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Forum Review

Mechanisms of Monocyte Recruitment in Vascular Repair After Injury

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ABSTRACT

The inflammatory response to acute vessel wall injury has been increasingly recognized to play a decisive role in neointima formation. In particular, the exuberant infiltration with monocytes aggravates neointimal growth and can thereby promote restenosis. The adhesion of circulating monocytes to the site of mechanical injury represents the key event in monocyte recruitment, and this review highlights recent insights into the molecular mechanisms of monocyte adhesion throughout the course of neointimal growth. An acute and a chronic phase of monocyte recruitment after vascular injury can be discerned. The adhesion of platelets to the denuded subendothelial matrix is the hallmark of the acute phase providing an adhesive substrate for monocytes, whereas chronic monocyte recruitment is regulated by the interaction with neointimal smooth muscle cells and recovering endothelial cells. Clearly, the mechanisms of monocyte rolling and adhesion differ considerably between these diverse substrates. This review is particularly focused on the contribution of chemokines and adhesion molecules to monocyte recruitment to injured vessels according to the different stages of neointimal growth, and on closely related functions of the chemokine-like molecule macrophage migration inhibitory factor. Understanding the complex molecular interactions of the injured vessel wall with circulating monocytes may enable therapeutic targeting to prevent the development of restenosis. *Antioxid. Redox Signal.* 7, 1249–1257.

INTRODUCTION

THE VESSEL WALL reacts quite uniformly to a wide variety of acute injuries, such as wire-induced denudation, balloon angioplasty, and cuff placement, with the formation of neointimal hyperplasia, which has been proposed as the central element of vascular wound healing (21). Following the acute incident, which mainly consists of endothelial denudation, platelet adhesion, and apoptosis of smooth muscle cells (SMCs) in the medial vessel wall layer, the accumulation of phenotypically unique SMCs in the intimal layer restores the integrity of the artery (70).

Mechanical injury to stenotic atherosclerotic lesions by percutaneous intervention such as balloon angioplasty or stenting is the most important clinically encountered form of acute vascular injury. All patients treated by interventional revascularization develop neointimal hyperplasia to some degree, but in 30–40% of these patients reocclusion of the target artery by exacerbated neointimal growth and constrictive remodeling, referred to as restenosis, occurs necessitating repeated interventions (5). Morphologically, the extent of macrophage infiltration in the target lesion is a strong predictor of restenosis (53). Furthermore, circulating monocytes become activated after percutaneous coronary intervention and this appears to be associated with recurrent disease (50). After coronary stent placement, macrophage infiltration appears even more pronounced around the stent struts in in-stent neointimal tissue (35). In detailed studies, cellular and molecular mechanisms of neointima formation have been evaluated in diverse animal models. Interestingly, hypercholesterolemia which induces vascular inflammation clearly changes the response to injury in these models by accelerating neointima

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formation and monocyte recruitment (20, 56, 74, 78), and thus represents a useful model for restenosis in patients. In cholesterol-fed rabbits, balloon injury results in early intimal monocyte infiltration preceding the accumulation of SMCs (76). After 3 weeks, monocyte-derived macrophages constitute 50% of the neointimal area, suggesting ongoing monocyte recruitment during neointimal growth (76). Therefore, the early monocyte recruitment may trigger a more sustained and chronic inflammatory response by the release of cytokines and growth factors (27, 41), leading to activation of SMCs and additional monocyte infiltration.

SURFACE-ADHERENT PLATELETS PROVIDE THE ADHESIVE SUBSTRATUM FOR EARLY MONOCYTE RECRUITMENT AFTER VASCULAR INJURY

The important role of early monocyte recruitment after vascular injury in neointimal formation has been convincingly demonstrated after transient monocyte depletion by treatment of hypercholesterolemic rabbits with liposomal clodronate (14, 15). The peripheral monocyte count was significantly reduced for several days by this approach, which was associated with a marked reduction of the neointimal area and macrophage infiltration (14, 15).

In contrast to native atherosclerosis where circulating monocytes adhere to activated endothelial cells, early monocyte recruitment after mechanical injury is mediated by platelets adhering to the denuded subendothelial matrix (73). The disruption of the endothelial monolayer and the subsequent platelet adhesion instantly alter the adhesive properties of the vessel wall. Whereas the initial tethering of platelets on the subendothelial matrix is mediated predominantly by glycoprotein (GP) Iba–von Willebrand factor and GPVI–collagen interactions, activation of the platelet integrins $\alpha 2\beta 1$ and $\alpha IIb\beta 3$ via GPVI signaling is required for firm arrest on collagen (49, 55). Collagen-adherent platelets induce the recruitment of monocytes and polymorphonuclear leukocytes, but not lymphocytes, and therefore monocytes become dramatically enriched on adherent platelets compared with whole blood (32). This process can be completely inhibited by blocking P-selectin expressed on activated platelets (32). Furthermore, Kuijper *et al.* have shown in a flow chamber assay that extracellular matrix (ECM)-adherent platelets enhance monocyte adhesion compared with only ECM (37). P-selectin and monocyte P-selectin glycoprotein ligand-1 (PSGL-1), a known P-selectin ligand, are critical for monocyte adhesion to adherent platelets under flow conditions (37). This effect of platelet P-selectin on early monocyte recruitment may contribute to the marked reduction in neointimal area and macrophage infiltration described in apolipoprotein E (ApoE)$-/-$ mice that were also deficient in P-selectin or platelet P-selectin (47, 48). The transition of rolling monocytes to firm adhesion on platelets is mediated by macrophage antigen-1 (Mac-1), whereas lymphocyte function-associated antigen-1, platelet-endothelial cell adhesion molecule-1, and $\beta 1$-integrins were not involved (37). Concordantly, the blockade of very late activation protein-4 receptor (VLA-4) by a monoclonal antibody after air-desiccation injury did not reduce early monocyte infiltration, but diminished neutrophil recruitment after 4 days (21). Platelet GPIbα has been identified as an important counterreceptor for monocytic Mac-1 inducing the stable arrest of rolling cells (72). Recently, junctional adhesion molecule-3 (JAM-3) expressed on platelets has been shown to bind almost exclusively to Mac-1, but its role in monocyte adhesion on adherent platelets remains to be determined (64).

In addition to selectins, integrins, and adhesion molecules, chemokines are needed to induce firm arrest of rolling monocytes by the activation of integrins and are centrally involved in atherogenic monocyte recruitment (82, 83). The CC-chemokine monocyte chemotactic protein-1 (MCP-1) and its receptor CC chemokine receptor 2 (CCR2) have been shown to be decisively involved in monocyte recruitment to spontaneous atherosclerotic lesions in hyperlipidemic mice (6, 16, 26). After acute mechanical injury, a rapid up-regulation of MCP-1 mRNA expression in vascular SMCs within 24 h has been described in several animal models (23, 79). Enhanced MCP-1 expression in SMCs can be induced by the platelet-derived growth factor (PDGF), which is stored in the α-granula of platelets and released after activation, and α-thrombin (79, 88). Interestingly, increased MCP-1 expression is not sustained, but decreases to baseline levels after 3–4 days in various models of acute vascular injury (23, 79). The contribution of the MCP-1–CCR2 axis to neointimal formation after vascular injury has been extensively studied. Indeed, inhibition of CC chemokine ligand 2 (CCL2) reduced neointimal area and macrophage infiltration in hypercholesterolemic rabbits following angioplasty (54). Although most studies using normocholesterolemic animals report that inhibition of the CCL2/CCR2 axis diminished lesion size (19, 23, 63), monocyte accumulation was reduced only after periarterial cuff placement (12). Rather, genetic deletion of CCR2 in mice or a blocking CCL2 antibody in rats decreased neointimal SMC content (19, 23). The role of CCL2/CCR2 in vascular repair may thus differ between normo- and hypercholesterolemia. Interestingly, MCP-1 has been demonstrated to bind human platelets, which do not express functional CCR2, with a low affinity (12). In hypercholesterolemic ApoE$-/-$ mice, wire-induced injury of the carotid artery resulted in a rapid up-regulation of MCP-1 in the vessel wall and binding of MCP-1 to platelets adherent to the injury site (69). *In vitro* CCL2 binding to murine platelets was confirmed at high concentrations (69). *Ex vivo* perfusion of carotid arteries from ApoE$-/-$ mice 24 h after wire injury revealed rapid and firm adhesion of monocytes at the injury site, which could be blocked by preperfusion of a blocking CCL2 antibody, whereas rolling of monocytes was not impaired (69). These findings imply a novel function of JE/CCL2 as an arrest chemokine in early monocyte recruitment after endothelial denudation, which appears to require its local concentration and presentation on adherent platelets (Fig. 1). This contrasts with the previously described role of MCP-1 in monocyte recruitment on endothelial cells, where MCP-1 is not adequately immobilized on the endothelial surface after tumor necrosis factor (TNF) stimulation, but is secreted in a soluble form and is functionally involved in transendothelial migration but not adhesion under flow conditions (85). Growth-related oncogene-α (GRO-α), on the other hand, is

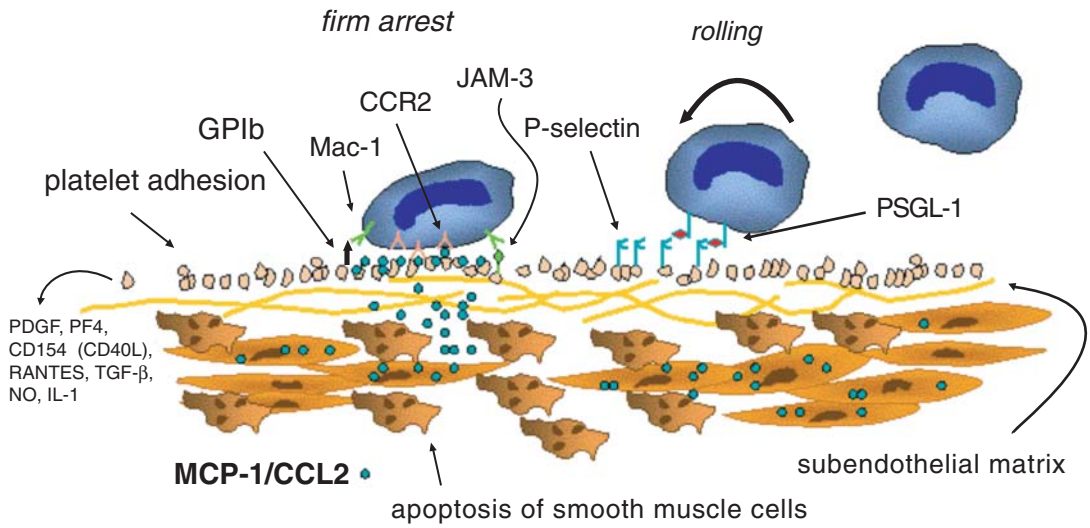

FIG. 1. Early monocyte recruitment after mechanical vascular injury. Surface-adherent platelets, which secrete various proinflammatory cytokines and growth factors, provide the adhesive substrate for the recruitment of monocytes in the early phase following denuding injury to the vessel wall. P-selectin expressed on activated platelets is critically involved in the initial rolling of circulating monocytes through interaction with its ligand PSGL-1. The binding of monocytic Mac-1 to GPIb and possibly JAM-3 expressed on activated platelets mediates the firm adhesion of circulating monocytes. The Mac-1-activating chemokine MCP-1 is expressed early after mechanical injury and induces firm monocyte adhesion, possibly via immobilization on surface-adherent platelets.

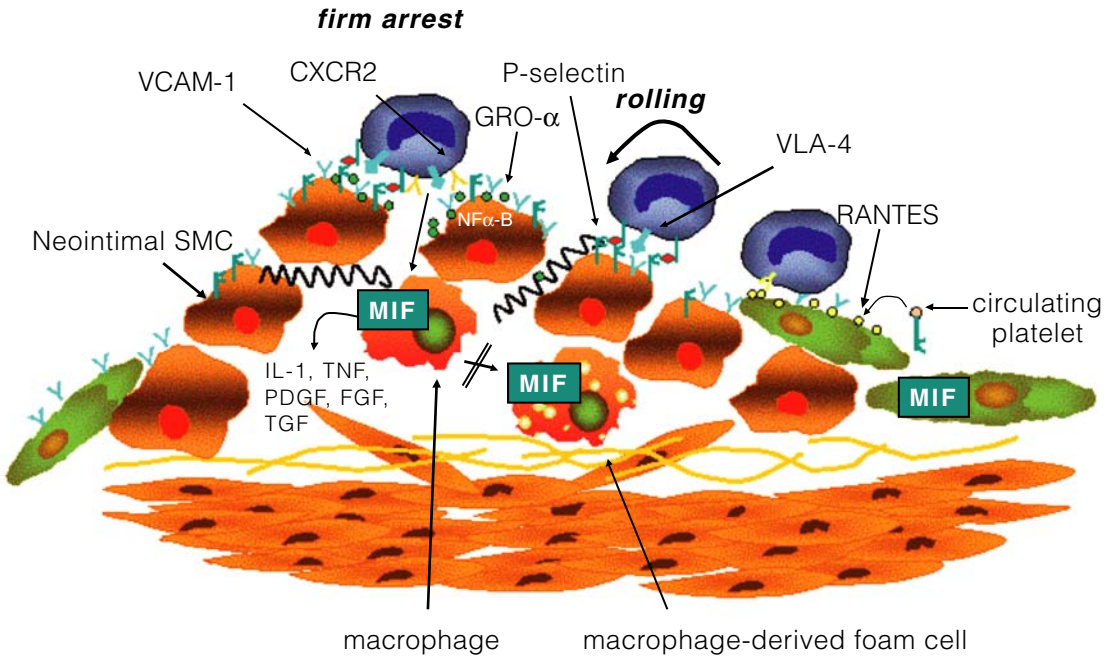

FIG. 2. Chronic monocyte recruitment on neointimal SMCs and recovering endothelial cells. Neointimal SMCs display a proinflammatory phenotype presumably mediated by sustained NF-κB activity. As in the early phase of monocyte recruitment, P-selectin expressed on neointimal SMCs is critical for the initial rolling and subsequent VCAM-1-dependent firm adhesion. Furthermore, fractalkine and GRO-α are up-regulated in neointimal SMCs and induce monocyte arrest most likely by activating VLA-4. Recovering endothelial cells resemble dysfunctional endothelium in many ways, including the immobilization of platelet-derived RANTES through a mechanism depending on platelet P-selectin. As in spontaneous atherosclerosis, RANTES immobilized on endothelial cells is centrally involved in monocyte recruitment after mechanical injury to arteries, presumably via CCR1 or CCR5 expressed on monocytes. MIF is expressed by neointimal macrophages and macrophage-derived foam cells, as well as in recovering endothelial cells. Whereas endothelial MIF can induce the firm arrest of monocytes under flow conditions, macrophage-derived MIF regulates macrophage activation and foam cell transformation.

very effectively immobilized on activated endothelium via heparin sulfate proteoglycans and induces the conversion of rolling into firm arrest of monocytes (85). In *ex vivo* perfused carotid arteries of ApoE−/− mice on a high cholesterol diet without wire-induced denudation, the closest murine orthologue to GRO-α, keratinocyte-derived chemokine (KC), and its receptor CXCR2, but not MCP-1, are involved in the arrest of monocytes (29). Solely the exogenous application of high concentrations of MCP-1 can trigger firm arrest on resting, but E-selectin-transduced, endothelium (24).

Firm arrest of monocytes on early atherosclerotic endothelium is mainly mediated by chemokine-triggered activation of VLA-4 (29), whereas adhesion of monocytes to adherent platelets is dependent on the β2-integrin Mac-1 (37). MCP-1 has been shown to induce Mac-1-dependent adhesion of monocytes to intercellular adhesion molecule-1 and ECM proteins such as laminin (31, 84). Therefore, the provision of Mac-1 binding sites by adherent platelets and the presentation of MCP-1 on the platelet surface, which can activate Mac-1 on monocytes, appear to regulate the adhesion of circulating monocytes in the early phase after endothelial denudation (Fig. 1).

CHRONIC MONOCYTE RECRUITMENT AFTER VASCULAR INJURY IS MEDIATED BY NEOINTIMAL SMCS AND RECOVERING ENDOTHELIAL CELLS

In animal models of mechanical vascular injury, persistent monocyte recruitment beyond the early infiltration via platelets is well established. Stent placement and hyperlipidemia appear to aggravate this chronic monocytic inflammation leading to exacerbated neointimal growth (35, 61, 74, 78). Whereas platelet adhesion to the denuded vessel wall is strongest in the first 24 h after denudation and gradually subsides thereafter (25), chronic monocyte recruitment is mainly mediated by neointimal SMCs and regenerating endothelial cells (39, 45). Interestingly, strong activation of nuclear factor-κB (NF-κB) and subsequently increased expression of NF-κB-dependent genes were found in both cell types following acute vascular injury that coincides with the luminal adhesion of monocytes (39, 44, 45). The sustained activation of NF-κB in the vessel wall after mechanical injury is known to play a central role in various processes regulating neointimal growth, such as matrix remodeling and the survival of neointimal cells (58). Several studies have recently established the prominent functional role of NF-κB activation following acute vascular injury (7, 90, 91). A key feature of all these studies using adenoviral delivery of IκB-α or NF-κB decoy oligodeoxynucleotides was a significant reduction of neointimal macrophage infiltration (7, 90, 91).

Following the acute denudation and platelet adhesion, SMCs accumulate in the developing neointimal lesion; these display a distinct phenotype compared with medial SMCs (71) and derive at least in part from circulating SMC progenitor cells (65, 67). As the complete reendothelialization of the denuded area takes several weeks in animal models of acute vascular injury (46) and severe damage to the vessel wall may result in a permanent replacement of endothelial cells by activated SMCs (60, 77), neointimal SMCs become exposed to the blood stream and might provide an eligible substrate for monocyte recruitment (44, 80). *In vitro* flow chamber assays using medial, uninjured rat SMCs and neointimal SMCs isolated after balloon injury have shown that monocytic cell adhesion was clearly enhanced on neointimal SMCs (92). The constitutively enhanced expression of P-selectin was found to be critical for the increased rolling and vascular cell adhesion molecule-1 (VCAM-1)-dependent arrest of monocytic cells on neointimal SMCs (92). In contrast to early monocyte recruitment, prolonged inhibition of the VCAM-1 ligand VLA-4 clearly reduces chronic monocyte infiltration and neointimal formation (2). This finding is in line with the hypothesis that monocyte adhesion to neointimal SMCs via VCAM-1 plays an important role after vascular injury. P-selectin, on the other hand, is known to mediate monocyte rolling on activated endothelial cells (59) and can increase the adhesive strength of monocyte binding to VCAM-1 under flow conditions (89). As P-selectin expression was demonstrated in neointimal SMCs at the luminal lining of the artery in ApoE−/− mice 2 weeks after wire injury, P-selectin on neointimal SMCs may participate in monocyte adhesion *in vivo* (92). Interestingly, ApoE/P-selectin double-deficient mice exhibit a much greater reduction of neointimal area and monocyte infiltration after wire denudation compared with ApoE−/− mice that do not have platelet P-selectin expression (47, 48). This difference may be partly explained by the possibility of monocyte recruitment via P-selectin expressing neointimal SMCs. Chemokines such as GRO-α and fractalkine were also up-regulated in neointimal SMCs and functionally involved in monocyte arrest under flow conditions (60). Overexpression of IκB-α in neointimal SMCs reduced monocyte arrest significantly by blocking the enhanced constitutive NF-κB activity (92), implying a central role of NF-κB activation in the proadhesive phenotype of neointimal SMCs (Fig. 2).

Soon after mechanical denudation of the vessel wall, reendothelialization is initiated and slowly progresses during the course of neointimal formation leading to an almost complete recovery of the arterial lining (28, 46). Although the reestablishment of a continuous endothelium appears to be associated with reduced neointimal thickening, regenerating endothelial cells have an impaired vasodilator response, an altered morphological appearance, and increased VCAM-1 expression, and may facilitate lipid accumulation in the underlying neointimal tissue (28, 35, 51, 86). This dysfunction of regenerating endothelial cells clearly deteriorates in the presence of hyperlipidemia, which promotes the excessive accumulation of monocytes (33, 87). In hyperlipidemic ApoE−/− mice, monocyte recruitment under flow conditions is regulated mainly by endothelial KC and platelet-derived RANTES (regulated on activation, normal T cell expressed and secreted) immobilized on the surface of activated endothelial cells (29, 81). It has been shown that deposition of platelet-derived RANTES critically depends on platelet P-selectin (30, 66). The results from our study using a RANTES receptor antagonist after carotid wire injury in ApoE−/− mice demonstrated a 30% decrease of the neointimal area and a significant reduction of foam cell infiltration and lipid

deposits (66). As RANTES was found on luminal endothelial cells 4 weeks after wire injury, but not in ApoE−/− mice that were deficient in P-selectin or platelet P-selectin, platelet-dependent RANTES deposition via P-selectin may contribute to macrophage infiltration and neointima formation via regenerating endothelial cells (66), (Fig. 2). This RANTES-dependent monocyte recruitment may be specific for the chronic inflammatory response after mechanical injury, because RANTES is not immobilized on platelets, which might explain the observation that RANTES does not support monocyte adhesion on adherent platelets (81). In contrast to the RANTES effect, blockade of KC in the ApoE−/− wire-injury model inhibited reendothelialization and aggravated neointimal growth, but revealed no effect on monocyte recruitment after mechanical injury (42).

Macrophage migration inhibitory factor (MIF) is a well known pleiotropic cytokine that is involved in various inflammatory diseases, such as endotoxic shock, chronic colitis, and delayed-type hypersensivity reaction (3, 4, 18). In a rat model of immunologically induced glomerulonephritis, blockade of MIF substantially reduced proteinuria, prevented the loss of renal function, and significantly reduced histological damage (38). This effect of anti-MIF treatment was associated with a substantially reduced renal monocyte and T-cell infiltration and activation (38). Furthermore, MIF is abundantly expressed by macrophages (9), critically regulates macrophage viability and proinflammatory function by inhibiting p53 activity (52), and is involved in intracellular signaling via activator protein-1 activity and its transcriptional coactivator Jun activation domain binding protein-1 (34). In the macrophage response to endotoxin and gram-negative bacteria, MIF deficiency results in a down-regulation of Toll-like receptor 4 with a concomitant profound reduction of NF-κB activity and TNF-α production (62). Macrophages release preformed MIF after stimulation with lipopolysaccharide (LPS), TNF, or interferon-γ (9), and MIF acts as a counterregulatory mediator of the inhibitory effect of glucocorticoids on cytokine secretion by LPS-stimulated monocytes (10). A major contribution of MIF to the progression of human atherosclerotic plaque has been proposed, because up-regulation of MIF has been detected in endothelial cells, SMCs, and macrophages in different stages of plaque growth (8). *De novo* MIF expression has been described in endothelial cells and activated macrophages in hypercholesterolemic rabbits (43). In MIF/low-density lipoprotein (LDL) receptor (LDL-R)-deficient mice, the initiation and progression of atherosclerotic plaques are markedly retarded and accompanied by reduced SMC proliferation (57). Wire-induced endothelial denudation of the carotid injury resulted in an up-regulation of MIF in medial SMCs. In advanced neointimal lesions, strong MIF expression could be detected in macrophage-derived foam cells and regenerated endothelial cells (68). A functional role of MIF in atherogenic monocyte recruitment could be deduced from the finding that the administration of a blocking MIF antibody leads to reduced neointimal macrophage infiltration and a diminished rate of macrophage-derived foam cells (68). As MIF has been shown to enhance the uptake of oxidized LDL by macrophages (1), MIF may play a pivotal role in the transformation of macrophages into foam cells, a cell type that is known to be critical in atherogenesis (40). Interestingly, the neointimal lesion area was not significantly reduced in ApoE−/− mice receiving the blocking MIF antibody after wire injury (68). This appears due to the compensatory expansion of neointimal SMCs and lesional collagen type I (68). In LDL-R−/− mice treated with a neutralizing MIF antibody, carotid injury resulted in diminished neointimal formation, which was associated with reduced inflammation, diminished cellular proliferation, and increased apoptosis (11). The observed differences in these mouse models can be largely attributed to the more pronounced foam cell formation in ApoE−/− mice. Considering the involvement of MIF in the transformation of macrophages into foam cells, the blockade of MIF may quite differently affect neointimal formation in ApoE−/− mice compared with LDL−/− mice. As exogenously added MIF induces adhesion molecule expression in endothelial cells (3) and oxidized LDL is known to up-regulate endothelial MIF expression (8), a role of MIF in monocyte recruitment has been hypothesized. *In vitro* flow chamber assay revealed that short-term incubation of endothelial cells with MIF significantly enhanced monocyte adhesion (68). Furthermore, monocyte arrest on oxidized LDL-stimulated endothelial cells was inhibited by a blocking MIF antibody, suggesting an autocrine feedback mechanism (68). This finding adds new evidence for the proposed chemokine-like function of MIF, similar to other unrelated molecules such as urokinase, interleukin-6 (IL-6), and anaphylatoxin C5a, which do not share the characteristic structural chemokine motifs (17). As strong MIF expression in recovering endothelial cells has been observed (68), MIF-dependent monocyte recruitment on reendothelialized neointimal areas may be a relevant mechanism, which is inhibited in MIF antibody-treated mice leading to diminished neointimal macrophage content (68). Therefore, a dual role of MIF in neointimal growth, affecting monocyte adhesion to endothelial cells and subsequent macrophage transformation into foam cells, can be assumed (Fig. 2).

CONCLUSIONS AND PERSPECTIVES

Monocytes and monocyte-derived macrophages have been increasingly recognized to play an important role in neointimal growth and restenosis after mechanical vascular injury (13, 14, 22, 53). Neointimal macrophages do not just simply expand the neointimal area by infiltrating the injured vessel, but initiate proliferation and activation of neointimal SMCs by macrophage-derived growth factors and cytokines (14, 41), such as PDGF-BB, transforming growth factor-β (TGF-β), IL-1β, TNF-α, and IL-8 (14). A cascade model of restenosis has been proposed in which mechanical injury results in increased acute cytokine gene expression with consecutive, self-sustaining autocrine and paracrine growth factor and cytokine expression by macrophages. This may shift the ordinary wound repair of an injured vessel to exacerbated plaque growth, similar to native atherosclerotic lesions (27). Hyperlipidemia activates macrophages in the neointimal lesion, and the uptake of oxidized LDL leads to formation of macrophage-derived foam cells, which are enriched in vulnerable plaques (74, 78). Therefore, the molecular mechanisms of

monocyte recruitment to injured arteries may be a promising target for the prevention of restenosis. Similar to spontaneous atherosclerosis, the multistep model of leukocyte adhesion and transmigration is also applicable for monocyte recruitment to denuded vessel (75). However, the involved adhesion molecules and chemokines vary considerably throughout the course of neointima formation depending on the respective adhesive substrate, *i.e.,* platelets in the early stage and neointimal SMCs and recovering endothelial cells thereafter.

ABBREVIATIONS

ApoE, apolipoprotein E; CCL, CC chemokine ligand; CCR, CC chemokine receptor; ECM, extracellular matrix; GP, glycoprotein; GRO, growth-related oncogene; IL, interleukin; JAM, junctional adhesion molecule; KC, keratinocyte-derived chemokine; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; LPS, lipopolysaccharide; Mac-1, macrophage antigen-1; MCP, monocyte chemotactic protein; MIF, macrophage migration inhibitory factor; NF-κB, nuclear factor-κB; PDGF, platelet-derived growth factor; PSGL-1, P-selectin glycoprotein ligand-1; RANTES, regulated on activation, normal T cell expressed and secreted; SMC, smooth muscle cell; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late activation protein-4 receptor.

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