of inflammation. It is now appreciated that atherosclerosis-prone conditions activate aortic vascular cells, upregulate adhesion molecules, and chemokines; thereby supporting leukocyte homing into the aorta (Galkina & Ley, 2007a) - a key step in the pathology of atherosclerosis.

2.1 Steps of the adhesion cascade

2.1.1 Selectins and rolling

The adhesion cascade is defined as series of overlapping and synergistic interactions among adhesion molecules and chemokines. There are several major steps of the leukocyte adhesion cascade including selectin-dependent tethering and rolling, selectin or arrest chemokine-dependent activation, integrin-dependent arrest, firm adhesion and diapedesis, which are closely interconnected and regulate cell-specific migration. The first steps of the adhesion cascade consist of tethering, capture, and rolling, which are initiated via selectin-carbohydrate ligand interactions along the endothelium (McEver, 2002). L-selectin is expressed by all leukocytes, mediates leukocyte rolling and can also participate in secondary capture, defined as leukocyte capture by adherent leukocytes (reviewed in (Ley et al., 2007)). P- and E-selectin are expressed by the activated endothelium and serve as rolling molecules for most leukocytes (McEver, 2002). Activated platelets also express P-selectin. P-selectin binds PSGL-1 expressing neutrophils, monocytes, and lymphocytes (Ley & Kansas, 2004). E-selectin binds PSGL-1, CD44, E-selectin ligand-1 (ESL-1) on myeloid cells and CD43 on T-helper 1 lymphocytes (reviewed in (Ley et al., 2007)). Selectins tightly control leukocyte rolling velocity via regulation of the rapid formation and dissociation of bonds between selectins and their ligands (Alon et al., 1997). L- and P-selectin support rolling at relatively fast velocities, while E-selectin supports leukocyte rolling at very slow velocities (Kunkel & Ley, 1996). Evidence suggests that selectin ligation by endothelial ligands can induce activation of integrins, and provide a link between rolling and the subsequent integrin-mediated firm adhesion (Zarbock et al., 2007).

2.1.2 Integrins, arrest chemokines, and firm adhesion

Following the steps of tethering and rolling, leukocyte integrins initiate slowing rolling, and induce further firm adhesion. The integrin family consists of α and β subunits that form heterodimers yielding a total of 24 integrins (Hynes, 2002). All leukocytes express leukocyte function-associated molecule (LFA-1, CD11a/CD18, or α-Lβ2), while myeloid cells predominately express Mac-1. Endothelial ligands for LFA-1 and Mac-1 include intercellular adhesion molecule 1 (ICAM-1) and ICAM-2. The α4β1 (VLA-4) integrin is a member of the α4
subfamily and is mostly expressed on extralymphoid monocytes and on lymphocytes (Luster et al., 2005). Vascular cell adhesion molecule-1 (VCAM-1) (Kinashi, 2007) and the CS-1 peptide of fibronectin (Guan & Hynes, 1990) serve as ligands for VLA-4. VCAM-1 is not constitutively expressed in most tissues, but is upregulated after stimulation with TNF-α and IL-1. Chemokines support migration via the formation of chemotactic gradients from emigrated leukocytes and resident tissue cells. Endothelial cells synthesize and present chemokines on the luminal surface. Most chemokines can be also immobilized by extracellular matrix components, including heparan sulfate and glycosaminoglycans, and presented to leukocytes (Ley et al., 2007). Several members of a specialized group of arrest chemokines play an essential role in integrin activation and firm adhesion.

2.1.3 JAMs, PECAM-1, VE-Cadherin and transmigration

Increased time of firm leukocyte adhesion reduces rolling velocities, and initiates cell crawling or locomotion in order to find an appropriate site for transmigration/diapedesis. There are two principal mechanisms of transmigration: via intercellular junctions or through the endothelial cell body (Carman & Springer, 2004; Shaw et al., 2004). To date, it is unclear which parameters preferentially affect the pathways of transmigration. CD99-related antigen (CD99L2), endothelial cell-selective adhesion molecule (ESAM) and junctional adhesion molecules (JAMs) are important regulators of diapedesis. JAMs belong to the members of immunoglobulin superfamily, which are localized to intercellular junctions of polarized endothelial and epithelial cells, but are also expressed on circulating leukocytes and platelets (Mandell & Parkos, 2005). JAMs participate in homophilic and heterophilic cell interactions, and thus, support the extravasation of leukocytes into tissues. JAM-A binds to LFA-1, JAM-B to VLA-4, and JAM-C to Mac-1 (Vestweber, 2007). VE-cadherin is expressed between endothelial cells and serves as a barrier for extravasating leukocytes in vivo (Lampugnani et al., 1992). ICAM-1 and ICAM-2 can also participate in leukocyte transmigration through the development of the specific structures that surround leukocytes during transmigration (Carman & Springer, 2004), and/or form ring-like clusters of LFA-1 at the interface between the transmigrating leukocyte and endothelial junctions (Shaw et al., 2004). Platelet endothelial cell adhesion molecule-1 (PECAM-1) is a member of the immunoglobulin superfamily that is expressed on leukocytes, platelets, and interendothelial junctions. PECAM-1 promotes leukocyte transmigration as an adhesion molecule (Newman, 1997), but can also serve as a signaling receptor (Vestweber, 2007).

3. Regulators of adhesion molecule expression in atherogenesis

Many inflammatory factors such as multiple cytokines, 5-lipoxygenase, 12/15-lipoxygenase, heme oxygenase-1, paraoxonases, C-reactive protein, reactive oxygen species, advanced glycation end products (AGE), oxidized-LDL, and blood flow conditions (reviewed by Tedgui & Mallat, 2006; Galkina & Ley, 2009), play crucial roles during atherogenesis. One of the many essential functions of these factors is the induction and the regulation of the expression of adhesion molecules and chemokines. As these factors have been reviewed in depth elsewhere (Galkina & 2009; Tedgui & Mallat, 2006), we will focus briefly only on some inflammatory molecules and conditions that have been demonstrated to affect the expression of adhesion molecules and chemokines within the vasculature.
3.1 Effects of cytokines on the expression of aortic adhesion molecules and chemokines

3.1.1 TNFα and the TNFα superfamily

The pro-inflammatory effects of TNF-α in atherogenesis are well established. TNF-α upregulates a variety of adhesion proteins, including LFA-1, VCAM-1, and ICAM-1 on human endothelial cells in vitro (Sprague & Khalil, 2009). Cleavage, but not the membrane bound form of TNF-α, is required for TNFα’s pro-atherogenic properties. Mast-cell-, MΦ-, and neutrophil-derived TNF-α and IL-6 similarly promote the expression of several adhesion molecules, including VCAM-1, ICAM-1, P- and E-selectin, in endothelial cells and further support the adherence of neutrophils under physiological shear stress conditions (Zhang et al., 2011). Another member of the TNF superfamily, Lymphotoxin-ǃ (LTǃ), can similarly promote CXCL13 and CCL21 induction in medial smooth muscle cells (Grabner et al., 2009). In addition, further investigation into the mechanisms behind LTβ-receptor mediated production of CXCL13 and CCL21 by smooth muscle cells revealed a synergistic interaction between TNF-α and LTβ-ǃ mediated activation of the NF-κB pathway that led in elevated expression of multiple chemokines in smooth muscle cells (Lötzer, et al. 2010).

3.1.2 The interleukin-17 family

Recently, several studies have demonstrated the presence of Th17 and other IL-17A+ cells within murine and human atherosclerotic tissues (Ait-Oufella et al., 2011). Th17 and other IL-17A+ T cells play critical roles in the defence against extracellular bacteria and fungi, but also promote inflammation in multiple autoimmune disorders through the production of several chemokines by IL-17 receptor expressing resident epithelial, endothelial cells, and fibroblasts. IL-17A may similarly be involved in atherogenesis through the production of multiple chemokines and adhesion molecules; however, the exact role of this cytokine is currently contested.

3.2 The effect of other inflammatory factors and flow conditions on the expression of adhesion molecules and chemokines

3.2.1 Modified LDL

In addition to oxLDL’s antigenic properties and its ability to induce foam cell formation and endothelial cell dysfunction, several studies have demonstrated that modified LDL may also directly affect the expression of adhesion molecules, and thereby affect the recruitment of leukocytes to the aorta. OxLDL can be trapped beneath the subendothelial matrix via heparin sulphate-dependent binding in vivo (Pillarisetti et al., 1997) and thus, locally affect vascular cells. OxLDL promotes P-selectin expression in activated human aortic endothelial cells (Gebuhrer et al., 1995), and monocyte transmigration through human umbilical vein endothelial cell layers (Hashimoto et al., 2007). Similarly, modified (Keiper et al., 2005; Parhami et al., 1993) or enzymatically degraded LDL (Klouche et al., 1999) induces CCL2, CXCL1, ICAM-1, PECAM-1, JAM-C, P- and E-selectin in endothelial cells in vitro. Several studies have demonstrated that lysophosphatidylcholine (LysoPTdCho), a component of oxidized LDL, functions as a chemotactic factor for monocytes (Quinn et al. 1988), and neutrophils (Murugesan et al. 2003), both directly (Quinn et al. 1987), and via regulation of endothelial VCAM-1, ICAM-1 (Kume et al. 1992), CCL2, and IL-8 (Murugesan et al. 2003).
Fig. 1. Regulators of adhesion molecule expression.

Several factors that may affect the expression of adhesion molecules during atherogenesis are shown. Multiple cytokines upregulate adhesion molecule expression in endothelial and smooth muscle cells. In addition, other pro-inflammatory conditions such as low shear stress, oscillatory blood flow (arrows, right), modified LDL, ROS and AGE (not shown) regulate endothelial and smooth muscle cell adhesion molecules. “Dec.” denotes adhesion molecules that have been demonstrated to be down regulated.

3.2.2 Flow conditions

Flow conditions at branching points of the vasculature may also affect the expression of adhesion molecules and account for anatomical variations in the sites of atherogenesis (VanderLaan et al., 2004). Shear stress, the force that acts on the endothelium as a result of blood flow, plays a critical role in the development of endothelial dysfunction and atherosclerosis. Areas of coronary arteries that exhibit low shear stress or areas where shear stress is oscillatory frequently contain atherosclerotic plaques (Davies et al., 2002; Pedersen et al., 1999). There are multiple lines of evidence indicating that the areas of low shear stress or oscillatory flow conditions display changes in the expression of adhesion molecules. Indeed, human aortic endothelial cell culture with oscillatory flow conditions in vitro upregulate VCAM-1 and ICAM-1 (Brooks et al., 2002). Similarly, in an in vivo model of oscillatory flow using a common carotid artery cast in Apoe-/- mice, several chemokines were upregulated in areas of low shear stress (CCL2, CXCL1, CXCL10, and CX3CL1) and oscillatory shear stress (CCL2, and CXCL1) (Cheng et al., 2007). Furthermore, in a study examining the response of endothelial cells to changes in shear stress, HAECs pre-stimulated with TNF-α and simultaneously exposed to a linear gradient of shear stress (0-16 dyne/cm²) resulted in the upregulation of VCAM-1, E-Selectin under lower shear stress conditions and ICAM-1 under high shear stress conditions (Tsou et al., 2008).
3.3 Soluble adhesion molecules and atherosclerosis

Multiple studies have demonstrated that soluble adhesion molecules, including sE-Selectin, sP-Selectin, sL-Selectin, sVCAM-1, sICAM-1, sCD40, and sCD40L, are elevated within the plasma of coronary artery disease patients and are associated with the severity of stenosis, as well as, several atherosclerotic disease risk factors including smoking, obesity, diabetes, hypertension, etc (reviewed in Roldan, et al. 2003). However, the functional relevance of these soluble adhesion molecules is currently unclear. Increased levels of soluble adhesion molecules may arise from cytokine-stimulated shedding, enzymatic cleavage, loss of membrane integrity, necrosis, and/or apoptosis (Pigot et al., 1992; Leeuwenber, et al. 1992; Newman, et al., 1993), and may play a role in antagonizing leukocyte recruitment (Tu, et al. 2001) or promote leukocyte recruitment through the formation of cellular aggregates. Ultimately, additional mechanistic studies will be required in order to pinpoint the functions of these soluble forms in vivo.

4. Leukocyte migration into aortas

4.1 Monocytes

4.1.1 Monocyte homing to the aortic wall

Monocytes play a key role in atherosclerosis (reviewed in (Galkina & Ley, 2009; Hansson & Hermansson, 2011)). Monocytes migrate into the sub-endothelial space of the aortic intima, where they differentiate into Mφ (Gerrity and Naito, 1980; Jonasson et al., 1986), and dendritic cells (Bobryshev and Lord, 1998). Although it has not been shown directly, some data suggest that environmental signals within the blood and aortas determine the differentiation programs that give rise to Mφ or dendritic cells in the aorta. Monocyte accumulation is progressive and proportional to the extent of atherosclerosis (Swirski et al., 2006). Monocyte-derived cells are found in both the aortic adventitia and in atherosclerotic lesions. Similar frequencies of adoptively transferred allelic CD45 isoform monocytes and recipient monocytes were found within the carotid lesions, but not the adventitia of recipients; suggesting that Mφ-derived foam cells arise mainly from blood-derived monocytes rather than resident Mφ (Lessner et al., 2002). Whether or not adventitial Mφ include a self-renewing pool remains unclear. The spleen can also serve as a reservoir of monocytes (Swirski et al., 2009). The role of splenic monocytes in atherosclerosis remains to be determined.

P-selectin was one of the first adhesion molecules that clearly showed its involvement in monocyte recruitment into the aorta. Blockade of P-selectin resulted in reduced monocyte rolling and attachment to the carotid endothelium (Ramos et al., 1999). Further experiments demonstrated that P-selectin deficiency caused a decrease in fatty streaks and reduction in Mφ numbers within the plaques (Table I). E-selectin expression is elevated within atherosclerotic aortas, and E-selectin deficiency causes slightly reduced plaque burden (Collins et al., 2000). There is a functional overlap between E-selectin and P-selectin as combined deficiency in E- and P-selectin decreases atherosclerosis by 80% (Dong et al., 1998). Recently, a potential role for β2 and β3 integrins and an intracellular protein-thrombopoiesis (TSP)-4 in monocyte migration was proposed. Deficiency in TSP-4 lead to reduced number of lesional Mφ, and decreased β2 and β3 integrin-dependent Mφ adhesion and migration in vitro (Frolova et al., 2010).
VCAM-1 is a central adhesion molecule that supports slow rolling and tight adhesion of monocytes to the atherosclerotic endothelium. Blockade of VCAM-1 or \(\alpha_4\) integrins resulted in increased rolling velocity and attenuated adhesion of monocytes in ex vivo models of isolated perfused carotid arteries (Huo et al., 2000; Ramos et al., 1999). Blockade of \(\alpha_4\) integrin using blocking Abs showed reduced influx of \(\Phi\) into plaques (Patel et al., 1998). Since VCAM-1-deficient mice are not viable, mice in which the fourth Ig domain of VCAM-1 was disrupted (\(Vcam^{D4D/D4D}\)) were generated (Cybulsky et al., 2001). Reduced levels of VCAM-1 resulted in the reduction of atherogenesis in \(Vcam^{1D4D/D4D}Ldlr-/-\) mice (Cybulsky et al., 2001). VCAM-1 levels affect plaque formation, since \(Vcam^{1D4D/+}Apoe^{-/-}\) mice showed a gene-dosage dependent influx of monocytes and plaque burden (Dansky et al., 2001).

Evidence suggests that several arrest chemokines expressed on the endothelium initiate integrin activation and firm leukocyte adhesion. CXCL1 (Huo et al., 2001) and CCL5 (Huo et al., 2003) either alone or as a heterodimer with CXCL4 (von Hundelshausen et al., 2005) have been discovered as aortic arrest chemokines for monocyte adhesion. CXCL1 and CCL5 and their receptors CXCR2 and CCR5 promote monocyte arrest on the atherosclerotic endothelium in the flow chamber system (Huo et al., 2001; Huo et al., 2003; Weber et al., 1999). CXCL7 also efficiently triggers monocyte arrest to the inflamed endothelium under flow conditions (Baltus et al., 2005). Migration inhibitory factor (MIF) regulates monocyte arrest via the interaction of the CXCR2/CD74 complex expressed on monocytes with MIF-expressing atherosclerotic endothelium (Bernhagen et al., 2007). Additionally, MIF deficiency or the blockade of MIF with anti-MIF Abs resulted in reduced lipid deposition, intimal thickening and \(\Phi\) infiltration in the aorta (Pan et al., 2004; Burger-Kentischer et al., 2006).

CCL2 is one of the key chemokines in monocyte biology. Classical CCR2\(^+\) monocytes exit the bone marrow in a CCL-2-dependent manner, and both CCL2 and CCL7 maintain monocyte homeostasis in the circulation (Serbina & Pamer, 2006; Tsou et al., 2007). Several studies suggest that the CCL2/CCR2 axis participates in atherogenesis by the modulation of monocyte recruitment into the aorta (Boring et al., 1998; Dawson et al., 1999; Gosling et al., 1999; Gu et al., 1998). Interestingly, since CCL2 has no effects on monocyte arrest on the early atherosclerotic endothelium (Huo et al., 2001), CCL2 may function as a regulator of monocytes egress from bone marrow or chemokine that regulates monocyte transmigration.

Deficiency of JAM-A reduces monocyte arrest and transmigration on activated JAM-A-deficient endothelial cells under flow conditions in vitro, and attenuates neointimal formation (Zernecke et al., 2006). In line with this notion, JAM-A is involved in monocyte adhesion to isolated perfused Apoe\(^{-/-}\) carotid arteries (Ostermann et al., 2005). JAM-C blockade decreases neointimal \(\Phi\) content and reduces neointimal hyperplasia indicating a potential role of JAM-C in the regulation of monocyte transmigration (Shagdarsuren et al., 2009). Inactivation of ESAM-1 leads to diminished transmigration of THP-1 cells in in vitro assays, and ESAM-deficient Apoe\(^{-/-}\) mice display attenuated atherosclerosis (Inoue et al., 2010). It is interesting that not only the adhesion molecules, but also one of the scavenger receptors – CD36 regulates \(\Phi\) migration. CD36 signaling in response to oxLDL alters cytoskeletal dynamics and inhibits the migration of \(\Phi\)s. This may be one of the mechanisms of \(\Phi\) accumulation in aortic lipid-rich areas (Park et al., 2009).
Table 1. Adhesion molecules and chemokine receptors that are involved in the recruitment of leukocytes into the aortic wall. (Adapted from (Galkina & Ley, 2007))

| Leukocyte type | Adhesion molecules, chemokine receptors | Effects | References |
|---------------|----------------------------------------|---------|------------|
| Monocytes, adhering | VCAM-1, VLA-4 (adhesion) | Increased rolling velocities with anti-VCAM-1 or anti-βintegrin Abs. Increased rolling velocities and decreased adhesion by blocking of VLA-4 binding to both VCAM-1 and fibronectin connecting segment-2 (FnII-3, an αvβ3–β1 integrin model of isolated perfused carotid artery). Blockade of VLA-4 with anti-VLA-4 Abs decreases monocyte migration in vivo. Reduced early atherosclerotic lesions (Viamin-<sup>−/−</sup>, Nbig<sup>−/−</sup>) mice). | (Huss et al., 2000; Rema et al., 1999) |
| Monocytes, integrins | ICAM-1 (adhesion) | Decreased short-term monocyte migration into plaques by blocking Abs to ICAM-1 (VLA-4) mAbs. Reduced lesions in Apoe<sup>−/−</sup> and Viamin-<sup>−/−</sup>, Nbig<sup>−/−</sup> mice on W LDL (Huss et al., 1998; Rema et al., 1999; von Handlhausen et al., 2005). | |
| Monocytes, chemokines | CXCL-1, CCL-5, CCL-3, CCL-7, MIF | Monocyte arrest in the flow chamber assay. Interactions via CXCL-1/CCL-5/CCL-7/MIF complex induce integrin activation. | (Barnes et al., 2007; Ohle et al., 1999; von Handlhausen et al., 2005) |
| Monocytes, chemokines | JAM-A (transmigration) | JAM-A blockade decreases neointimal MIF after wire injury of carotid artery. | (Zumsteg et al., 2006) |
| Monocytes, chemokines | JAM-C (transmigration) | JAM-C blockade decreases neointimal MIF after wire injury of carotid artery. | (Zumsteg et al., 2006) |
| Monocytes, chemokines | CD35 | Regulate cell migration dynamics to inhibit migration and enhance MIF spreading. Adhesion and migration assays with CCL-5 monocytes in vitro. | (Parks et al., 2006) |
| Inflammatory and Paracrine monocytes | COR5, COR2, CXCR3, CCR5 | COR5 blockade with neutralizing Abs, Corz<sup>−/−</sup> and Ccr5<sup>−/−</sup> monocytes in inflammatory functions using T cell assays to distinguish between monocyte subtypes. | (Barnes et al., 2007; Tickle et al., 2007) |
| Possible effects | COR7 | Blockade of CCR5<sup>−/−</sup> cell migration by blocking Abs to CCL-1 and CCL-21 or CCR5<sup>−/−</sup> in transgenic model of atherosclerosis. | (Feig et al., 2012; Troger et al., 2008) |
| T cells | L-selectin (lipoprotein) | Reduced migration of Sflk<sup>−/−</sup> T cells into aortas of C57BL/6 and Apoe<sup>−/−</sup> mice (adverse transplantation), L-selectin deficiency reduces primary and secondary capture (intravital microscopy of femoral arteries). | (Galkina et al., 2006; Eller et al., 2006) |
| CCL-5 (adhesion/migration) | Reduced migration of Sflk<sup>−/−</sup> T cells into aortas of C57BL/6 and Apoe<sup>−/−</sup> mice (adverse transplantation), L-selectin deficiency reduces primary and secondary capture (intravital microscopy of femoral arteries). | (Galkina et al., 2006; Eller et al., 2006) |
| CXCR3 (adhesion/migration) | Reduced migration of Sflk<sup>−/−</sup> T cells into aortas of C57BL/6 and Apoe<sup>−/−</sup> mice (adverse transplantation), L-selectin deficiency reduces primary and secondary capture (intravital microscopy of femoral arteries). | (Galkina et al., 2006; Eller et al., 2006) |
| CXCR6 (adhesion/migration) | Reduced migration of Sflk<sup>−/−</sup> T cells into aortas of C57BL/6 and Apoe<sup>−/−</sup> mice (adverse transplantation), L-selectin deficiency reduces primary and secondary capture (intravital microscopy of femoral arteries). | (Galkina et al., 2006; Eller et al., 2006) |
| MIF (adhesion/migration) | Reduced migration of Sflk<sup>−/−</sup> T cells into aortas of C57BL/6 and Apoe<sup>−/−</sup> mice (adverse transplantation), L-selectin deficiency reduces primary and secondary capture (intravital microscopy of femoral arteries). | (Galkina et al., 2006; Eller et al., 2006) |
| B cells | L-selectin (lipoprotein) | Reduced homing of adoptively transferred L-selectin-deficient B cells into normal and atherosclerotic aortas. | (Galkina et al., 2006) |
| Neutrophils | CXCL-12/CXCR4 (migration) | Blockade of CCL-12/CXCR4 by a small-molecule antagonist, CXCR4 deficiency results in leukopenia and increased neutrophil content in the plaques of CCR5<sup>−/−</sup> mice. | (Zumsteg et al., 2007) |
| MIG (migration) | Reduced migration of Cor1, Cor2, Ccr5 and Ccr5-deficient neutrophils into atherosclerotic plaques of Apoe<sup>−/−</sup> mice. | (Dorschel et al., 2010) |
Two subsets of human monocytes representing CD14<sup>high</sup> and CD14<sup>dim</sup> human monocytes that patrols blood vessels has been added (Cros et al., 2010). Similarly, there are two distinct subsets of blood circulating murine monocytes: Ly6C<sup>high</sup>/CCR2+/CX3CR1<sup>low</sup> inflammatory monocytes and Ly6C<sup>low</sup>/CCR2+/CX3CR1<sup>high</sup> monocytes (Geissmann et al., 2003). Both circulate through lymphoid and non-lymphoid organs under homeostatic conditions (Geissmann et al., 2003; Tacke et al., 2007). Hypercholesterolemia induces monocytosis in Apoe<sup>-/-</sup> mice with a predominant increase in the numbers of Ly6C<sup>high</sup> monocytes (Swirski et al., 2007; Tacke et al., 2007). As different repertoires of chemokine receptors and adhesion molecules are expressed by each monocyte subset, these cells use different mechanisms to traffic into the aorta. Ly6C<sup>low</sup> monocytes enter the atherosclerotic wall in a CCR5-dependent manner, but do not require CX3CR1 or CCR2 (Tacke et al., 2007). Surprisingly, Ly6C<sup>high</sup>/CCR2<sup>+</sup> monocytes require not only CCR2, but also CX3CR1 and CCR5 for their recruitment into the aorta (Tacke et al., 2007). Monocyte subsets also differently express several adhesion molecules, which can affect their homing capacity. L-selectin is expressed by Ly6C<sup>high</sup> monocytes and likely provides primary and secondary capture of monocytes to the endothelium. Ly6C<sup>low</sup> monocytes express low levels of L-selectin and CD54, but elevated levels of CD43 (Sunderkotter et al., 2004). Endothelial E-selectin may provide initial rolling of Ly6C<sup>low</sup> monocytes on endothelium. Further understanding of the pathways that govern the recruitment of monocyte subsets into atherosclerotic aorta is crucial to advance our efforts to reduce the frequency of aortic pro-inflammatory monocytes/macrophages and thus, further aortic chronic inflammation.

4.1.2 Egress of macrophages and dendritic cells from atherosclerotic aortas

Elevated levels of monocyte-derived cells in atherosclerotic plaques could be the result of several processes including: 1) hyperlipidemia-induced monocytosis and increased monocyte recruitment, 2) increased proliferation, 3) altered balance of survival/apoptosis/clearance, 4) attenuated egress from the aorta. Evidence suggests that reduced numbers of plaque MΦs orchestrate the regression of atherosclerosis repression; however, the cellular and molecular mechanisms underlying this process are not well understood. One of the first studies that focused on the potential mechanisms of MΦ and dendritic cell egress from atherosclerotic plaques were performed using a surgical model of plaque regression. In this model, plaque-bearing aortas from Apoe<sup>-/-</sup> donor mice were transplanted into C57BL/6 mice with low levels of circulating cholesterol, such that the surgically transferred segment became a functional segment of the recipient's aorta (Llodra et al., 2004). Significant migration of CD68<sup>+</sup> cells out of the plaque was detected in C57BL/6 recipients, whereas little emigration was detected from progressive plaques in Apoe<sup>-/-</sup> recipients (Llodra et al., 2004). Further experiments determined a role of the chemokine receptor CCR7 (Trogan et al., 2006). Liver X receptor α (LXRα) and LXRβ – are nuclear hormone receptors that play key roles in maintaining cholesterol homeostasis in MΦ, primarily by regulating multiple components of the reverse cholesterol transport pathway (Bradley & Tontonoz, 2005). Interestingly, emigrated CD68<sup>+</sup> cells expressed LXRα mRNA in foam cells in the regression environment (Trogan et al., 2006). LXR increases expression of CCR7 on CD68<sup>+</sup> cells, and thus supports CCR7-dependent regression of CD68<sup>+</sup> cells from the aorta (Feig et al., 2010). In line with this notion, beneficial effects of
HDL on aortic Mφ egress were observed in a model of atherosclerosis regression. Transplantation of advanced atherosclerotic segments from Apoe−/− donors to recipient mice bearing different levels of HDL cholesterol levels revealed that normalization of HDL decreases plaque burden and emigration of CD68+ cells from aortas. Thus, these data establish that HDL can serve as a regulator of in vivo egress of CD68+ cells from the plaque (Feig et al., 2011). It is likely that the balance of “In and Out” processes regulates MΦ and dendritic cells cellularity in the plaque. New data also suggest that normalization of cholesterol can correct monocyte recruitment into the aorta and additionally, lead to decreased MΦ content in atherosclerotic aortas. Treatment of Apoe−/− with apoE-encoding adenoviral vectors induced plaque regression, and attenuated CCR7-independent aortic MΦ content (Potteaux et al., 2011). Thus, interfering with monocyte recruitment into and possible egress from atherosclerotic plaques may be therapeutically beneficial, in parallel with aggressive lipid lowering therapies, to maintain and reinforce the reduction in monocyte recruitment to the aorta.

**Fig. 2. Mechanisms of leukocyte recruitment in atherosclerosis**

Different steps of the adhesion cascade and adhesion molecules control the recruitment of leukocytes to atherosclerotic plaques. The aortic adventitia, elastic lamina, smooth muscle, endothelial layers, as well as tertiary lymphoid aggregates and vasa vasorum are shown. The adhesion proteins and chemokines involved in the rolling and tethering (1), arrest and firm adhesion (2), and transmigration (3) of leukocytes to the endothelium are shown. Factors that play a role in the recruitment of leukocyte subsets in atherogenesis are denoted by question marks. While neutrophils and monocytes are known to be recruited from the lumen, it is not clear if NK, NKT, and mast cells are recruited from the lumen as well.

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4.2 T cell recruitment

4.2.1 Naive and effector T cell homing

Initially T cells were found within human atherosclerotic plaques, predominantly in the regions of fibrous cap (Jonasson et al., 1986). Interestingly, CD8+ T cells were almost as frequent as CD4+ T cells in the plaques; this differs from the CD4/CD8 ratio normally seen in the blood or other peripheral lymphoid tissue (Jonasson et al., 1986). Even at the earlier stages of atherogenesis, activated T cells have been discovered within the intimal fatty streaks of the human aortic wall (Munro et al., 1987). Importantly, T cells were also detected in non-diseased young aortas (Wick et al., 1997). Leukocytes are distributed at the site-specific areas around the ostia of intercostal arteries of grossly normal aorta (Kishikawa et al., 1993). T cells also reside in the aortic adventitia of C57BL/6 (Galkina et al., 2006) and Apoe−/− mice (Galkina et al., 2006; Moos et al., 2005). Adoptive transfer of T cells into C57BL/6 mice revealed that T cells preferentially migrate into the aortic adventitia and to a lesser extent into the aortic layers of normal aortas. Indirect evidence suggests that T cell migration occurs likely through the vasa vasorum (Galkina et al., 2006). T cells also preferentially migrate into the adventitia of Apoe−/− mice, indicating that T cells use similar routes of homing to the atherosclerotic and healthy aorta (Galkina et al., 2006).

There are many examples of tissue-specific sets of adhesion molecules that provide selective recruitment (reviewed in (Ley et al., 2007)). Little is known about lymphocyte recruitment into the aorta, and it is unclear whether a specific set of adhesion molecules and chemokines are responsible for the influx of the different types of leukocytes into healthy and atherosclerosis-prone aortas. At least one of the selectins, L-selectin, supports the migration of T cells into the aorta (Galkina et al., 2006). L-selectin might not only directly interact with aortic endothelium, but rather provide secondary capture through L-selectin/PSGL-1 interactions (Eriksson et al., 2001; Kunkel et al., 1998). In support of this notion, L-selectin-dependent secondary capture was observed by intravital microscopy in the femoral artery and abdominal aorta (Eriksson et al., 2001).

Evidence demonstrates that different subsets of T cells, including naïve, Tregs, Th1 and Th17 cells are present within the atherosclerotic aortas. Although we are still far from understanding how these different populations accumulate in aortas, some mechanistic details have been already shown. CCL5 is expressed on the luminal surface of carotid arteries, and platelet-dependent CCL5 deposition has been reported (Huo et al., 2003; von Hundelshausen et al., 2001). Deficiency in CCR5 reduced aortic CD4+ cells in parallel with attenuated atherosclerosis in Ccr5−/−Apoe−/− mice (Braunersreuther et al., 2007), indicating the importance of the CCL5/CCR5 axis for T cell migration into aortas. Naïve T cells express CCR7, which plays important functions in T cell recruitment into secondary lymphoid tissues and sites of inflammation. Importantly, CCR7 deficiency attenuates atherosclerosis via the regulation of T cell egress (Luchtedfeld et al., 2010). The ligand for CCR7, CCL19 is expressed by SMCs and MΦ in the plaques (Reape et al., 1999), CXCL9, CXCL11 (Mach et al., 1999; Ranjbaran et al., 2006), and CXCL12 (Biyounes et al., 2000), are also detected in the lesions. CXCL10 and CXCL9 mediate the CXCR3-dependent rapid shear-resistant arrest of T cells on stimulated EC (Piali et al., 1998). It was also shown that CXCL10 participates in T cell homing into atherosclerotic aortas (Heller et al., 2006).
CXCL16 is detected in human and mouse atherosclerosis-prone tissues and serves in the membrane-bound form as a scavenger receptor and in the soluble form as a chemokine. CXCL16 protects against atherosclerosis, likely through a benefit of CXCL16 as a scavenger receptor (Aslanian and Charo, 2006). Subsets of $T_{EFF}$ cell express CXCR6, a chemokine receptor for CXCL16 (Matloubian et al., 2000). The absence of CXCR6 in $Cxxr6^{-/-}Apoe^{-/-}$ mice leads to reduced homing of CXCR6+ T cells into atherosclerotic aortas (Galkina et al., 2007). CXCR2 and CXCR4 were recently identified as functional receptors for macrophage migration inhibition factor (MIF) (Bernhagen et al., 2007b). Blockade of MIF resulted in a diminished number of monocytes/MΦ and T cells within the aortas.

Tregs play an important role in the maintenance of the immunological tolerance (review in Sakaguchi et al., 2008)). Induction of a regulatory T cell type 1 (Treg type 1) responses and adoptive transfer of naturally arising CD4+CD25+ Tregs reduce atherosclerosis in $Apoe^{-/-}$ mice (Mallat et al., 2003; Ait-Oufella et al., 2006). Foxp3+ cells in human atherosclerotic lesions colocalize with the Treg-associated chemokine receptor CCR4 and its ligand, CCL17 (Heller et al., 2006). The molecular mechanisms that regulate homing of Treg cells into aortas are not well understood.

Th17 cells are a new lineage of CD4+ T cells that play important roles in acute inflammation and autoimmune diseases (Bettelli et al., 2007). Expression of CCR6 and CCR4 characterizes a unique subset of IL-17+ human peripheral blood T cells (Costa-Rodriguez et al., 2007). Th17 cells also express homeostatic CCR7 and CXCR5 and share some chemokine receptors with other T cell lineages. Although IL-17A+ cells are less abundant than Th1 cells, IL-17A+ T cells are present in both atherosclerotic human and mouse arteries. While the mechanisms of Th17 cell homing into aortas are unclear, some ligands such as CCL2, CCL20, and CCL21 are expressed within the plaques and could be used by Th17 and other IL-17+ cells to home to aortas.

4.3 B cell influx
In 1981, B cells were discovered within the adventitia (Parums & Mitchinson, 1981), and immunoglobulin-positive cells were detected within the subendothelial intima of atherosclerotic and non-atherosclerotic rabbits (Hansson et al., 1980). CD22+ B cells were also detected in atherosclerotic plaques of $Apoe^{-/-}$ mice (Zhou & Hansson, 1999). B cells reside in the adventitia of $C57BL/6$ aortas as a consequence of constitutive L-selectin-dependent homing to the aorta (Galkina et al., 2006). The phenotype of B cells within the aorta and surrounding adventitia is unclear, and further studies are needed to characterize adhesion molecule and chemokine receptor repertoire of aortic B cells. Recently, a role for smooth muscle cells (SMCs) in the regulation of lymphocyte homing was suggested. SMCs induce the production of CCL7, CCL9, CXCL13, CCL19, CXCL16, VCAM-1, and ICAM-1 (Lotzer et al., 2010). Supernatants of TNF receptor superfamily member 1A (TNFR-1) and LTβ-receptor-activated SMC markedly supported migration of B cells in vitro (Lotzer et al., 2010). It remains unclear whether elevated levels of endothelial homeostatic chemokines lead to accelerated recruitment of B cells into atherosclerosis-prone vessels.

4.4 Neutrophil recruitment in atherosclerosis
Despite a clear association between neutrophilia, neutrophil activation, and coronary artery disease (Baetta & Corsini, 2010; Mazzone et al., 1993), neutrophils are relatively low in
abundance within human atherosclerotic plaques (Baetta & Corsini, 2010). While neutrophils in atherosclerosis have been understudied to date, several lines of evidence suggest that neutrophil recruitment occurs during atherogenesis. CXCR4 and its ligand CXCL12 are involved in the efflux of neutrophils from bone marrow and in the regulation of neutrophil recruitment to atherosclerotic plaques (Zernecke et al., 2008). In addition, neutrophils were shown to adhere to the endothelium on the shoulder regions of atherosclerotic plaques (Rotzius et al., 2010). CXCR4 blockade-induced neutrophilia resulted in elevated plaque neutrophil content. In addition, as neutrophil chemotaxis to atherosclerotic plaques was impaired in CCR1, CCR2, CCR5, and CXCR2 deficient Apoe<sup>-/-</sup> mice, CCL2 and platelet-derived CCL5 supported neutrophil recruitment to carotid arteries. Based on several studies, neutrophils might migrate to developing plaques in a CCR1- and CCR5-dependent manner where they participate in promoting atherogenesis by supporting monocyte recruitment (Soehnlein et al., 2009) and inflammation (Nicholls & Hazen, 2009).

4.5 Mast cells in atherogenesis
While vascular mast cells are rare, they are nonetheless present within the adventitia and shoulder regions of atherosclerotic plaques (Lindstedt et al., 2007). Mast cell deficient Kit<sup>W<sub>−/−</sub></sup> mice display alterations in ApoE and ApoAI-dependent cholesterol efflux (Lee et al., 2002). Interestingly Kit<sup>W<sub>−/−</sub></sup> mice on the Ldlr<sup>-/-</sup> background demonstrated increased collagen content, fibrous cap development and reduced plaque T cell and MΦ cellularity (Sun et al., 2007). Mast cell activation correlated with MΦ and endothelial cell apoptosis, vascular leakage, CXCR2 and VLA-4-mediated recruitment of leukocytes to atheroma (Bot, et al., 2007). Mast cells play a pro-inflammatory role in atherogenesis; however, little is known about the recruitment of mast cells during atherosclerosis. Lesional mast cells express CCR3, suggesting that mast cells may utilize eotaxin, which is expressed by vascular smooth muscle cells, to migrate toward atherosclerotic plaques (Haley et al., 2000).

4.6 Natural killer (NK) cell recruitment in atherogenesis
NK cells are found within the shoulder regions of early and advanced human atherosclerotic lesions. While there is currently no NK-deficient mouse model of atherosclerosis, there are several lines of evidence to suggest that NK cells play a role during atherosclerosis (reviewed in Galkina & Ley, 2007, 2009). However, little is known about NK cell recruitment during atherogenesis. NK cells express a variety of adhesion molecules, including L-selectin, PSGL-1, β2 and α4 integrins, and chemokine receptors, including CXCR3, CCR2, and CX3CR1 (Galkina & Ley, 2007). Further studies are necessary. Further studies are necessary to identify the players in the migration cascade of NK cells to atherosclerotic aortas.

4.7 Natural killer T (NKT) cell recruitment in atherogenesis
Several lines of evidence support the pro-atherogenic nature of NKT-cells during the development of atherosclerosis in both humans and mice (Galkina and Ley, 2009). As glycolipid antigens can be presented by CD1 to CD1-restricted T cells, NKT cells possibly play an important role in responding to lipid antigen presentation within the aortic wall. NKT cells express receptors for inflammation-related chemokines, including CCR2, CCR5, CXCR3, and CXCR6 and CCL2. Thus, NKT cells likely use CCL5, CXCL9-11 and CXCL16 chemokines to migrate to atherosclerotic plaques.
5. Leukocyte recruitment during experimental atherosclerosis: Luminal “inside-out” migration vs extra-luminal “outside-in” recruitment

Traditionally, leukocyte migration during atherosclerosis has been considered to occur in an “inside-out” manner, focusing on monocyte adhesion to the endothelium on the luminal side of the artery and transmigration through the endothelium to arrive at the developing atherosclerotic plaque. Several lines of evidence support this model. Rolling and firm adherence of monocytes to the endothelium was demonstrated to occur in ex vivo carotid artery adhesion models as well as in vivo models (reviewed in (Galkina & Ley, 2007b; Zernecke and Weber, 2010)). However at present, there is no direct intravital microscopic evidence to support direct lymphocyte recruitment from the arterial lumen. Adoptive transfers of lymphocytes into Apoe-/- mice demonstrated that lymphocytes accumulate within the associated arterial adventitia suggesting a possible route of migration via adventitial vasa vasorum. Interestingly, the inhibition of plaque neovascularisation reduces Mφ accumulation and the progression of advanced atherosclerosis (Moreno et al., 2006). Recent studies have also revealed that the vasa vasorum can penetrate the media, enter the media (Moreno et al., 2006; Ritman & Lerman, 2007; Mulligan-Kehoe, 2010). Furthermore, administration of growth factors in acid gelatine hydrogel microspheres around the periaortic area in 10-11 week old male Apoe-/- mice strongly promoted vasa vasorum neovascularisation of the aorta and corresponded with larger atherosclerotic plaques (Tanaka et al., 2011). Recently three studies have further implicated adventitial inflammation in the pathogenesis of atherosclerosis. Several reports have demonstrated that T and B cell aggregates accumulate within the aortic adventitia in atherosclerotic aortas (Galkina et al., 2003; Moos et al., 2005; Zhao et al., 2004). LTα was required for the formation of aortic tertiary lymphoid organs within the adventitia (Grabner, et. al. 2009). Interestingly, these tertiary lymphoid structures were characterized by distinct clusters of germinal centers, proliferating T cells, and elevated production of the lymphorganogenic chemokines CXCL13 and CCL21. Mechanistic experiments utilizing LTβ-receptor deficient smooth muscle cells revealed that TNF-α and LTβ-dependent activation of the NF-κB pathway was sufficient to induce the expression of multiple chemokines, including CCL2, CCL5, CXCL1, CX3CL1, CCL7, CCL9, CXCL13, CCL19, and CXCL16 (Lötzer, et al. 2010). Together, these studies suggest that the adventitia plays an important structural role as the site of antigen presentation. In addition, neovascularisation from the adventitia to the arterial medial layer may provide a route of access for adventitial leukocytes to migrate to the media. Further studies will be necessary to truly determine the spatio-temporal relationship between the vasa vasorum, aortic tertiary lymphoid structures, and atherogenesis; and how these activities relate to leukocyte recruitment.

6. Conclusions

Our understanding of the mechanisms of leukocyte recruitment during atherogenesis has progressed notably since the early 1980s. The mechanisms of monocyte subset migration have been thoroughly studied; however, there are still many fundamental questions that remain to be investigated. To date, it is unclear what mechanisms are responsible for the recruitment of neutrophils, B cells, mast cells, NKT and NK cells into the aorta. In addition, while the recruitment of monocytes and neutrophils has been demonstrated to occur in an arterial lumen-to-plaque fashion, the directions of lymphocyte and mast cell recruitment in...
atherogenesis has yet to be defined. While several studies have highlighted the importance of the vasa vasorum and adventitial lymphoid structures, the effects of these anatomical structures on leukocyte recruitment have yet to be explored. With progress in tissue-specific drug targeting, one potential alternative approach to halting the progression of atherosclerosis would be to develop blocking agents against crucial adhesion molecules within the aorta that play critical roles in aortic leukocyte recruitment at the different stage of atherosclerosis.

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8. References

Ait-Oufella, H., Salomon, B.L., Potteaux, S., Robertson, A.K., Gourdy, P., Zoll, J., Merval, R., Esposito, B., Cohen, J.L., Fisso, S., Flavell, R.A., Hansson, G.K., Klatzmann, D., Tedgui, A., & Mallat, Z. (2006). Natural regulatory T cells control the development of atherosclerosis in mice. *Nat. Med.* 12, 178-180, ISSN 1078-8956.

Ait-Oufella, H., Taleb, S., Mallat, Z., & Tedgui, A. (2011). Recent advances on the role of cytokines in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 31, 969-979, ISSN 1524-4636.

Alon, R., Chen, S., Puri, K.D., Finger, E.B., & Springer, T.A. (1997). The kinetics of L-selectin tethers and the mechanics of selectin-mediated rolling. *J. Cell Biol.* 138, pp. 1169-1180, ISSN 0021-9525.

Aslanian, A.M. & Charo, I.F. (2006). Targeted disruption of the scavenger receptor and chemokine CXCL16 accelerates atherosclerosis. *Circulation* 114, pp. 583-590, ISSN 1524-4539.

Baltus, T., von Hundelshausen, P., Mause, S.F., Buhr, W., Rossaint, R., & Weber, C. (2005). Differential and additive effects of platelet-derived chemokines on monocyte arrest on inflamed endothelium under flow conditions. *J. Leukoc. Biol.* 78, pp. 435-441, ISSN 0741-5400.

Bernhagen, J., Krohn, R., Lue, H., Gregory, J.L., Zernecke, A., Koenen, R.R., Dewor, M., Georgiev, I., Schober, A., Leng, L., Kooistra, T., Fingerle-Rowson, G., Ghezzi, P., Kleemann, R., McColl, S.R., Bucala, R., Hickey, M.J., & Weber, C. (2007). MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. *Nat. Med.*., pp. 587-96, ISSN 1078-8956.

Bettelli, E., Korn, T., & Kuchroo, V.K. (2007). Th17: the third member of the effector T cell trilogy. *Curr. Opin. Immunol.* 19, 652-657, ISSN 0952-7915.
Bi-Younes, S., Sauty, A., Mach, F., Sukhova, G.K., Libby, P., & Luster, A.D. (2000). The stromal cell-derived factor-1 chemokine is a potent platelet agonist highly expressed in atherosclerotic plaques. *Circ. Res.* 86, 131-138, ISSN 1524-4571.

Bobryshev, Y.V. & Lord, R.S. (1998). Detection of vascular dendritic cells accumulating calcified deposits in their cytoplasm. *Tissue Cell* 30, 383-388, ISSN 0040-8166.

Boring, L., Gosling, J., Cleary, M., & Charo, I.F. (1998). Decreased lesion formation in CCR2-/- mice reveals a role for chemokines in the initiation of atherosclerosis. *Nature* 394, 894-897, ISSN 0028-0836.

Bot, L.; de Jager, S.C.; Zernecke, A.; Lindstedt, K.A.; van Berkel, T.J.; Weber, C.; Biessen, E.A. (2007). Perivascular mast cells promote atherogenesis and induce plaque destabilization in apolipoprotein E-deficient mice. *Circulation*, 115, 2516-25, ISSN 1524-4539.

Bradley, M.N. & Tontonoz, P. (2005). Lesion macrophages are a key target for the antiatherogenic effects of LXR agonists. *Arterioscler. Thromb. Vasc. Biol.* 25, 10-11, ISSN 1524-4636.

Braunersreuther, V., Zernecke, A., Arnaud, C., Liehn, E.A., Steffens, S., Shagdarsuren, E., Bidzhekov, K., Burger, F., Pelli, G., Luckow, B., Mach, F., & Weber, C. (2007). Ccr5 but not Ccr1 deficiency reduces development of diet-induced atherosclerosis in mice. *Arterioscler. Thromb. Vasc. Biol.* 27, 373-379, ISSN 1524-4636.

Brooks, A.R., Leikes, P.I., & Rubanyi, G.M. (2002). Gene expression profiling of human aortic endothelial cells exposed to disturbed flow and steady laminar flow. *Physiol Genomics* 9, 27-41, ISSN 1531-2267.

Burger-Kentischer, A., Gobel, H., Kleemann, R., Zernecke, A., Bucala, R., Leng, L., Finkelmeier, D., Geiger, G., Schaefer, H.E., Schober, A., Weber, C., Brunner, H., Rutten, H., Ihling, C., & Bernhagen, J. (2006). Reduction of the aortic inflammatory response in spontaneous atherosclerosis by blockade of macrophage migration inhibitory factor (MIF). *Atherosclerosis* 184, 28-38, ISSN 0021-9150.

Carman, C.V. & Springer, T.A. (2004). A transmigratory cup in leukocyte diapedesis both through individual vascular endothelial cells and between them. *J. Cell Biol.* 167, 377-388, ISSN 0021-9525.

Cheng, C., Tempel, D., van, H.R., de Boer, H.C., Segers, D., Huisman, M., van Zonneveld, A.J., Leenen, P.J., van der, S.A., Serruys, P.W., de, C.R., & Krams, R. (2007). Shear stress-induced changes in atherosclerotic plaque composition are modulated by chemokines. *J. Clin. Invest* 117, 616-626, ISSN 0021-9738.

Collins, R.G., Velji, R., Guevara, N.V., Hicks, M.J., Chan, L., & Beaudet, A.L. (2000). P-Selectin or intercellular adhesion molecule (ICAM)-1 deficiency substantially protects against atherosclerosis in apolipoprotein E-deficient mice. *J. Exp. Med.* 191, 189-194, ISSN 0022-1007.

Costa-Rodriguez, E.V., Rivolo, L., Geginat, J., Jarrossay, D., Gattorno, M., Lanzavecchia, A., Sallusto, F., & Napolitani, G. (2007). Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat. Immunol.* 8, 639-646, ISSN 1529-2908.

Cros, J., Cagnard, N., Woolard, K., Patey, N., Zhang, S.Y., Senechal, B., Puel, A., Biswas, S.K., Moshous, D., Picard, C., Jais, J.P., D'Cruz, D., Casanova, J.L., Trouillet, C., &
Mechanisms of Leukocyte Recruitment Into the Aorta During Atherosclerosis

Geissmann, F. (2010). Human CD14dim monocytes patrol and sense nucleic acids and viruses via TLR7 and TLR8 receptors. *Immunity.*, 33, 375-386, ISSN 1097-4180.

Cybulsky, M.I., Iiyama, K., Li, H., Zhu, S., Chen, M., Iiyama, M., Davis, V., Gutierrez-Ramos, J.C., Connelly, P.W., & Milstone, D.S. (2001). A major role for VCAM-1, but not ICAM-1, in early atherosclerosis. *J. Clin. Invest.* 107, 1255-1262, ISSN 0021-9738.

Dansky, H.M., Barlow, C.B., Lominska, C., Sikes, J.L., Kao, C., Weinsaft, J., Cybulsky, M.I., & Smith, J.D. (2001). Adhesion of monocytes to arterial endothelium and initiation of atherosclerosis are critically dependent on vascular cell adhesion molecule-1 gene dosage. *Arterioscler. Thromb. Vasc. Biol.* 21, 1662-1667, ISSN 1524-4636.

Davies, P.F., Polacek, D.C., Shi, C., & Helmke, B.P. (2002). The convergence of haemodynamics, genomics, and endothelial structure in studies of the focal origin of atherosclerosis. *Biorheology* 39, 299-306, ISSN 0006-355X.

Dawson, T.C., Kuziel, W.A., Osahar, T.A., & Maeda, N. (1999). Absence of CC chemokine receptor-2 reduces atherosclerosis in apolipoprotein E-deficient mice. *Atherosclerosis* 143, 205-211, ISSN 0021-9150.

Dong, Z.M., Brown, A.A., & Wagner, D.D. (2000). Prominent role of P-selectin in the development of advanced atherosclerosis in ApoE-deficient mice. *Circulation* 101, 2290-2295, ISSN 1524-4539.

Dong, Z.M., Chapman, S.M., Brown, A.A., Frenette, P.S., Hynes, R.O., & Wagner, D.D. (1998). The combined role of P- and E-selectins in atherosclerosis. *J. Clin. Invest.* 102, 145-152, ISSN 0021-9738.

Eriksson, E.E., Xie, X., Werr, J., Thoren, P., & Lindbom, L. (2001). Importance of primary capture and L-selectin-dependent secondary capture in leukocyte accumulation in inflammation and atherosclerosis in vivo. *J. Exp. Med.* 194, 205-218, ISSN 0022-1007.

Feig, J.E., Pinedo-Torra, I., Sanson, M., Bradley, M.N., Vengrenyuk, Y., Bogunovic, D., Gautier, E.L., Rubinstein, D., Hong, C., Liu, J., Wu, C., van, R.N., Bhardwaj, N., Garabedian, M., Tontonoz, P., & Fisher, E.A. (2010). LXR promotes the maximal egress of monocyte-derived cells from mouse aortic plaques during atherosclerosis regression. *J. Clin. Invest.* 120, 4415-4424, ISSN 1558-8238.

Feig, J.E., Rong, J.X., Shamir, R., Sanson, M., Vengrenyuk, Y., Liu, J., Rayner, K., Moore, K., Garabedian, M., & Fisher, E.A. (2011). HDL promotes rapid atherosclerosis regression in mice and alters inflammatory properties of plaque monocyte-derived cells. *Proc. Natl. Acad. Sci. U. S. A.* 108, 7166-7171, ISSN 1091-6490.

Frolova, E.G., Pluskota, E., Krukovets, I., Burke, T., Drumm, C., Smith, J.D., Blech, L., Febratio, M., Bornstein, P., Plow, E.F., & Stenina, O.I. (2010). Thrombospondin-4 regulates vascular inflammation and atherogenesis. *Circ. Res.* 107, 1313-1325, ISSN 1524-4571.

Galkina, E., Harry, B.L., Ludwig, A., Liehn, E.A., Sanders, J.M., Bruce, A., Weber, C., & Ley, K. (2007). CXCR6 promotes atherosclerosis by supporting T-cell homing, interferon-gamma production, and macrophage accumulation in the aortic wall. *Circulation* 116, 1801-1811, ISSN 1524-4539.

Galkina, E., Kadl, A., Sanders, J., Varughese, D., Sarembock, I.J., & Ley, K. (2006). Lymphocyte recruitment into the aortic wall before and during development of atherosclerosis is partially L-selectin dependent. *J. Exp. Med.* 203, 1273-1282, ISSN 1524-4539.

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Atherogenesis

Galkina, E. & Ley, K. (2007a). Leukocyte influx in atherosclerosis. *Curr. Drug Targets.* 8, 1239-1248, ISSN 0022-1007.

Galkina, E. & Ley, K. (2007b). Vascular adhesion molecules in atherosclerosis. *Arterioscler Thromb Vasc Biol* 27, 2292-2301, ISSN 1524-4636.

Galkina, E. & Ley, K. (2009). Immune and inflammatory mechanisms of atherosclerosis (*). *Annu. Rev. Immunol.* 27, 165-197, ISSN 0732-0582.

Gebuhrer, V., Murphy, J.F., Bordet, J.C., Reck, M.P., & McGregor, J.L. (1995). Oxidized low-density lipoprotein induces the expression of P-selectin (GMP140/PADGEM/CD62) on human endothelial cells. *Biochem. J.* 306 (Pt 1), 293-298, ISSN 0264-6021.

Geissmann, F., Jung, S., & Littman, D.R. (2003). Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity.* 19, 71-82, ISSN 1074-7613.

Gerrity, R.G. & Naito, H.K. (1980). Ultrastructural identification of monocyte-derived foam cells in fatty streak lesions. *Artery* 8, 208-214, ISSN 0098-6127.

Gosling, J., Slaymaker, S., Gu, L., Tseng, S., Zlot, C.H., Young, S.G., Rollins, B.J., & Charo, I.F. (1999). MCP-1 deficiency reduces susceptibility to atherosclerosis in mice that overexpress human apolipoprotein B. *J. Clin. Invest.* 103, 773-778, ISSN 0021-9738.

Grabner, R., Lotzer, K., Dopping, S., Hildner, M., Radke, D., Beer, M., Spanbroek, R., Lippert, B., Reardon, C.A., Getz, G.S., Fu, Y.X., Hehligans, T., Mebius, R.E., van der, W.M., Kruspe, D., Englert, C., Lovas, A., Hu, D., Randolph, G.J., Weih, F., & Habenicht, A.J. (2009). Lymphotoxin beta receptor signaling promotes tertiary lymphoid organogenesis in the aorta adventitia of aged ApoE/- mice. *J. Exp. Med.* 206, 233-248, ISSN 1545-9538.

Gu, L., Okada, Y., Clinton, S.K., Gerard, C., Sukhova, G.K., Libby, P., & Rollins, B.J. (1998). Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. *Mol. Cell.* 2, 275-281, ISSN 1097-2765.

Guan, J.L. & Hynes, R.O. (1990). Lymphoid cells recognize an alternatively spliced segment of fibronectin via the integrin receptor alpha 4 beta 1. *Cell* 60, 53-61, ISSN 0092-8674.

Haley, K.J., Lilly, C.M., Yang, J.H., Feng, Y., Kennedy, S.P., Turi, T.G., Thompson, J.F., Sukhova, G.H., Libby, P., & Lee, R.T. (2000). Overexpression of eotaxin and the CCR3 receptor in human atherosclerosis: using genomic technology to identify a potential novel pathway of vascular inflammation. *Circulation* 102, 2185-2189, ISSN 1524-4539.

Hansson, G.K., Bondjers, G., Bylock, A., & Hjalmarsson, L. (1980). Ultrastructural studies on the localization of IgG in the aortic endothelium and subendothelial intima of atherosclerotic and nonatherosclerotic rabbits. *Exp. Mol. Pathol.* 33, 302-315, ISSN 0014-4800.

Hansson, G.K. & Hermansson, A. (2011). The immune system in atherosclerosis. *Nat. Immunol.* 12, 204-212, ISSN 1529-2916.

Hashimoto, K., Kataoka, N., Nakamura, E., Tsujioka, K., Kajiy, F. (2007). Oxidized LDL specifically promotes the initiation of monocyte invasion during transendothelial migration with upregulated PECAM-1 and downregulated VE-cadherin on endothelial junctions. *Atherosclerosis* 194, e9-e17, ISSN 1879-1484.
Mechanisms of Leukocyte Recruitment into the Aorta During Atherosclerosis

Heller,E.A., Liu,E., Tager,A.M., Yuan,Q., Lin,A.Y., Ahluwalia,N., Jones,K., Koehn,S.L., Lok,V.M., Aikawa,E., Moore,K.J., Luster,A.D., & Gerszten,R.E. (2006). Chemokine CXCL10 promotes atherogenesis by modulating the local balance of effector and regulatory T cells. Circulation 113, 2301-2312, ISSN 1524-4539.

Hirschberg,H., Bergh,O.J., & Thorsby,E. (1980). Antigen-presenting properties of human vascular endothelial cells. J. Exp. Med. 152, 249s-255s, ISSN 0022-1007.

Huo,Y., Hafezi-Moghadam,A., & Ley,K. (2000). Role of vascular cell adhesion molecule-1 and fibronectin connecting segment-1 in monocyte rolling and adhesion on early atherosclerotic lesions. Circ. Res. 87, 153-159, ISSN 0003-1999-7330.

Huo,Y., Schober,A., Forlow,S.B., Smith,D.F., Hyman,M.C., Jung,S., Littman,D.R., Weber,C., & Ley,K. (2003). Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. Nat. Med. 9, 61-67, ISSN 1078-8956.

Huo,Y., Weber,C., Forlow,S.B., Sperandio,M., Thatte,J., Mack,M., Jung,S., Littman,D.R., & Ley,K. (2001). The chemokine KC, but not monocyte chemotactrant protein-1, triggers monocyte arrest on early atherosclerotic endothelium. J. Clin. Invest 108, 1307-1314, ISSN 0021-9738.

Hynes,R.O. (2002). Integrins: bidirectional, allosteric signaling machines. Cell 110, 673-687, ISSN 0092-8647.

Inoue,M., Ishida,T., Yasuda,T., Toh,R., Hara,T., Cangara,H.M., Rikitake,Y., Taira,K., Sun,L., Kundu,R.K., Quertermous,T., & Hirata,K. (2010). Endothelial cell-selective adhesion molecule modulates atherosclerosis through plaque angiogenesis and monocyte-endothelial interaction. Microvasc. Res. 80, 179-187, ISSN 1095-9319.

Johnson,R.C., Chapman,S.M., Dong,Z.M., Ordovas,J.M., Mayadas,T.N., Herz,J., Hynes,R.O., Schafer,E.J., & Wagner,D.D. (1997). Absence of P-selectin delays fatty streak formation in mice. J. Clin. Invest 99, 1037-1043, ISSN 0021-9738.

Jonasson,L., Holm,J., Skalli,O., Bondjers,G., & Hansson,G.K. (1986). Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. Arteriosclerosis 6, 131-138, ISSN 0276-5047.

Jonasson,L., Holm,J., Skalli,O., Gabbiani,G., & Hansson,G.K. (1985). Expression of class II transplantation antigen on vascular smooth muscle cells in human atherosclerosis. J. Clin. Invest 76, 125-131, ISSN 0021-9738.

Keiper,T., Al-Fakhri,N., Chavakis,E., Athanasopoulos,A.N., Isermann,B., Herzog,S., Safrich,R., Hersemeyer,K., Bohle,R.M., Haendeler,J., Preisner,K.T., Santoso,S., & Chavakis,T. (2005). The role of junctional adhesion molecule-C (JAM-C) in oxidized LDL-mediated leukocyte recruitment. FASEB J. 19, 2078-2080, ISSN 1530-6860.

Kinashi,T. (2007). Integrin regulation of lymphocyte trafficking: lessons from structural and signaling studies. Adv. Immunol. 93, 185-227, ISSN 0065-2776.

Kishikawa,H., Shimokama,T., & Watanabe,T. (1993). Localization of T lymphocytes and macrophages expressing IL-1, IL-2 receptor, IL-6 and TNF in human aortic intima. Role of cell-mediated immunity in human atherogenesis. Virchows Arch. A Pathol. Anat. Histopathol. 423, 433-442, ISSN 0174-7398.

Klouche,M., May,A.E., Hemmes,M., Messner,M., Kanse,S.M., Preisner,K.T., & Bhakdi,S. (1999). Enzymatically modified, nonoxidized LDL induces selective adhesion and

www.intechopen.com
transmigration of monocytes and T-lymphocytes through human endothelial cell monolayers. *Arterioscler. Thromb. Vasc. Biol.* 19, 784-793, ISSN 1079-5642.

Kume, N., Cybulsky, M.I., Gimbrone Jr., M.A. (1992) Lyso phosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells. *J. Clin. Invest.*, 90 (3), 1138-1144, ISSN 0021-9738

Kunkel, E.J., Chomatas, J.E., & Ley, K. (1998). Role of primary and secondary capture for leukocyte accumulation in vivo. *Circ. Res.* 82, 30-38, ISSN 0009-7330.

Kunkel, E.J. & Ley, K. (1996). Distinct phenotype of E-selectin-deficient mice. E-selectin is required for slow leukocyte rolling in vivo. *Circ. Res.* 79, 1196-1204, ISSN 0009-7330.

Lampugnani, M.G., Resnati, M., Raiteri, M., Pigott, R., Pisacane, A., Houen, G., Ruco, L.P., & Dejana, E. (1992). A novel endothelial-specific membrane protein is a marker of cell-cell contacts. *J. Cell Biol.* 118, 1511-1522, ISSN 0021-9738.

Lee, M., Calabresi, L., Chiesa, G., Franceschini, G., & Kovanen, P.T. (2002). Mast cell chymase degrades apoE and apoA-II in apoA-I-knockout mouse plasma and reduces its ability to promote cellular cholesterol efflux. *Arterioscler. Thromb. Vasc. Biol.* 22, 1475-1481, ISSN 1524-4636.

Lessner, S.M., Prado, H.L., Waller, E.K., & Galis, Z.S. (2002). Atherosclerotic lesions grow through recruitment and proliferation of circulating monocytes in a murine model. *Am. J. Pathol.* 160, 2145-2155, ISSN 0002-9440.

Leeuwenberg, J.F., Smeets, E.F., Neefjes, J.J., Shaffer, M.A., Cinek, T., Jeunhomme, T.M., Ahern, T.J., Buurman, W.A. (1992). E-selectin and intercellular adhesion molecule-1 are released by activated human endothelial cells in vitro. *Immunology*. 77(4). 543-549. ISSN 0019-2805

Ley, K., Laudanna, C., Cybulsky, M., & Nourshargh, S. (2007). Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat.Rev.Immunol.*, ISSN 1474-1741.

Ley, K. & Kansas, G.S. (2004). Selectins in T-cell recruitment to non-lymphoid tissues and sites of inflammation. *Nat. Rev. Immunol.* 4, 325-335, ISSN 1474-1733.

Lindstedt, K.A., Mayranpaa, M.I., & Kovanen, P.T. (2007). Mast cells in vulnerable atherosclerotic plaques—a view to a kill. *J. Cell Mol. Med.* 11, 739-758, ISSN 1582-1838.

Llodra, J., Angeli, V., Liu, J., Trogan, E., Fisher, E.A., & Randolph, G.J. (2004). Emigration of monocyte-derived cells from atherosclerotic lesions characterizes regressive, but not progressive, plaques. *Proc. Natl. Acad. Sci. U. S. A* 101, 11779-11784, ISSN 0027-8424.

Lotzer, K., Dopping, S., Connert, S., Grabner, R., Spanbrock, R., Lemser, B., Beer, M., Hildner, M., Heiligans, T., van der, W.M., Mebius, R.E., Lovas, A., Randolph, G.J., Weih, F., & Habenicht, A.J. (2010). Mouse aorta smooth muscle cells differentiate into lymphoid tissue organizer-like cells on combined tumor necrosis factor receptor-1/lymphotoxin beta-receptor NF-kappaB signaling. *Arterioscler. Thromb. Vasc. Biol.* 30, 395-402, ISSN 1524-4636.

Luchtefeld, M., Grothusen, C., Gaglick, A., Jagavelu, K., Schuett, H., Tietge, U.J., Pabst, O., Grote, K., Drexler, H., Forster, R., & Schieffer, B. (2010). Chemokine receptor 7
Knockout attenuates atherosclerotic plaque development. *Circulation* 122, 1621-1628, ISSN 1524-4539.

Luster, A.D., Alon, R., & von Andrian, U.H. (2005). Immune cell migration in inflammation: present and future therapeutic targets. *Nat. Immunol.* 6, 1182-1190, ISSN 1529-2908.

Mach, F., Sauty, A., Larossi, A.S., Sukhova, G.K., Neote, K., Libby, P., & Luster, A.D. (1999). Differential expression of three T lymphocyte-activating CXC chemokines by human atheroma-associated cells. *J. Clin. Invest* 104, 1041-1050, ISSN 0021-9738.

Mallat, Z., Gojo, A., Brun, V., Esposito, B., Fournier, N., Cottrez, F., Tedgui, A., & Groux, H. (2003). Induction of a regulatory T cell type 1 response reduces the development of atherosclerosis in apolipoprotein E-knockout mice. *Circulation* 108, 1232-1237, ISSN 1524-4539.

Mandell, K.J. & Parkos, C.A. (2005). The JAM family of proteins. *Adv. Drug Deliv. Rev.* 57, 857-867, ISSN 0169-409X.

Matloubian, M., David, A., Engel, S., Ryan, J.E., & Cyster, J.G. (2000). A transmembrane CXC chemokine is a ligand for HIV-coreceptor Bonzo. *Nat. Immunol.* 1, 1182-1190, ISSN 1529-2908.

Mayerl, C., Lukasser, M., Sedivy, R., Niederegger, H., Seiler, R., & Wick, G. (2006). Atherosclerosis research from past to present—on the track of two pathologists with opposing views, Carl von Rokitansky and Rudolf Virchow. *Virchows Arch.* 449, 96-103, ISSN 0945-6317.

Mazzzone, A., De, S.S., Ricevuti, G., Mazzucchelli, I., Fossati, G., Pasotti, D., Bramucci, E., Angoli, L., Marsico, F., & Specchia, G. (1993). Increased expression of neutrophil and monocyte adhesion molecules in unstable coronary artery disease. *Circulation* 88, 358-363, ISSN 0009-7322.

McEver, R.P. (2002). Selectins: lectins that initiate cell adhesion under flow. *Curr. Opin. Cell Biol.* 14, 581-586, ISSN 0955-0674.

Meth, H. & Weis, M. (2007). Atherosclerosis and inflammation—was Virchow right? *Nephrol. Dial. Transplant.* 22, 1823-1827, ISSN 0931-0509.

Moos, M.P., John, N., Grabner, R., Nossmann, S., Gunther, B., Vollandt, R., Funk, C.D., Kaiser, B., & Habenicht, A.J. (2005). The lamina adventitia is the major site of immune cell accumulation in standard chow-fed apolipoprotein E-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* 25, 2386-2391, ISSN 1524-4636.

Moreno, P.R., Purushothaman, K.R., Sirol, M., Levy, A.P., & Fuster, V. (2006). Neovascularization in human atherosclerosis. *Circulation* 113, 2245-2252, ISSN 1524-4539.

Mulligan-Kehoe, M.J. (2010). The vasa vasorum in diseased and nondiseased arteries. *Am. J. Physiol Heart Circ. Physiol* 298, H295-H305, ISSN 1522-1539.

Munro, J.M., van der Walt, J.D., Munro, C.S., Chalmers, J.A., & Cox, E.L. (1987). An immunohistochemical analysis of human aortic fatty streaks. *Hum. Pathol.* 18, 375-380, ISSN 0046-8177.

Murugesan, G., Sandhya Rani, M.R., Gerber, C.E., Mukhopadhyay, C., Ransohoff, R.M., Chisolm, G.M., Kottke-Marchant, K. (2003). Lysophosphatidylcholine regulates human microvascular endothelial cell expression of chemokines. *J. Mol. Cell. Cardiol.* 35 (11), 1375-1384, ISSN 0022-2828.

www.intechopen.com
Nageh, M.F., Sandberg, E.T., Marotti, K.R., Lin, A.H., Melchior, E.P., Bullard, D.C., & Beaudet, A.L. (1997). Deficiency of inflammatory cell adhesion molecules protects against atherosclerosis in mice. *Arterioscler. Thromb. Vasc. Biol.* 17, 1517-1520, ISSN 1079-5642.

Newman, P.J. (1997). The biology of PECAM-1. *J. Clin. Invest* 99, 3-8, ISSN 0021-9738.

Newman, W., Beall, L.D., Carson, C.W., Hunder, G.G., Graben, N., Randhawa, Z.I., Gopal, T.V., Wiener-Kronish, J., Matthy, M.A. (1993). Soluble E-selectin is found in supernatants of activated endothelial cells and is elevated in the serum of patients with septic shock. *J. Immunol.* 150(2), 644-654. ISSN 0022-1767.

Nicholls, S.J. & Hazen, S.L. (2009). Myeloperoxidase, modified lipoproteins, and atherogenesis. *J. Lipid Res.* 50 Suppl, S346-S351, ISSN 0022-2275.

Ostermann, G., Fraemohs, L., Baltus, T., Schober, A., Lietz, M., Zernecke, A., Liehn, E.A., & Weber, C. (2005). Involvement of JAM-A in mononuclear cell recruitment on inflamed or atherosclerotic endothelium: inhibition by soluble JAM-A. *Arterioscler. Thromb. Vasc. Biol.* 25, 729-735, ISSN 1524-4636.

Pan, J.H., Sukhova, G.K., Yang, J.T., Wang, B., Xie, T., Fu, H., Zhang, Y., Satoskar, A.R., David, J.R., Metz, C.N., Bacala, R., Fang, K., Simon, D.I., Chapman, H.A., Libby, P., & Shi, G.P. (2004). Macrophage migration inhibitory factor deficiency impairs atherosclerosis in low-density lipoprotein receptor-deficient mice. *Circulation* 109, 3149-3153, ISSN 1524-4539.

Parhami, F., Fang, Z.T., Fogelman, A.M., Andalibi, A., Territo, M.C., & Berliner, J.A. (1993). Minimally modified low density lipoprotein-induced inflammatory responses in endothelial cells are mediated by cyclic adenosine monophosphate. *J. Clin. Invest* 92, 471-478, ISSN 0021-9738.

Park, Y.M., Febbraio, M., & Silverstein, R.L. (2009). CD36 modulates migration of mouse and human macrophages in response to oxidized LDL and may contribute to macrophage trapping in the arterial intima. *J. Clin. Invest* 119, 136-145, ISSN 0021-9738.

Parums, D. & Mitchinson, M.J. (1981). Demonstration of immunoglobulin in the neighbourhood of advanced atherosclerotic plaques. *Atherosclerosis* 38, 211-216, ISSN 0021-9150.

Passlick, B., Flieger, D., & Ziegler-Heitbrock, H.W. (1989). Identification and characterization of a novel monocyte subpopulation in human peripheral blood. *Blood* 74, 2527-2534, ISSN 0006-4971.

Patel, S.S., Thiagarajan, R., Willerson, J.T., & Yeh, E.T. (1998). Inhibition of alpha4 integrin and ICAM-1 markedly attenuate macrophage homing to atherosclerotic plaques in ApoE-deficient mice. *Circulation* 97, 75-81, ISSN 0009-7322.

Pedersen, E.M., Oyre, S., Agerbaek, M., Kristensen, I.B., Ringgaard, S., Boesiger, P., & Paaske, W.P. (1999). Distribution of early atherosclerotic lesions in the human abdominal aorta correlates with wall shear stresses measured in vivo. *Eur. J. Vasc. Endovasc. Surg.* 18, 328-333, ISSN 1078-5884.

Piali, L., Weber, C., LaRosa, G., Mackay, C.R., Springer, T.A., Clark-Lewis, I., & Moser, B. (1998). The chemokine receptor CXCR3 mediates rapid and shear-resistant adhesion-
induction of effector T lymphocytes by the chemokines IP10 and Mig. *Eur. J. Immunol.* 28, 961-972, ISSN 0014-2980.

Pigot, R., Dillon, L.P., Hemingway, I.H., Gearing, A.J. (1992). Soluble forms of E-Selectin, ICAM-1 and VCAM-1 are present in the supernatants of cytokine activated cultured endothelial cells. *Biochem Biophys Res Commun.* 187(2), 584-589. ISSN 0006-291X

Pillarsetti, S., Paka, L., Obunike, J.C., Berglund, L., & Goldberg, I.J. (1997). Subendothelial retention of lipoprotein (a). Evidence that reduced heparan sulfate promotes lipoprotein binding to subendothelial matrix. *J. Clin. Invest* 100, 867-874, ISSN 0021-9738.

Pober, J.S., Gimbrone, M.A., Jr., Cotran, R.S., Reiss, C.S., Burakoff, S.J., Fiers, W., & Ault, K.A. (1983). Ia expression by vascular endothelium is inducible by activated T cells and by human gamma interferon. *J. Exp. Med.* 157, 1339-1353, ISSN 0022-1007.

Potteaux, S., Gautier, E.L., Hutchison, S.B., van Rooijen, N., Rader, D.J., Thomas, M.J., Sorci-Thomas, M.G., & Randolph, G.J. (2011). Suppressed monocyte recruitment drives macrophage removal from atherosclerotic plaques of Apoe-/- mice during disease regression. *J. Clin. Invest* 121, 2025-2036, ISSN 1558-8238.

Quinn, M.T., Parthasarathy, S., Fong, L.G., Steinberg, D. (1987). Oxidatively modified low density lipoproteins: a potential role in recruitment and retention of monocyte/macrophages during atherogenesis. *Proc. Natl. Acad. Sci. USA.*, 84(9), 2995-2998, ISSN 0027-8424

Quinn, M.T., Parthasarathy, S., Steinberg, D. (1988). Lyso phosphatidylcholine: a chemotactic factor for human monocytes and its potential role in atherogenesis. *Proc. Natl. Acad. Sci. USA.*, 85(8), 2805-2809, ISSN 0027-8424

Ramos, C.L., Huo, Y., Jung, U., Ghosh, S., Manka, D.R., Sarembock, I.J., & Ley, K. (1999). Direct demonstration of P-selectin- and VCAM-1-dependent mononuclear cell rolling in early atherosclerotic lesions of apolipoprotein E-deficient mice. *Circ. Res.* 84, 1237-1244, ISSN 0009-7330.

Ranjbaran, H., Wang, Y., Manes, T.D., Yakimov, A.O., Akhtar, S., Kluger, M.S., Pober, J.S., & Tellides, G. (2006). Heparin displaces interferon-gamma-inducible chemokines (IP-10, I-TAC, and Mig) sequestered in the vasculature and inhibits the transendothelial migration and arterial recruitment of T cells. *Circulation* 114, 1293-1300, 1524-4539.

Reape, T.J., Rayner, K., Manning, C.D., Gee, A.N., Barnette, M.S., Burnand, K.G., & Groot, P.H. (1999). Expression and cellular localization of the CC chemokines PARC and ELC in human atherosclerotic plaques. *Am. J. Pathol.* 154, 365-374, ISSN 0002-9440.

Ritman, E.L. & Lerman, A. (2007). The dynamic vasa vasorum. *Cardiovasc. Res.* 75, 649-658, ISSN 0008-6363.

Roldan, V., Marin, F., Lip, G.Y.H., Blann, A.D. (2003). Soluble E-selectin in cardiovascular disease and its risk factors. A review of the literature. *Throm. Haemost.* 90(6), 1007-1020, ISSN 0340-6245

Rotzius, P., Thams, S., Soehnlein, O., Kenne, E., Tseng, C.N., Bjorkstrom, N.K., Malmberg, K.J., Lindbom, L., & Eriksson, E.E. (2010). Distinct infiltration of neutrophils in lesion shoulders in ApoE-/- mice. *Am. J. Pathol.* 177, 493-500, ISSN 1525-2191.
Sakaguchi,S., Yamaguchi,T., Nomura,T., & Ono,M. (2008). Regulatory T cells and immune tolerance. *Cell* 133, 775-787, ISSN 1879-0372.

Serbina,N.V. & Pamer,E.G. (2006). Monocyte emigration from bone marrow during bacterial infection requires signals mediated by chemokine receptor CCR2. *Nat. Immunol.* 7, 311-317, ISSN 1529-2908.

Shagdarsuren,E., Djalali-Talab,Y., Aurrand-Lions,M., Bidzhekiov,K., Liehn,E.A., Imhof,B.A., Weber,C., & Zernecke,A. (2009). Importance of junctional adhesion molecule-C for neointimal hyperplasia and monocyte recruitment in atherosclerosis-prone mice—brief report. *Arterioscler. Thromb. Vasc. Biol.* 29, 1161-1163, ISSN 1524-4636.

Shaw,S.K., Ma,S., Kim,M.B., Rao,R.M., Hartman,C.U., Froio,R.M., Yang,L., Jones,T., Liu,Y., Nusrat,A., Parkos,C.A., & Lusincskas,F.W. (2004). Coordinated redistribution of leukocyte LFA-1 and endothelial cell ICAM-1 accompany neutrophil transmigration. *J. Exp. Med.* 200, 1571-1580, ISSN 0022-1007.

Soehnlein,O., Lindbom,L., & Weber,C. (2009). Mechanisms underlying neutrophil-mediated monocyte recruitment. *Blood* 114, 4613-4623, ISSN 1528-0020.

Sprague, A.H., Khalil, R.A. (2009) Inflammatory cytokines in vascular dysfunction and vascular disease. *Biochem Pharmacol*, 78(6): 539-552, ISSN 1873-2968.

Sun,J., Sukhova,G.K., Wolters,P.J., Yang,M., Kitamoto,S., Libby,P., MacFarlane,L.A., Mallen-St,C.J., & Shi,G.P. (2007). Mast cells promote atherosclerosis by releasing proinflammatory cytokines. *Nat. Med.* 13, 719-724, ISSN 1078-8956.

Sunderkotter,C., Nikolic,T., Dillon,M.J., van Rooijen N., Stehling,M., Drevets,D.A., & Leenen,P.J. (2004). Subpopulations of mouse blood monocytes differ in maturation stage and inflammatory response. *J. Immunol.* 172, 4410-4417, ISSN 0022-1767.

Swirski,F.K., Libby,P., Aikawa,E., Alcaide,P., Lusincskas,F.W., Weissleder,R., & Pittet,M.J. (2007). Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. *J. Clin. Invest* 117, 195-205, ISSN 0021-9738.

Swirski,F.K., Nahrendorf,M., Etzrodt,M., Wildgruber,M., Cortez-Retamozo,V., Panizzi,P., Figueiredo,J.L., Kohler,R.H., Chudnovskiy,A., Waterman,F., Aikawa,E., Mempel,T.R., Libby,P., Weissleder,R., & Pittet,M.J. (2009). Identification of splenic reservoir monocytes and their deployment to inflammatory sites. *Science* 325, 612-616, ISSN 1095-9203.

Swirski,F.K., Pittet,M.J., Kircher,M.F., Aikawa,E., Jaffer,F.A., Libby,P., & Weissleder,R. (2006). Monocyte accumulation in mouse atherogenesis is progressive and proportional to extent of disease. *Proc. Natl. Acad. Sci. U. S. A* 103, 10340-10345, ISSN 0027-8424.

Tacke,F., Alvarez,D., Kaplan,T.J., Jakubzick,C., Spanbroek,R., Llodra,J., Garin,A., Liu,J., Mack,M., van,R.N., Lira,S.A., Habenicht,A.J., & Randolph,G.J. (2007). Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J. Clin. Invest* 117, 185-194, ISSN 0021-9738.

Tanaka,K., Nagata,D., Hirata,Y., Tabata,Y., Nagai,R., & Sata,M. (2011). Augmented angiogenesis in adventitia promotes growth of atherosclerotic plaque in apolipoprotein E-deficient mice. *Atherosclerosis* 215, 366-373, ISSN 1879-1484.

www.intechopen.com
Mechanisms of Leukocyte Recruitment Into the Aorta During Atherosclerosis

Tedgui, A. & Mallat, Z. (2006). Cytokines in atherosclerosis: pathogenic and regulatory pathways. *Physiol. Rev.* 86, 515-581, ISSN 0031-9333.

Trojan, E., Feig, J.E., Dogan, S., Rothblat, G.H., Angeli, V., Tacke, F., Randolph, G.J., & Fisher, E.A. (2006). Gene expression changes in foam cells and the role of chemokine receptor CCR7 during atherosclerosis regression in ApoE-deficient mice. *Proc. Natl. Acad. Sci. U. S. A* 103, 3781-3786, ISSN 0027-8424.

Tsou, C.L., Peters, W., Si, Y., Slaymaker, S., Aslanian, A.M., Weisberg, S.P., Mack, M., & Charo, I.F. (2007). Critical roles for CCR2 and MCP-3 in monocyte mobilization from bone marrow and recruitment to inflammatory sites. *J. Clin. Invest* 117, 902-909, ISSN 0021-9738.

Tsou, J.K., Gower, R.M., Ting, H.J., Schaff, U.Y., Insana, M.F., Passerini, A.G., & Simon, S.I. (2008). Spatial regulation of inflammation by human aortic endothelial cells in a linear gradient of shear stress. *Microcirculation*. 15, 311-323, ISSN 1073-9688.

Tu, L., Poe, J.C., Kadono, T., Venturi, G.M., Bullard, D.C., Tedder, T.F., Steeber, D.A. (2002). A functional role for circulating mouse L-selectin in regulating leukocyte/endothelial cell interactions in vivo. *J. Immunol.* 169(4), 2034-2043. ISSN 0022-1767.

VanderLaan, P.A., Reardon, C.A., & Getz, G.S. (2004). Site specificity of atherosclerosis: site-selective responses to atherosclerotic modulators. *Arterioscler. Thromb. Vasc. Biol.* 24, 12-22, ISSN 1524-4636.

Vestweber, D. (2007). Adhesion and signalling molecules controlling the transmigration of leukocytes through endothelium. *Immunol. Rev.* 218, 178-196, ISSN 0105-2896.

von Hundelshausen, P., Koenen, R.R., Sack, M., Mause, S.F., Adriaens, W., Proudfoot, A.E., Hackeng, T.M., & Weber, C. (2005). Heterophilic interactions of platelet factor 4 and RANTES promote monocyte arrest on endothelium. *Blood* 105, 924-930, ISSN 0006-4971.

von Hundelshausen, P., Weber, K.S., Huo, Y., Proudfoot, A.E., Nelson, P.J., Ley, K., & Weber, C. (2001). RANTES deposition by platelets triggers monocyte arrest on inflamed and atherosclerotic endothelium. *Circulation* 103, 1772-1777, ISSN 1524-4539.

Weber, K.S., von Hundelshausen, P., Clark-Lewis, I., Weber, P.C., & Weber, C. (1999). Differential immobilization and hierarchical involvement of chemokines in monocyte arrest and transmigration on inflamed endothelium in shear flow. *Eur. J. Immunol.* 29, 700-712, ISSN 0104-2980.

Wick, G., Romen, M., Amberger, A., Metzler, B., Mayr, M., Falkensammer, G., & Xu, Q. (1997). Atherosclerosis, autoimmunity, and vascular-associated lymphoid tissue. *FASEB J.* 11, 1199-1207, ISSN 0892-6638.

Zarbock, A., Lowell, C.A., & Ley, K. (2007). Spleen tyrosine kinase Syk is necessary for E-selectin-induced alpha(L)beta(2) integrin-mediated rolling on intercellular adhesion molecule-1. *Immunity* 26, 773-783, ISSN 1074-7613.

Zhang, J., Alcaide, P., Liu, L., Sun, J., He, A., Luscinskas, F.W., Shi, G.P. (2011). Regulation of endothelial cell adhesion molecule expression by mast cells, macrophages, and neutrophils. *PLoS One.* 14; 1-10, ISSN 1932-6203.

Zhou, X., & Hansson G.K. Detection of B cells and proinflammatory cytokines in atherosclerotic plaques of hypercholesterolaemic apolipoprotein E knockout mice. (1999). *Scand. J. Immunol.* 50, 25-30, ISSN 1365-3083.
Zernecke, A., Bot, I., Djalali-Talab, Y., Shagdarsuren, E., Bidzhakov, K., Meiler, S., Krohn, R., Schober, A., Sperandio, M., Soehnlein, O., Bornemann, J., Tacke, F., Biessen, E. A., & Weber, C. (2008). Protective role of CXC receptor 4/CXC ligand 12 unveils the importance of neutrophils in atherosclerosis. Circ. Res. 102, 209-217, ISSN 1524-4571.

Zernecke, A., Liehn, E. A., Fraemohs, L., von Hundelshausen, P., Koenen, R. R., Corada, M., Dejana, E., & Weber, C. (2006). Importance of junctional adhesion molecule-A for neointimal lesion formation and infiltration in atherosclerosis-prone mice. Arterioscler. Thromb. Vasc. Biol. 26, e10-e13, ISSN 1524-4636.

Zernecke, A. & Weber, C., (2010). Chemokines in the vascular inflammatory response of atherosclerosis. Cardiovasc. Research. 86, 192-201, ISSN 1755-3245.
This monograph will bring out the state-of-the-art advances in the dynamics of cholesterol transport and will address several important issues that pertain to oxidative stress and inflammation. The book is divided into three major sections. The book will offer insights into the roles of specific cytokines, inflammation, and oxidative stress in atherosclerosis and is intended for new researchers who are curious about atherosclerosis as well as for established senior researchers and clinicians who would be interested in novel findings that may link various aspects of the disease.

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