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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, β2-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 demonstarted (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-γ (IFN-γ) 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-DR$^+$ cells, CD4$^+$ and CD8$^+$ T cells in carotid entarterectomy 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-selecin 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 $\alpha_4\beta_1$ (VLA-4) integrin is a member of the α_4

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-β (LTβ), 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-β 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).

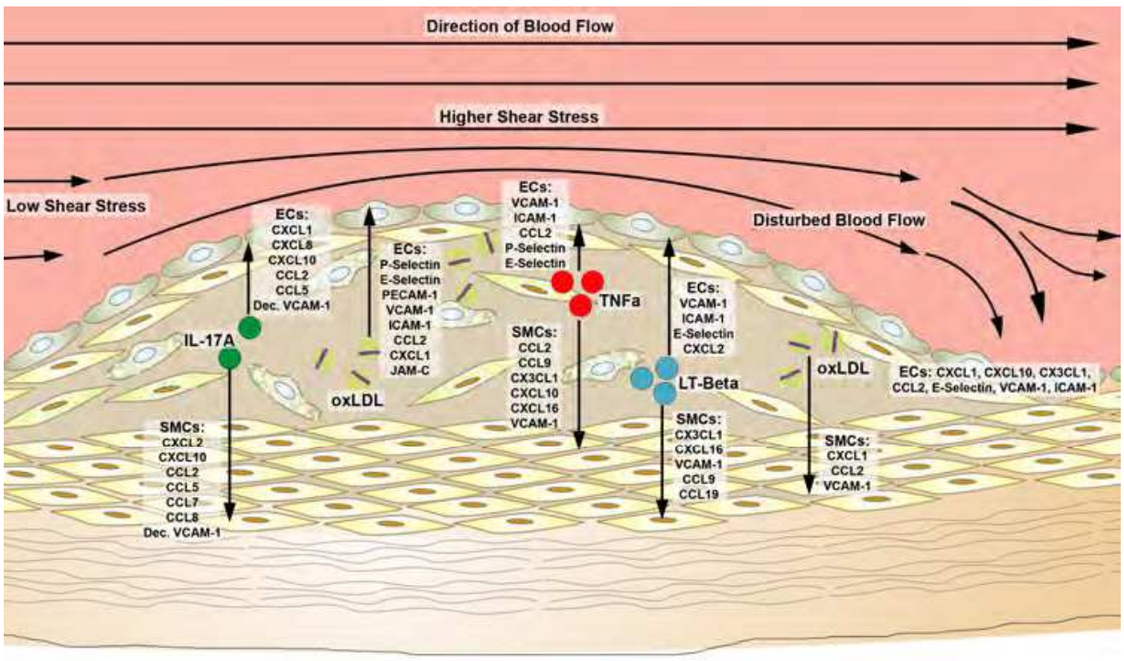

Fig. 1. Regulators of adhesion molecule expression.

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 arties 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/cm^2) 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; Leeuwenbern, 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-thrombopspondin (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 α_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 α_4 integrin using blocking Abs showed reduced influx of MΦ 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-1*$^{D4D/D4D}$) were generated (Cybulsky et al., 2001). Reduced levels of VCAM-1 resulted in the reduction of atherogenesis in *Vcam1*$^{D4D/D4D}$*Ldlr*$^{-/-}$ mice (Cybulsky et al., 2001). VCAM-1 levels affect plaque formation, since *Vcam-1*$^{D4D/+}$*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 MΦ 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 MΦ 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 MΦ migration. CD36 signaling in response to oxLDL alters cytoskeletal dynamics and inhibits the migration of MΦs. This may be one of the mechanisms of MΦ accumulation in aortic lipid-rich areas (Park et al., 2009).

Leukocyte type	Adhesion molecules, chemokine receptors	Effects	References
Monocytes, selectins	P-selectin (rolling)	Reduced rolling and attachment with anti-P-selectin or PSGL-1 Abs (an ex vivo model of isolated carotid arteries). Reduced lesion size and MΦ content (Selp$^{-/-}$ mice on C57BL/6, Ldlr$^{-/-}$, and Apoe$^{-/-}$ background).	(Ramos et al., 1999) (Collins et al., 2000; Dong et al., 2000; Johnson et al., 1997; Nageh et al., 1997)
	E-selectin (rolling)	Slightly reduced lesions (Sele$^{-/-}$Apoe$^{-/-}$ mice). Reduced lesions for all stages of atherogenesis (Selp$^{-/-}$Sele$^{-/-}$Ldlr$^{-/-}$ mice).	(Collins et al., 2000) (Dong et al., 1998)
Monocytes, integrins	VCAM-1/VLA-4 (adhesion)	Increased rolling velocities with anti-VCAM-1 or anti-α_4 integrin Abs. Increased rolling velocities and decrease adhesion by blocking of VLA-4 binding to both VCAM-1 and fibronectin connecting segment-1 (both, an ex vivo model of isolated perfused carotid arteries). Blockade of VLA-4 with anti-VLA-4 Abs decreases monocyte migration in vivo. Reduced early atherosclerotic lesions (Vcam-1$^{D4D/D4D}$Ldlr$^{-/-}$ mice). Gene-dosage dependent influx of monocytes and lesion development (Vcam-1$^{D4D/+}$ Apoe$^{-/-}$ mice). Decreased short-term monocyte migration into plaques by blocking Abs to ICAM-1 (Apoe$^{-/-}$ mice). Reduced lesions in Itgb2$^{-/-}$ and Icam-1$^{-/-}$Itgb2$^{-/-}$ (C57BL/6 mice on WD).	(Huo et al., 2000; Ramos et al., 1999) (Patel et al., 1998) (Cybulsky et al., 2001) (Dansky et al., 2001) (Patel et al., 1998) (Nageh et al., 1997)
	ICAM-1 (adhesion)		
Monocytes, chemokines	migration/arrest CXCL1, CCL5 CCL5/CXCL4 CXCL7 MIF	Monocyte arrest in the flow chamber assay. Interactions via CXCL2/CD74 complex induce integrin activation. MIF deficiency reduces lipid deposition, and MΦ infiltration in the aorta. Reduced MΦ content in Apoe$^{-/-}$ mice that received neutralizing Abs to MIF.	(Huo et al., 2001; Weber et al., 1999; von Hundelshausen et al., 2005) (Bernhagen et al., 2007b), (Pan et al., 2004; Burger-Kentischer et al., 2006)
Monocytes JAM-A (transmigration) JAM-C (transmigration) CD36	JAMs CD36	Reduced monocyte arrest and transmigration on activated F11r$^{-/-}$/Apoe$^{-/-}$ endothelial cells in the flow chamber assays; wire injury of carotid artery . JAM-C Ab blockade decreases neointimal MΦ after wire injury of carotid arteries. Regulate oxLDL-induced cytoskeletal dynamics to inhibit migration and enhance MΦ spreading. Adhesion and migration assays with Cd36$^{-/-}$ monocytes in vitro.	(Zernecke et al., 2006) (Shagdarsuren et al., 2009) (Park et al., 2009)
Inflammatory and Patrolling monocytes	CCR5 CCR2, CX3CR1, CCR5	CCR5 blockade with neutralizing Abs, Ccr2$^{-/-}$ and Cx3cr1$^{-/-}$monocytes in the homing experiments using latex beads technology to distinguish between monocyte subsets.	(Swirski et al., 2007; Tacke et al., 2007)
Possible egress	CCR7	Blockade of CD68^{+} cell regression by blocking Abs to CCL19 and CCL21 or CCR7 deficiency in transplantational model of atherosclerosis.	(Feig et al., 2010; Trogan et al., 2006)
T cells	L-selectin (Rolling)	Reduced migration of Sele$^{-/-}$ T cells into aortas of C57BL/6 and Apoe$^{-/-}$ mice (adoptive transfers). L-selectin deficiency reduces primary and secondary capture (intravital microscopy of femoral arteries).	(Galkina et al., 2006) (Eriksson et al., 2001)
	CCL5 (adhesion/migration)	Reduced content of CD4 and Th1-related Tim3 expression in Ccr5$^{-/-}$Apoe$^{-/-}$ mice.	(Braunersreuther et al., 2007; Feig et al., 2010)
	CXCL10 (adhesion/migration)	Cxcl10$^{-/-}$/Apoe$^{-/-}$ T cells into aortas were significantly reduced.	(Heller et al., 2006)
	CXCR6 CXCL16 (adhesion/migration)	Reduced migration of Cxcr6$^{-/-}$ T cells into atherosclerotic aortas. But increased atherogenesis in Cxcl16$^{-/-}$Apoe$^{-/-}$ mice.	(Galkina et al., 2007; Aslanian & Charo, 2006)
	MIF (adhesion/migration)	Blockade of MIF with neutralizing Abs resulted in diminished number of T cells within the aortas and reduction of atherosclerosis in Apoe$^{-/-}$ mice.	(Bernhagen et al., 2007a)
	CCR7 (entry/egress)	Ccr7$^{-/-}$Ldlr$^{-/-}$ mice have reduced number of T cells in atherosclerotic lesions.	(Luchtefeld et al., 2010)
B cells	L-selectin (rolling)	Reduced homing of adoptively transferred L-selectin-deficient B cells into normal and atherosclerotic aortas.	(Galkina et al., 2006)
Neutrophils	CXCL12/CXCR4 (migration/adhesion)	Blockade of CXCL12/CXCR4 by a small-molecule agonist, CxcR4 deficiency results in leukocytosis and increased neutrophil content in the plaques of Ldlr$^{-/-}$ mice.	(Zernecke et al., 2008)
	CCL2, CCL5 (migration/adhesion)	Impaired migration of Ccr1, CCr2, CCr5 and Cxcr2-deficient neutrophils into atherosclerotic plaques of Apoe$^{-/-}$ mice.	(Drechsler et al., 2010)

Table 1. Adhesion molecules and chemokine receptors that are involved in the recruitment of leukocytes into the aortic wall. (Adapted from (Galkina & Ley, 2007))

Two subsets of human monocytes representing $CD14^{high}$ and $CD14^{+}CD16^{+}$ cells have been described (Passlick et al., 1989), and a new additional subset of $CD14^{dim}$ human monocytes that patrols blood vessels has been added (Cros et al., 2010). Similarly, there are two distinct subsets of blood circulating murine monocytes: $Ly6C^{high}/CCR2^{+}/CX3CR1^{low}$ inflammatory monocytes and $Ly6C^{low}/CCR2^{-}/CX3CR1^{high}$ 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*$^{-/-}$ mice with a predominant increase in the numbers of $Ly6C^{high}$ 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. $Ly6C^{low}$ monocytes enter the atherosclerotic wall in a CCR5-dependent manner, but do not require CX3CR1 or CCR2 (Tacke et al., 2007). Surprisingly, $Ly6C^{high}/CCR2^{+}$ 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 $Ly6C^{high}$ monocytes and likely provides primary and secondary capture of monocytes to the endothelium. $Ly6C^{low}$ 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 $Ly6C^{low}$ 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 MFs 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*$^{-/-}$ 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 $CD68^{+}$ cells out of the plaque was detected in *C57BL/6* recipients, whereas little emigration was detected from progressive plaques in *Apoe*$^{-/-}$ 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 $CD68^{+}$ cells expressed LXRα mRNA in foam cells in the regression environment (Trogan et al., 2006). LXR increases expression of CCR7 on CD68+ cells, and thus supports CCR7-dependent regression of CD68+ 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.

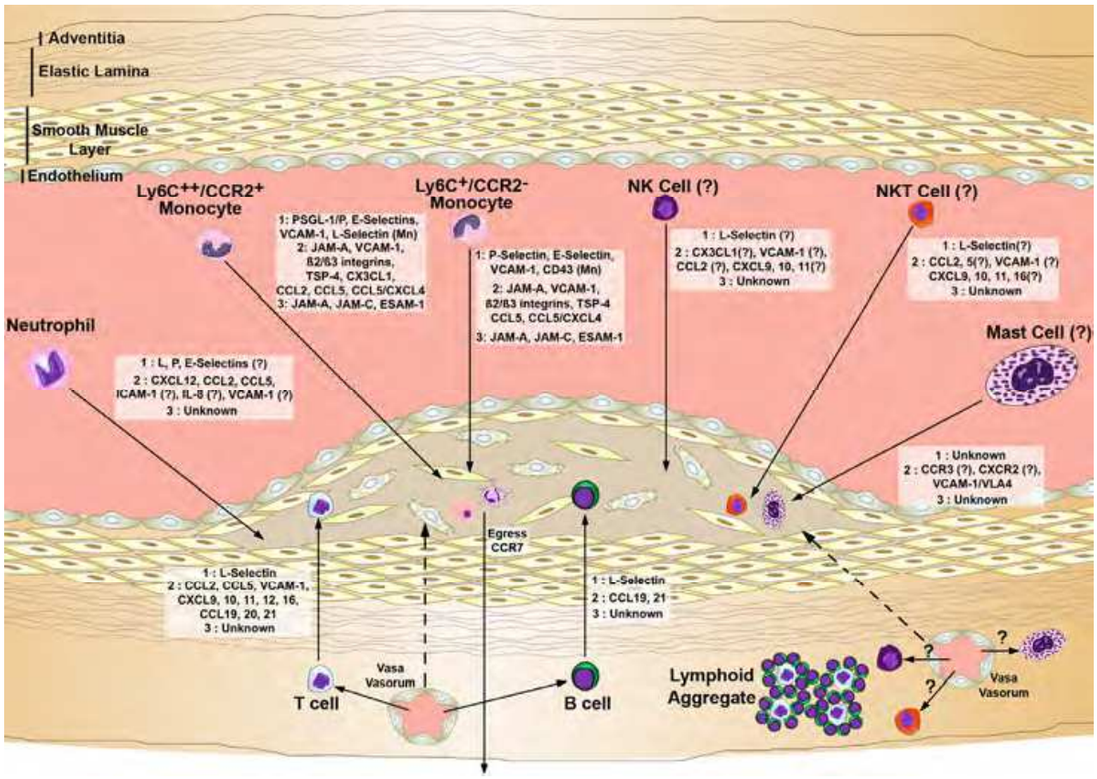

Fig. 2. Mechanisms of leukocyte recruitment in atherosclerosis
Different steps of the adhesion cascade and adhesion molecules control the recruitment of leukocytes to atherosclerotic plaques. The aortic adventitia, elastic laminia, smooth muscle, endothelial layers, as well as tertiary lymphoid aggregates 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.

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 (Luchtefeld 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 (Bi-Younes 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 *Cxcr6*$^{-/-}$*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$^{/+}$ T regs 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*$^{-/-}$ 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*$^{W\text{-}sh/W\text{-}sh}$ mice display alterations in ApoE and ApoAII-dependent cholesterol efflux (Lee et al., 2002). Interestingly *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice on the *Ldlr*$^{-/-}$ 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 atheroma, and come close to the arterial lumen (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). LTβ 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 aoritc leukocyte recruitment at the different stage of atherosclerosis.

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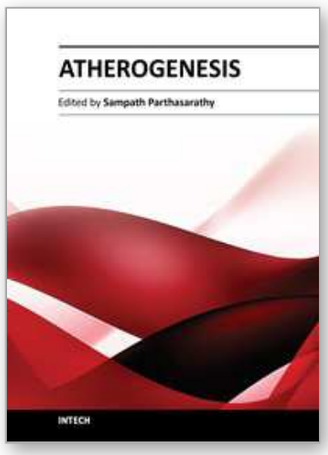

Atherogenesis

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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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