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Leukocyte Integrins: Role in Leukocyte Recruitment and as Therapeutic Targets in Inflammatory Disease

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Abstract

Infection or sterile inflammation triggers site-specific attraction of leukocytes. Leukocyte recruitment is a process comprising several steps orchestrated by adhesion molecules, chemokines, cytokines and endogenous regulatory molecules. Distinct adhesive interactions between endothelial cells and leukocytes and signalling mechanisms contribute to the temporal and spatial fine-tuning of the leukocyte adhesion cascade. Central players in the leukocyte adhesion cascade include the leukocyte adhesion receptors of the β2-integrin family, such as the αLβ2 and αMβ2 integrins, or of the β1-integrin family, such as the α4β1- integrin. Given the central involvement of leukocyte recruitment in different inflammatory and autoimmune diseases, the leukocyte adhesion cascade in general, and leukocyte integrins in particular, represent key therapeutic targets. In this context, the present review focuses on the role of leukocyte integrins in the leukocyte adhesion cascade. Experimental evidence that has implicated leukocyte integrins as targets in animal models of inflammatory disorders, such as experimental autoimmune encephalomyelitis, psoriasis, inflammatory bone loss and inflammatory bowel disease as well as preclinical and clinical therapeutic applications of antibodies that target leukocyte integrins in various inflammatory disorders are presented. Finally, we review recent findings on endogenous inhibitors that modify leukocyte integrin function, which could emerge as promising therapeutic targets.

Keywords

integrin, leukocyte adhesion, natalizumab, efalizumab, vedolizumab, Del-1

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Leukocyte integrins: Role in leukocyte recruitment and as therapeutic targets in inflammatory disease

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Abstract

Infection or sterile inflammation triggers site-specific attraction of leukocytes. Leukocyte recruitment is a process comprising several steps orchestrated by adhesion molecules, chemokines, cytokines and endogenous regulatory molecules. Distinct adhesive interactions between endothelial cells and leukocytes and signalling mechanisms contribute to the temporal and spatial fine-tuning of the leukocyte adhesion cascade. Central players in the leukocyte adhesion cascade include the leukocyte adhesion receptors of the β2-integrin family, such as the αLβ2 and αMβ2 integrins, or of the β1-integrin family, such as the α4β1- integrin. Given the central involvement of leukocyte recruitment in different inflammatory and autoimmune diseases, the leukocyte adhesion cascade in general, and leukocyte integrins in particular, represent key therapeutic targets. In this context, the present review focuses on the role of leukocyte integrins in the leukocyte adhesion cascade. Experimental evidence that has implicated leukocyte integrins as targets in animal models of inflammatory disorders, such as experimental autoimmune encephalomyelitis, psoriasis, inflammatory bone loss and inflammatory bowel disease as well as preclinical and clinical therapeutic applications of antibodies that target leukocyte integrins in various inflammatory disorders are presented. Finally, we review recent findings on endogenous inhibitors that modify leukocyte integrin function, which could emerge as promising therapeutic targets.

Keywords

integrin; leukocyte adhesion; natalizumab; efalizumab; vedolizumab; Del-1

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Introduction

Leukocyte trafficking to sites of injury or infection is tightly regulated by the leukocyte adhesion cascade. The cascade starts with selectin-dependent leukocyte rolling, followed by chemokine-induced leukocyte activation and leukocyte slow rolling, mediated by the collaboration between selectin and integrins and the interactions thereof with their respective ligands. Slow rolling paves the way for the integrin-dependent steps comprising firm leukocyte adhesion/arrest, adhesion strengthening and leukocyte crawling on the endothelium, that finally enable the transendothelial migration of leukocytes mostly through endothelial junctions to the subendothelium (Figure 1) (Ley et al., 2007; Chavakis, 2012). The present review will focus particularly on the function of integrins in the leukocyte adhesion cascade, endogenous factors and molecular mechanisms contributing to the regulation of integrin activity, animal models, in which the role of integrins in the context of leukocyte recruitment has been studied, as well as therapeutic approaches targeting leukocyte integrins in inflammatory diseases.

Integrins; an overview

Integrins are a family of adhesion molecules that exist as transmembrane heterodimers, consisting of one α- and one β-subunit (Hogg et al., 2011; Moser et al., 2009). In mammals, eighteen α and eight β subunits have been described, forming 24 different integrin heterodimers (Herter and Zarbock, 2013; Hynes, 2002).

Activated integrins participate in mediating cell adhesion; the strength of integrin-mediated cell adhesion is defined as integrin avidity (Carman and Springer, 2003). Both integrin affinity and integrin valency contribute to integrin avidity (Carman and Springer, 2003). Affinity represents the strength of the individual bond between a single integrin and its ligand and is regulated by the conformational status of integrin subunits, whereas integrin valency is mediated by the clustering of integrin receptors on the cell surface, thereby bringing together several individual bonds (Carman and Springer, 2003). In the absence of activating signals, integrins have an inactive, bent conformation (Askari et al., 2009). Upon activation by different signals, e.g., deriving from chemokines, or PSGL-1 ligation, integrins undergo major conformational changes, which results in exposure of their ligand-binding site in the extracellular domains (Arnaout et al., 2005; Hogg et al., 2011, Moser et al., 2009; Tiwari et al., 2011; Wegener et al., 2007). Another feature of the process of integrin activation is its strong dependency on the presence of divalent cations, especially Mn^{2+} and Mg^{2+} ions, which control the conformational changes of the integrin molecules (Gailit and Ruoslahti, 1988; reviewed in Arnaout et al., 2002; Dransfield et al., 1992; Tiwari et al., 2011).

In the present review, we will focus on leukocyte integrins, in particular, β2-integrins as well as integrin α4β1 (very late antigen (VLA)-4; CD49d/CD29) and integrin α4β7 (LPAM-1), which play a role in leukocyte recruitment and in inflammatory disorders. The β2-integrins consist of a common β subunit (CD18) that associates with 4 different α subunits. They comprise the αLβ2-integrin (lymphocyte function-associated antigen 1 [LFA-1]; CD11a/CD18) and the αMβ2-integrin (macrophage-1 antigen [Mac-1] also designated complement

receptor 3 [CR3]; CD11b/CD18), which are the most crucial β2-integrins for leukocyte recruitment, as well as the αXβ2 (CD11c/CD18; p150,95; CR4) and the αDβ2 (CD11d/CD18) integrins (Chavakis, 2012; Moser et al., 2009). LFA-1 is expressed by neutrophils, monocytes and lymphocytes, whereas Mac-1 is found mainly on neutrophils and monocytes and VLA-4 is expressed on monocytes and T lymphocytes (Chan et al., 2001; Hyun et al., 2009; Chavakis, 2012; Moser et al., 2009). αXβ2 is present on macrophages and dendritic cells (DCs) (O'Doherty et al., 1994; Wu et al., 2009), and αDβ2 is expressed on monocytes / macrophages, especially foam cells, which are macrophages found in atherosclerotic lesions (Van der Vieren et al., 1995).

The leukocyte adhesion cascade

The leukocyte adhesion cascade is initiated with leukocyte capture from the blood stream and rolling on the luminal surface of endothelial cells (Kunkel et al., 1998). Rolling serves as a break for circulating leukocytes and is mediated by E-, P- and L-selectins (Kansas, 1996, Kuwano et al., 2010). E-selectin and P-selectin are expressed in endothelial cells. L-selectin is constitutively expressed on most leukocytes (McEver, 2002) and plays a significant role in the migration of naïve and central memory T cells to lymph nodes (von Andrian and Mempel, 2003). Upon inflammation, the abundance of P- and E-selectin on the luminal endothelial cell surface is enhanced. Elevated surface expression of endothelial selectins is mediated either by exocytosis mechanisms in the case of P-selectin, which is released from cytosolic vesicles (designated Weibel-Palade bodies) or by enhanced transcriptional gene expression of E-selectin (McEver, 2002). On the other hand, leukocyte activation results in rapid shedding of L-selectin from their surface (Kishimoto et al., 1989), which contributes to the modulation of leukocyte rolling velocity (Hafezi-Moghadam and Ley, 1999).

Selectins interact with the P-selectin glycoprotein ligand-1 (PSGL-1) (McEver and Cummings, 1997) as well as other glycosylated ligands, such as CD44 and E-selectin ligand 1 (Hidalgo et al., 2007, reviewed in Zarbock et al., 2011). Leukocyte rolling under flow conditions is mediated by the rapid formation and dissociation of bonds between selectins and their ligands (Alon et al, 1995). These transient selectin-dependent adhesive interactions result in a progressive reduction in the rolling velocity of leukocytes, enabling cells to receive signals deriving from chemokines present on the endothelial cell surface; these signals activate integrins, thus allowing subsequent steps of the cascade to take over (Zarbock et al, 2011).

The interaction between selectins and their ligands leads to intracellular signaling cascades, which cooperate with chemokine-derived signals, resulting in the activation of integrins and thus firm leukocyte adhesion (Zarbock et al., 2007a; Yago et al., 2010; Zarbock et al., 2011). For instance, signalling pathways triggered by E-selectin are mediated by the Src family kinases Fgr, Hck and Lyn (Yago et al., 2010; Zarbock et al., 2008) also involving the adaptor proteins DAP12 and FcRγ and the spleen tyrosine kinase (Zarbock et al., 2008; Urzainqui et al., 2002). This pathway results in activation of phospholipase C-γ2 (Mueller et al., 2010; Yago et al., 2010; Zarbock et al., 2011), culminating in the activation of the small GTPase RAS-related protein 1 (Rap1) (Stadtmann et al., 2011), which can promote integrin

affinity (Chavakis, 2012). Thus, intracellular signalling induced by PSGL-1 and other selectin ligands is considered a major driver of the leukocyte adhesion cascade as it transforms a rolling/selectin-induced signal into activation of leukocyte integrins, thereby initiating the later steps of the cascade.

Upon activation, integrins mediate firm leukocyte adhesion and crawling. The α4-integrins VLA-4 and α4β7 as well as the β2-integrins are the most important integrins involved in leukocyte recruitment (Chavakis, 2012; Berlin et al., 1993) interacting with endothelial lignads/counter-receptors.

Inflammatory activation of the endothelium triggers the production or upregulation of several molecules promoting leukocyte recruitment: a) endothelial cells secrete a variety of chemokines, which are deposited on their apical surface and induce 'inside-out' signalling leukocyte integrin activation, and b) they induce or upregulate cell adhesion molecules on their luminal cell surface, which function as counter-receptors of integrins on leukocytes, thereby mediating leukocyte adhesion (reviewed in Ley et al., 2007; Chavakis et al., 2009; Chavakis, 2012).

Chemokines act *via* their G-protein-coupled receptors and induce signalling cascades called 'inside-out' signalling, which lead to the activation of the extracellular domains of integrins (reviewed in Chavakis et al., 2009; Ley et al., 2007). Chemokine-induced inside-out signalling comprises several inter-dependent pathways, including a) activation of phospholipase C, which leads to intracellular Ca^{2+} flux from the endoplasmatic reticulum and generation of inositol-1,4,5-trisphosphate (InsP3) and diacylglycerol (DAG) (Zarbock et al., 2011), b) activation of small GTPases, such as Rap1 (RAS-related protein 1) by guanine-nucleotide-exchange factors (Shimonaka et al., 2003; Lafuente and Boussiotis, 2006; Chavakis et al., 2009; Gahmberg et al., 2009) and c) interaction of intracellular proteins, such as talin-1, kindlin-3, cytohesin-1 and 14-3-3-family members, with the cytoplasmic tail of integrins. The binding of the latter proteins to the β subunit of e.g. LFA-1 results in separation of the two cytoplasmic tails thereby inducing and sustaining the conformational changes in the extracellular domain (reviewed in Alon and Feigelson, 2012, Hogg et al., 2011; Moser et al, 2009; Choi et al., 2008a; Chavakis et al., 2009; Kinashi, 2005; Fagerholm et al., 2002; Kolanus et al, 1996; Gahmberg et al., 2009). Besides chemokines and PSGL-1-ligation, Toll-like receptors also induce integrin activation (Harokopakis et al., 2006; Harokopakis and Hajishengallis, 2005). Recently, Toll like receptor 2 (TLR2)- and Toll like receptor 5 (TLR5)-ligation was shown to rapidly activate integrin-dependent leukocyte adhesion to immobilized intercellular cell-adhesion molecule 1 (ICAM-1) or fibronectin through activation of a pathway requiring Rac1, NADPH oxidase 2-mediated reactive oxygen species production and activation of Rap1-GTPase (Chung et al, 2014). Furthermore, TLRs activate *via* Ras the PI3K isoform p100γ, which then promotes activation of the α4β1-integrin (Schmid et al., 2011). The distinct triggering signals and pathways involved in 'inside-out' signalling ensure a great diversity in integrin activation and thereby stimulation of inflammatory cell recruitment under different inflammatory conditions (Hyduk et al., 2007; Kinashi, 2005; Lafuente and Boussiotis, 2006; Shamri et al., 2005; Wegener et al., 2007 and reviewed in Chavakis et al., 2009; Hogg et al., 2011; Ley et al., 2007).

Upon activation, integrins bind to their ligands, mediating slow rolling, leukocyte adhesion and crawling and participate in transendothelial migration (Ley et al., 2007). Moreover, leukocyte integrins may participate in other functions such as immune synapse formation or phagocytosis (Dupuy and Caron, 2008; Springer and Dustin, 2012). Integrin activation cooperates with selectins to mediate slow rolling. LFA-1 or Mac-1-deficient mice both show significantly increased leukocyte rolling velocities under inflammatory conditions, indicating that β2-integrins contribute to "slowing-down" of rolling neutrophils (Dunne et al., 2002).

VLA-4 binds to the vascular cell-adhesion molecule (VCAM)-1 and autotaxin (Kanda et al., 2008; Gahmberg et al., 2009), while LFA-1 and Mac-1 interact with ICAM-1 and ICAM-2 (reviewed in Springer, 1994; Chavakis, 2012; Chavakis et al., 2009; Gahmberg et al., 2009). Mac-1 is a very promiscuous receptor interacting with numerous other ligands. For instance, it binds to iC3b, thereby promoting complement-dependent phagocytosis by macrophages (Micklem and Sim, 1985; Dupuy and Caron, 2008). Mac-1 also interacts with fibrinogen (Altieri et al., 1990), which was shown to be of importance for bacterial elimination by leukocytes (Flick et al., 2004). Furthermore it binds heparin (Diamond et al., 1995), elastase (Cai and Wright, 1996) and other proteolytic enzymes, such as kininogen components, plasminogen, fragments thereof, urokinase or its receptor (Chavakis et al., 1999; Chavakis et al., 2001; Chavakis et al., 2005; Pluskota et al., 2003, Wei et al, 1996; Simon et al., 1996), thereby orchestrating cell surface-associated proteolytic activity. Mac-1 was also demonstrated to interact with the receptor for advanced glycation end products (RAGE) (Orlova et al., 2007; Chavakis et al., 2003a; Frommhold et al., 2010), an interaction that could be relevant in diabetes-associated vascular inflammation (Yamamoto and Yamamoto, 2013). It also interacts with membrane glycoprotein GPIbα (Ehlers et al., 2003; Chavakis et al., 2003b; Simon et al., 2000) and Junctional Adhesion Molecule-C (JAM-C) on platelets (Santoso et al., 2002), thereby mediating leukocyte-platelet interactions. Finally, α4β7 on lymphocytes interacts with the mucosal vascular addressin cell-adhesion molecule 1 (MAdCAM1) (Berlin et al., 1993; and reviewed in Springer, 1994; Ley et al., 2007; Chavakis et al., 2009).

Leukocyte-platelet cross-talks play also an important role in promoting leukocyte adhesion and leukocyte recruitment (Langer and Chavakis, 2009). Upon vascular injury, platelets adhere to the vascular endothelium where they stimulate leukocytes indirectly by the release of chemokines and inflammatory cytokines (von Hundelshausen and Weber, 2007; Zarbock et al., 2007b), as well as directly through cell-to-cell contact (Zarbock et al., 2007b). For instance, platelets secrete CC-chemokine ligand 5 (CCL5 or RANTES), CXC-chemokine ligand 4 (CXCL4) and CXCL5, thereby triggering monocyte arrest (Huo et al., 2003). Furthermore, platelet P-selectin interacts with PSGL-1 on leukocytes (Moore et al., 1992; Larsen et al., 1989), while GPIb, JAM-C and platelet-associated fibrinogen all bind to leukocyte Mac-1 (Ehlers et al., 2003; Santoso et al., 2002; Weber and Springer, 1997). These interactions contribute to the formation of direct platelet-leukocyte cell-to-cell interactions (Massberg et al., 2002; Massberg et al., 2005; Burger and Wagner, 2003; Zarbock, 2007b; Santoso et al., 2002; Simon et al., 2000). The significance of leukocyte-platelet interactions in vascular inflammation is evidenced by their critical role in the formation of atherosclerotic lesions (Massberg et al., 2002; Huo et al., 2003).

Ligand binding of integrins triggers signalling pathways designated 'outside-in signalling', which lead to strengthening of leukocyte adhesion and subsequent spreading. Ligation of β2-integrin induces the activation of the Src proteins Hck and Fgr (Giagulli et al., 2006) and phosphorylation of spleen tyrosine kinase (Mocsai et al., 2006; reviewed in Hogg et al., 2011). In T cells, proteins involved in outside-in signalling are the Lck and ζ-chain-associated protein kinase of 70kDa (Evans et al., 2011). During this step, integrins associate intracellulary with cytoskeletal proteins; for instance α4β1-integrin interacts with paxillin (Liu et al., 1999), which contributes to the stability of activated integrin conformation (Goldfinger et al., 2003; Kinbara et al., 2003). Moreover leukocyte integrins associate with further cytoskeletal proteins, such as vinculin or actinin (Mace et al., 2010; Stanley et al., 2008); this association facilitates formation of focal adhesions and further integrin-dependent steps (Kinbara et al., 2003). Following firm arrest, leukocytes crawl on the endothelial cell surface in a manner dependent on β2-integrins, a process also named locomotion (Schenkel et al., 2004; Phillipson et al, 2006) that allows leukocytes to identify an appropriate site to migrate through the endothelial cell monolayer.

Transmigration through venular walls is the final step in the process of leukocyte emigration into inflamed tissues. Leukocytes mainly transmigrate paracellularly at interendothelial junctions, although transcellular migration through the endothelial cell body also rarely takes place (Nourshargh et al., 2010; Woodfin et al., 2011; Choi et al., 2009).

The critical role of LFA-1 and Mac-1 during transmigration has long been established (Smith et al., 1989; Henderson et al., 2001). Shaw *et al*. have shown that the distribution of LFA-1 in transmigrating neutrophils rapidly changes to form a ring-like cluster at the neutrophil-endothelial junctions, while endothelial ICAM-1 co-localizes with LFA-1 in these clusters (Shaw et al., 2004). ICAM-2 also mediates neutrophil transmigration, due to its interaction with Mac-1 and LFA-1 (Staunton et al., 1989; Xie et al., 1995), as shown by genetic or antibody-mediated inactivation of ICAM-2 (Huang et al., 2006). Furthermore, there is ample evidence that integrins interact with JAM proteins in the process of transmigration. LFA-1 was shown to bind to JAM-A, while Mac-1 interacts with JAM-C; these interactions may promote leukocyte diapedesis (Chavakis et al., 2004; Lamagna et al., 2005; Keiper et al., 2005; Orlova and Chavakis, 2007; Ostermann et al., 2002). The important role of JAM-C in leukocyte transmigration *in vivo* has been shown in a study by Woodfin *et al*., linking the reverse transendothelial migration with reduced expression of JAM-C at the endothelial cell junctions (Woodfin et al., 2011). Furthermore, JAM-A was recently demonstrated to promote monocyte recruitment to the arterial wall during atherosclerosis (Schmitt et al., 2014).

Numerous other endothelial molecules, primarily located at junctions, such as platelet/endothelial-cell adhesion molecule 1 (PECAM-1, CD31), CD99 and endothelial cell selective adhesion molecule are also involved in leukocyte transmigration (Ley et al., 2007; Nourshargh et al., 2010; Muller, 2003; Muller, 2014; Schenkel et al., 2002; Wegmann et al., 2006). Interestingly, ICAM-2, JAM-A and PECAM-1 play a rather sequential role during leukocyte transmigration (Woodfin et al., 2009). Endothelial PECAM-1 promotes leukocyte transmigration by undergoing homophilic interactions with PECAM-1 on monocytes (Mamdouh et al., 2003; Muller et al., 2003), through which it can up-regulate α6β1-integrin

(Dangerfield et al., 2002); in addition, PECAM-1 also undergoes a heterophilic interaction with CD177, which may contribute to transmigration (Sachs et al., 2007).

CD99 through homophilic interactions (Muller et al., 2003 Schenkel et al., 2002) and CD99L2 (Bixel et al., 2010), also promote leukocyte transmigration (Schenkel et al., 2002; Bixel et al., 2004; Bixel, 2010). Finally, VE-cadherin, the most important gatekeeper of vascular endothelial integrity may be transiently distributed away from the junctional regions during diapedesis thus permitting trans-endothelial leukocyte migration, whereas phosphorylation of VE-cadherin also plays a regulatory role in the process of diapedesis (Shaw et al., 2001; Vestweber et al., 2009; Wessel et al., 2014).

Leukocyte integrins as targets in inflammatory disease models

Leukocyte recruitment into an inflamed tissue is a cardinal hallmark in several inflammatory diseases. Infiltrating leukocytes induce, promote and perpetuate inflammation, whereas their clearance is critical for the resolution of the inflammatory process. Due to their critical role in leukocyte recruitment, leukocyte integrins have emerged as therapeutic targets in several inflammatory diseases (Yonekawa and Harlan, 2005). In the following section, we review the importance of leukocyte integrins in different animal models of inflammatory disorders, in which integrin targeting has been proven to be beneficial (Figure 2).

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by demyelination. The clinical course ranges from relapsing-remitting to progressive forms and can lead to severe disability and mortality (Bhat and Steinman, 2009; Confavreux et al., 2000; Confavreux and Vukusic, 2006; Lassmann et al., 2012). The rodent model of MS is experimental autoimmune encephalomyelitis (EAE); pathology in this model (and most likely in MS as well) is triggered by infiltration of autoreactive T cells, which are targeted against antigens of the myelin sheath through the blood-brain barrier (BBB) into CNS. This initiates a strong neuroinflammatory response, involving BBB disruption (Minagar and Alexander, 2003) and recruitment of further immune cells (Bhat and Steinman, 2009; Korn, 2008). Thus, leukocyte recruitment is a critical event in the pathogenesis of EAE and MS (Goverman, 2009; Popescu and Lucchinetti, 2012; Simmons et al., 2013).

The role of α4β1-integrin in leukocyte recruitment to the inflamed CNS in the course of EAE has been extensively investigated (Sheremata et al., 2005). The identification of this integrin as a major player in EAE and MS resulted in the development of natalizumab, a monoclonal antibody against α4, which has been approved for the treatment of patients with MS (Weinstock-Guttman, 2013). Initial studies demonstrated that leukocyte adherence to the inflamed endothelium in the CNS was mediated by the α4β1-integrin / VCAM-1 interaction; consistently, blockade of α4β1-integrin prevented disease development in rats (Yednock et al., 1992) and mice (Baron et al., 1993). By using a model of adoptive transfer in EAE, Baron *et al*. further demonstrated that only antigen-specific T cells expressing α4β1-integrin were able to migrate into the brain parenchyma and that blocking α4-integrin with antibodies preferentially inhibited the recruitment of these cells to the inflamed CNS

(Baron et al., 1993). The effect of α4 antibodies was mediated by blockade of α4β1- rather than α4β7-integrin, as clarified by inhibition studies with antibodies against α4β7 heterodimer or β7-integrin (Engelhardt et al., 1998), whereas endothelial overexpression of the α4β7-integrin counter-receptor MAdCAM-1 did not affect EAE severity (Döring et al., 2011). Intravital microscopy approaches underlined the importance of α4-integrin and its collaboration with P-selectin for the adhesion of leukocytes to the brain endothelium (Kerfoot and Kubes, 2002). Additional *in vitro* and *in vivo* studies, using intravital microscopy, further supported the involvement of α4β1-integrin binding to VCAM-1 in the adhesion of T cells to the vasculature of the white matter (Laschinger and Engelhardt, 2000; Vajkoczy et al., 2001). Blocking of α4β1-integrin with natalizumab was shown to inhibit firm adhesion of human T cells to the inflamed BBB in mice with EAE, without affecting the rolling or initial contact of these cells (Coisne et al., 2009). Moreover, α4β1-integrin was shown to mediate initial recruitment of encephalitogenic T cells as well as the secondary infiltration of inflammatory cells, thereby being involved in initiating and sustaining CNS inflammation (Brocke et al., 1999). Experiments with cell-specific deletion of β1-integrin demonstrated that T cells, rather than myeloid cells, were dependent on α4β1-integrin for their migration to the inflamed CNS, supporting the notion that the therapeutic effect of antibodies against α4 is largely mediated by the inhibition of T cell extravasation (Bauer et al., 2009). However, α4β1-integrin is involved in the recruitment of additional immune cells in the inflamed CNS, including immature DCs (Jain et al., 2010) and Natural Killer (NK) cells (Gan et al., 2012). The different observations from rodent EAE establishing a major role for α4β1-integrin in disease pathogenesis resulted in the clinical use of α4β1-integrin inhibition as a therapeutic principle in MS, which will discussed in the following section.

Several studies investigated whether inhibition of β2-integrins or their ligands could be of potential benefit in EAE and MS. Using antibodies against CD11a and CD11b, Gordon *et al*. demonstrated that targeting these β2-integrins could block or delay the onset of EAE (Gordon et al., 1995). Dugger *et al*. performed transfer of $CD11a^{-/-}$ T cells to wild type mice and demonstrated that these cells, even though they infiltrate lymph nodes and CNS, caused less severe disease than wild-type controls. On the other hand, transfer of wild type encephalitogenic T cells to $CD11a^{-/-}$ mice worsened the outcome of EAE, thereby indicating that CD11a may have both effector and suppressor functions in EAE pathogenesis (Dugger et al., 2009). Specifically, these seemingly contradictory findings could be attributed to the fact that LFA-1 is involved in different functions besides T cell trafficking, including functioning as a co-stimulatory molecule (Van Seventer et al., 1991) or as a molecule that regulates the function of regulatory T cells (Treg) (Tran et al., 2009). For instance, LFA-1 deficiency resulted in an altered balance between effector T cells and Tregs in favor of the former, which led to increased severity of EAE in CD11a-deficient mice (Gültner et al., 2010). Based on the fact that both Th1 lymphocytes and Th17 lymphocytes contribute to EAE development (Jäger et al., 2009; Kebir et al., 2007; Kleinschek et al., 2007), the involvement of LFA-1 in the recruitment of these separate lymphocyte populations into the CNS was addressed. The infiltration of lymphocytes to the draining lymph node following immunization as well as the development of Th17 cells were significantly impaired in $LFA\text{-}1^{-/-}$ mice, thereby resulting in reduced disease severity (Wang et al., 2007). Rothhammer *et al*. further demonstrated that LFA-1 is also important

for Th17 trafficking to the inflamed CNS. In this study, it was reported that Th1 and Th17 cells engage different integrins for their migration to the CNS. Blockade of α4-integrin protected from EAE induced by adoptive transfer of Th1 but not of Th17 lymphocytes. The latter entered the CNS in an α4 integrin-independent manner. In contrast, the infiltration of Th17 cells into the brain parenchyma was mediated by LFA-1. Thus, Th17 cell migration to the CNS requires LFA-1, whereas Th1 cells preferentially use α4-integrin for this process (Rothhammer et al., 2011, Glatigny et al., 2011). With regards to the role of LFA-1 in the migration of T lymphocytes across the BBB, Laschinger *et al*. demonstrated that LFA-1 participates in the transendothelial migration but not in endothelial adhesion (Laschinger et al., 2002). The effect of inhibiting the LFA-1 ligand ICAM-1 in the course of EAE was also studied. Even though studies using inhibitory antibodies against ICAM-1 have shown contradictory results (Archelos et al., 1993; Morrissey et al., 1996; Willenborg et al., 1993), EAE development was significantly attenuated in ICAM-$1^{-/-}$ mice (Bullard et al, 2007b), as well as by targeting ICAM-1 with a staphylococcal-derived anti-adhesive protein (Xie et al., 2006). Besides CD11a, deficiency of CD11b (Bullard et al., 2005) or CD11c (Bullard et al., 2007a) has also been demonstrated to ameliorate development of EAE. Moreover, the CD11b-mediated interaction of leukocytes with platelets contributes to inflammatory cell recruitment to the CNS in the course of EAE pathogenesis. Inhibition of the leukocyte-platelet interaction by blocking the binding of Mac-1 to platelet GPIb resulted in significant amelioration of disease severity (Langer et al., 2012).

Psoriasis

Psoriasis is a chronic inflammatory disease of the skin, which is characterized by erythematous scales; recent evidence has suggested an important role of IL-17 derived from different cells as a pathogenic component in psoriasis (Krueger et al., 2012; Leonardi et al., 2012; Martin et al., 2013; Pantelyushin et al., 2012). Th1, Th17 cells, γδ T cells, innate lymphocytes and DCs are abundant inflammatory cell populations in psoriatic lesions (Chamian and Krueger, 2004; Chamian et al., 2005; Lowes et al., 2008; Pantelyushin et al., 2012). Treatment of patients with efalizumab, a monoclonal antibody that targets CD11a resulted in significant reduction of TNF and iNOS-expression and of DC numbers in lesions (Lowes et al., 2005). In a psoriatic model engaging human skin-SCID (severe combined immunodeficiency) mouse chimeras, treatment with efalizumab limited skin inflammation in the transplant (Zeigler et al., 2001; Stenderup et al., 2011). Besides LFA-1 blockade, Schön *et al*. demonstrated that Mac-1 blockade ameliorates skin manifestations in the flaky skin mice (fsn−/− mice) that develop psoriasiform skin lesions. Histological analysis revealed that treatment with an antibody against CD11b resulted in decreased neutrophil and T cell infiltration. This finding implies Mac-1 on neutrophils in the inflammatory process that characterizes at least this model of psoriasis (Schön et al., 2000). The effect of Mac-1 blockade was also confirmed in another murine model of experimental psoriasiform dermatitis (Leon et al., 2006). One of the Mac-1 counter-receptors on the endothelium is RAGE (Chavakis et al., 2003a; Orlova et al., 2007; Frommhold et al., 2010). Interestingly, RAGE serves also as the receptor for S100A7, also designated psoriasin, which is overespressed in psoriatic lesions and exerts a strong chemotactic activity for neutrophils (Wolf et al., 2008; Wolf et al., 2010). Whether blockade of the interaction of RAGE with its

counter-receptor Mac-1, or its S100 ligands could be therapeutically relevant in psoriasis is worth assessing.

In addition to β2-integrins LFA-1 and Mac-1, blocking of α1β1-integrin (VLA-1), which serves as a collagen receptor, inhibited the infiltration of epidermal T cells in a xenotransplantation psoriasis model. This study, moreover, established that the presence of α1β1-integrin in epidermal effector T cells was associated with the expression of high levels of interferon-γ. Thus, α1β1-integrin may represent a potential therapeutic target in psoriasis (Conrad et al., 2007).

Interestingly the β2-integrin was demonstrated to play a regulatory role in the development of psoriasis as well. Mice bearing a hypomorphic CD18 mutation ($CD18^{hypo}$PL/J mice), resulting in decreased CD18 expression, develop psoriasiform dermatitis (Peters et al., 2006), featured by increased accumulation of CD4+ and γδ T cells (Gatzka et al., 2013) and decreased presence of regulatory T cells (Singh et al., 2013) at the skin lesions. β2-integrin deficiency has been previously associated with dysregulation of IL-17 production, due to defective neutrophil recruitment to peripheral tissues and subsequently reduced clearance of apoptotic neutrophils by macrophages (Stark et al., 2005; Moutsopoulos et al., 2014), as discussed in the following section. The resulting reduction of IL-23 production by macrophages leads to γδ T cell activation, which then produce IL-17 (Stark et al., 2005). This mechanism could be a possible explanation for the aforementioned findings in mice with decreased CD18 expression.

Inflammatory bone loss

Inflammatory cell recruitment is a common denominator of several disorders involving bone loss, with rheumatoid arthritis (RA) being the most prominent one. Synovial inflammation in RA results from infiltrating neutrophils, T cells, B cells, plasma cells, DCs and macrophages. Inflammatory cells together with osteoclasts present in the synovial membrane act synergistically in the destruction of the adjacent bone (Choy, 2012). Presentation of arthritis-specific antigens by DCs, macrophages and B cells to CD4+ T cells is considered an important trigger in disease development (Choy, 2012).

The role of leukocyte integrins in RA has been addressed in several animal models. In the rat model of adjuvant arthritis, T cell infiltration was shown to be independent of the β2-integrins LFA-1 and Mac-1, whereas a partial inhibition of neutrophil recruitment was observed when LFA-1 was inhibited. However, upon concomitant blockade of both LFA-1 and Mac-1, neutrophil recruitment was abolished (Issekutz and Issekutz, 1993). In the same model, T cell recruitment was shown to depend on α4β1-integrin (Issekutz and Issekutz, 1991); this integrin mediated infiltration of adoptively transferred arthritogenic T cells to the synovium (Issekutz et al., 2003). Furthermore, combined blockade of LFA-1 and VLA-4-integrins was required for the complete inhibition of monocyte infiltration (Issekutz and Issekutz, 1995).

The involvement of β2-integrins in the development of murine arthritis was studied in the model of K/B xN serum transfer arthritis. Watts *et al*. demonstrated that mice deficient in the common β2 subunit were protected from arthritis development. Additionally, CD11a

deficient mice did not develop arthritis, whereas no effect was observed in CD11b deficient mice, suggesting that LFA-1 but not Mac-1 contributes to disease induction. LFA-1 was required not only for arthritis development but also for maintenance of synovial inflammation, as shown by disease amelioration after administration of anti-LFA-1 antibody in mice with already established arthritis, thereby suggesting a therapeutic potential for LFA-1 targeting in RA (Watts et al., 2005).

LFA-1 is also involved in bone loss in the context of inflammatory arthritis. Barck *et al*. studied the effect of LFA-1 blockade in the formation of bone erosions in the murine model of collagen induced arthritis. Using 3-dimensional micro-CT of mouse paws to evaluate joint cortical bone volume, they demonstrated that treatment with anti-LFA-1 antibody ameliorated both the clinical course and the radiographic findings (Barck et al., 2004).

Furthermore, α2β1 integrin, a receptor for collagen type I, was shown to promote arthritis in the antigen-induced arthritis (AIA) and the human TNF-transgenic mouse model. Mice deficient in α2β1 showed reduced cartilage erosions and joint pathology, as compared to wild-type mice (Peters et al., 2012).

A link between inflammatory bone loss and LFA-1 has been recently demonstrated in periodontitis. LFA-1 deficiency was associated with severe periodontal bone loss and lack of neutrophil recruitment in the periodontal tissue in both mice and men with type I leukocyte adhesion deficiency (LAD-I). This was attributed to dysregulated overproduction of IL-17 as a result of a defective “neutrostat”-feedback mechanism in mice and individuals with defective leukocyte recruitment (Moutsopoulos et al., 2014). Specifically, when neutrophils cannot transmigrate to peripheral tissues (as occurs in LAD-I), the inhibitory signals for IL-23 expression by phagocytes (normally associated with apoptotic cell efferocytosis) are abrogated leading to T cell overexpression of IL-17. IL-17 in turn promotes granulopoiesis through G-CSF, consistent with blood neutrophilia in LAD-I patients and relevant mouse models (Stark et al., 2005). Interestingly, topical inhibition of IL-17 blocked inflammatory bone loss in mouse models mimicking LAD-I-associated periodontitis (Moutsopoulos et al., 2014).

Inflammatory bowel disease

Inflammatory bowel diseases (IBD), namely Crohn’s disease (CD) and ulcerative colitis (UC), are chronic disorders of the gastrointestinal tract. Advances in the understanding of the pathogenesis of intestinal inflammation enabled the development of specific therapies, with monoclonal antibodies e.g. targeting TNF (Kontoyiannis et al., 2002; Dassopoulos et al., 2013).

Studies with animal models of IBD revealed the critical involvement of leukocyte integrins in intestinal inflammation, which enabled the development of targeted therapies for the treatment of CD and UC, as discussed below. Early studies demonstrated the central role of β7-integrins for the formation of gut-associated lymphoid tissue (GALT), which includes Peyer’s patches, lamina propria lymphocytes and intra-epithelial lymphocytes of the intestine (Koboziev et al., 2010; Gorfu et al., 2009). Mice deficient in the β7-integrin subunit have hypoplastic GALT, which was further attributed to defective T cell recruitment

(Wagner et al., 1996). Furthermore, antibodies targeting α4 integrin, an epitope present on the α4β7-integrin or the β7 subunit significantly attenuated T cell homing to Peyer's patches, without affecting homing to peripheral lymph nodes. In the same study, it was also shown that the mucosal addressin MAdCAM-1 mediates T cell infiltration in mucosal lymphoid tissue (Hamann et al., 1994). Using $\beta7^{-/-}$ mice, Kunkel et al. confirmed the involvement of β7-integrin in adhesion of leukocytes to Peyer's patch endothelial venules (Kunkel et al., 1998). Treatment with anti-β7 and anti-MAdCAM-1 antibodies was shown to ameliorate experimental murine chronic colitis, by affecting T cell recruitment to the colonic mucosa and mesenteric lymph nodes (Picarella et al., 1997). The involvement of β7-integrins in the development of mouse colitis was also shown in the SAMP1/YitFc model of inflammatory Crohn's disease-like ileitis. In this model, β7-integrin blockade was efficient to significantly suppress inflammation, only when combined with L-selectin inhibition (Rivera-Nieves et al., 2005). In the same model, β7-integrin deficiency ameliorated colitis by inhibiting B cell homing to mesenteric lymph nodes on top of blocking T cell infiltration (Gorfu et al., 2010). Inhibition of αEβ7-integrin reduced mucosal inflammation in $IL\text{-}2^{-/-}$ mice immunized with TNP-OVA, even when mice were treated after the establishment of colitis (Ludviksson et al., 1999). However, β7-deficiency in mice did not significantly ameliorate colitis course (Sydora et al., 2002). On the other hand, Apostolaki *et al*. have shown the dependency of T cell recruitment to intestinal mucosa on β7-integrins in a TNF-dependent model of Crohn's disease; moreover, β7-deficiency completely abrogated colitis development (Apostolaki et al., 2008). Furthermore, a recent study by Villablanca *et al*. demonstrated that mice deficient in β7-integrin in the innate immune compartment show increased susceptibility to T cell mediated colitis. The authors proposed that the reduced migration of β7-deficient tolerogenic mononuclear phagocytes into gut mucosa contributes to this phenotype (Villablanca et al., 2014).

Several studies suggested a role of β2-integrins in experimental colitis. In the rat model of 2,4,6-trinitrobenzene sulfonic acid-induced colitis, administration of antibodies against Mac-1 resulted in significant inhibition of inflammatory cell recruitment, which was associated with a decreased mucosal damage (Palmen et al., 1995). By transferring $CD11a^{-/-}$ $CD4^{+}CD25^{-}$ T cells to $RAG^{-/-}$ recipients, Pavlick *et al*. demonstrated that expression of LFA-1 on T cells is required for disease induction and for the infiltration of CD4+ T cells to mesenteric lymph nodes and to intestinal lamina propria (Pavlick et al., 2006). Using the same approach CD18 on T cells was identified to promote colitis induction (Ostanin et al., 2007).

The identified role of leukocyte integrins in models of IBD paved the way for the development of targeted therapeutic agents, as discussed in the following section.

Leukocyte integrin blockade in clinical use

As a result of the large body of evidence regarding the central role of leukocyte integrins in animal models of inflammatory diseases, different leukocyte integrin targeting strategies have reached clinical use (Yonekawa and Harlan, 2005) (Table 1).

Beta2-integrins

Efalizumab (Raptiva, anti-CD11a, Genentech) is a humanized monoclonal IgG1 antibody that is directed against the alpha chain (CD11a) of the β2-integrin LFA-1, that blocks the interaction between leukocyte LFA-1 and ICAM-1 (Dedrick et al., 2002). Phase III clinical trials demonstrated that efalizumab administration results in the amelioration of dermatologic features of psoriasis (Gordon et al., 2003; Lebwohl et al., 2003, Leonardi et al., 2005), which can be attributed to reduction of inflammatory cell recruitment and reversal of keratinocyte hyperplasia at psoriatic lesions (Reich et al., 2012; Gottlieb et al., 2002). Despite having beneficial effect on the skin manifestations, it was not effective in the treatment of psoriatic arthritis (Papp et al., 2007), while several reports suggest that treatment with efalizumab might even result in new-onset severe arthritis (Viguier et al., 2008; Myers et al., 2006). Despite its effectiveness, it was withdrawn in 2009 due to the high risk of John Cunningham (JC) polyomavirus reactivation and development of progressive multifocal leukoencephalopathy (PML) in patients under long-term efalizumab administration (Weger, 2010).

Alpha4-integrins

Natalizumab (Antegren, Tysabri; Elan Pharma Ltd., Letchworth, UK and Biogen-Idec, Durham, NC, USA) is a recombinant humanised monoclonal IgG4 antibody against the α4-integrin subunit, blocking both α4β1- and α4β7-integrins. It prevents the migration of leukocytes across the blood–brain barrier into the CNS by blocking the interaction between α4β1-integrin and VCAM-1 (Rudick and Sandrock, 2004; Ransohoff, 2007; Rudick et al., 2013); moreover, it inhibits the interaction of α4β7-integrin with endothelial MAdCAM-1 and thereby homing of lymphocytes to gastrointestinal lymphoid tissue (Hamann et al., 1994). Studies in patients with MS have shown that natalizumab administration significantly reduced the numbers of total leukocytes, CD4+ T cells, CD8+ T cells, B cells and plasma cells in the cerebrospinal fluid (Stüve et al., 2006). A significant reduction in the number of CD209+ antigen presenting DCs in cerebral perivascular spaces and decreased expression of major histocompatibility complex class II was also observed in brain autopsies from a patient with PML that had received natalizumab (del Pilar Martin et al., 2008). These effects are localized to the CNS, as natalizumab did not reduce the numbers of CD4+ and CD8+ T cells in the periphery (Kivisäkk et al., 2009).

After successfully completing phase III clinical trials (Polman et al., 2006, Rudick et al., 2006), natalizumab was approved as the first targeted therapy for the treatment of relapsing-remitting multiple sclerosis. Natalizumab is associated with increased risk for reactivation of latent JC virus infection and development of PML (Bloomgren et al., 2012); however, a recently published study confirmed the beneficial role of natalizumab in stabilizing disease activity and diminishing the risk of relapses in patients with relapsingremitting multiple sclerosis (O'Connor et al., 2014). Phase II and III studies have also shown that natalizumab is effective as an induction and maintenance therapy in patients with Crohn's disease (Ghosh et al., 2003; Sandborn et al., 2005; Targan et al., 2007). However, due to the risk for PML development it is approved in the United States under a restricted distribution program (Chen et al., 2013).

Furthermore, antibodies targeting the interaction between α4β7-integrin and MAdCAM have been developed. Vedolizumab and etrolizumab target α4β7-integrin, whereas PF-00547659 targets MAdCAM (Bamias et al, 2013). The selective blockade of α4β7-integrin leaving α4β1 unaffected should minimize the risks associated with the inhibition of leukocyte recruitment to the CNS. Vedolizumab (Millennium Pharmaceuticals) is a humanized IgG1 monoclonal antibody that is effective as an induction and maintenance therapy for moderate to severe UC and Crohn's disease, as well as in patients with moderate to severe Crohn's disease that did not previously respond to other treatments (Feagan et al., 2013; Sandborn et al., 2013; Sands et al., 2014). Vedolizumab was recently approved by the FDA for the treatment of Crohn's disease.

Etrolizumab is a humanised monoclonal antibody that selectively binds the β7-subunit of both the α4β7 and αEβ7-integrin heterodimers, antagonizing both α4β7-MAdCAM-1-mediated lymphocyte recruitment and the αEβ7-E-cadherin interaction (Lin and Mahadevan, 2014), which mediates adhesion of αEβ7 T cells to epithelial cells (Cepek et al, 1993; Hadley and Higgins, 2014). In a recently published phase II clinical trial, etrolizumab was shown to have a beneficial effect as an induction therapy in the treatment of patients with moderate to severe IBD (Vermeire et al., 2014).

Despite the high efficacy of integrin-targeted therapies in inflammatory diseases, the relatively frequent occurrence of severe adverse events precludes the administration of such agents to a wider spectrum of patients with inflammatory diseases.

Endogenous inhibitors of leukocyte recruitment

Besides the aforementioned antibodies and inhibitors that have been developed to therapeutically target integrins and block leukocyte recruitment, the recent discovery of endogenous negative regulators of the leukocyte adhesion cascade may pave the way for the development of novel, more efficient strategies to therapeutically target leukocyte adhesion in inflammatory and autoimmune pathologies (Chavakis, 2012; Hajishengallis and Chavakis, 2013). We will therefore summarize here recent knowledge on endogenous inhibitors of leukocyte recruitment with a special focus on the integrin inhibitor Developmental endothelial locus-1 (Del-1).

Del-1: an endogenous anti-inflammatory factor blocking leukocyte β2-integrins

Del-1, also designated epidermal growth factor (EGF)-like repeats and discoidin-I-like domains 3 (EDIL3) is a glycoprotein with three EGF-like repeats and two C-terminal discoidin I-like domains; the latter can interact with phosphatidylserine and phospholipids (Dasgupta et al., 2012; Chavakis et al., 2009). It is expressed and secreted by endothelial cells and can associate with the extracellular matrix as well as the endothelial cell surface (Chavakis et al., 2009). Association with the endothelial cell surface is mediated by binding to surface proteoglycans or to integrin αvβ3 by means of an Arg–Gly–Asp motif on the second EGF-like repeat (Chavakis et al., 2009; Hidai et al., 2007). Although expressed by endothelial cells, it is not present in all tissues and organs. Its expression is highest in the brain, followed by the lung, the adrenal or the gingiva, whereas it is hardly expressed in the liver, thereby pointing to the diversity and heterogeneity of the endothelium of different

tissues / organs (Choi et al., 2008b; Kanczkowski et al., 2013). We identified Del-1 to act as a negative regulator of the leukocyte integrin LFA-1. Del-1 binds to LFA-1 integrin and antagonizes binding of the latter to ICAM-1, thereby blocking LFA-1-dependent leukocyte adhesion onto the vascular endothelium (Choi et al., 2008b). Besides LFA-1, Del-1 was recently shown to interact with Mac-1 as well, thereby blocking the binding of Mac-1 with complement component iC3b. This results in a Del-1-mediated inhibition of complement/Mac-1-dependent phagocytosis, an action that could also contribute to the anti-inflammatory functions of Del-1 (Mitroulis et al., 2014). The role of Del-1 as a negative regulator of leukocyte recruitment stands in keeping with its highest expression levels in immune privileged organs, such as the brain or the eye. Del-1-deficient mice displayed elevated LFA-1-dependent neutrophil recruitment in LPS-induced acute lung injury and in the dorsal skinfold chamber model. Injection of soluble Del-1 could ameliorate inflammatory cell recruitment to the lung or the peritoneum in acute models of inflammation (Choi et al., 2008b). Additionally, Del-1-deficiency was recently shown to enhance bleomycin-induced lung fibrosis (Kang et al., 2014) and systemic inflammation-related adrenal dysfunction (Kanczkowski et al., 2013). Thus, Del-1 might represent an interesting novel approach for the treatment of inflammatory lung diseases.

Interestingly, Del-1 expression in endothelial cells is down-regulated by inflammatory factors, such as LPS, TNF or IL-17A but not IL-17F (Choi et al., 2008b; Eskan et al., 2012; Shin et al., 2013), which suggests that inflammatory stimuli do not only elevate expression of integrin ligands ICAM-1 and VCAM-1 on the endothelium, but at the same time reduce the levels of the integrin inhibitor Del-1; both actions function synergistically to promote leukocyte adhesion. The IL-17-mediated down-regulation of endothelial Del-1 expression promoted neutrophil recruitment and inflammatory bone loss in the context of periodontitis, which is a chronic neutrophil-dependent disease (Eskan et al., 2012). Del-1 expression is diminished in the gingival tissue of old mice, correlating with hallmarks of periodontitis, such as excessive neutrophil recruitment and IL-17-dependent inflammatory bone loss (Eskan et al., 2012). Consistent with this, Del-1-deficient mice develop spontaneous periodontitis at a young age, accompanied by heavy neutrophil infiltration in the gingiva in a manner dependent on LFA-1. The periodontitis due to Del-1 deficiency was reversed in mice with Del-1/LFA-1- or Del-1/IL-17-receptor-double deficiency. Interestingly, local periodontal treatment with soluble Del-1 in old mice inhibited IL-17 production, LFA-1-dependent neutrophil infiltration, and associated bone loss (Eskan et al., 2012). Analysis of biopsies from patients with periodontitis revealed decreased levels of Del-1 and enhanced levels of IL-17 in the diseased tissue, as compared to the adjacent healthy tissue, thereby suggesting that the inflammatory IL-17/Del-1-loop is operative in human periodontitis as well (Eskan et al., 2012). These findings suggest that Del-1 and IL-17 are reciprocally cross-regulated and that Del-1 confers a self-regulated homeostatic control mechanism of neutrophil recruitment, being constantly ‘on’ to prevent chronic inflammation, but being turned ‘off’ when neutrophil recruitment is needed. Additionally, local application of Del-1 seems a promising therapeutic strategy to prevent chronic inflammatory bone loss in the context of periodontitis (Eskan et al., 2012).

More recently, Del-1 was also shown to prevent IL-17-dependent neuroinflammation in the course of EAE. Specifically, Del-1 expression was reduced in both chronic active MS

lesions and in the inflamed spinal cord of mice subjected to EAE. Del-1-deficiency resulted in enhanced EAE disease severity, accompanied by elevated IL-17-dependent neuro-inflammation. Interestingly, administration of soluble Del-1 ameliorated progression of relapsing-remitting EAE (Choi et al., 2014 in press). Together, application of Del-1 may represent a promising therapeutic approach in IL-17-dependent inflammatory disorders.

Further endogenous inhibitors of inflammatory cell recruitment

Further endogenous inhibitors of leukocyte recruitment have been identified. Pentraxin-3 (PTX-3) is a member of the long pentraxin family of soluble pattern-recognition molecules. PTX-3 expression in myeloid cells is upregulated in response to TLR signalling and inflammatory cytokines. In neutrophils, PTX-3 is released from intracellular granules upon inflammation (Maina et al., 2009). PTX-3 reduces neutrophil rolling by binding to P-selectin, thereby inhibiting the interaction of P-selectin with its leukocyte counter-receptor, PSGL-1 (Hajishengallis and Chavakis, 2013; Inforzato et al., 2012; Deban et al., 2010). In accordance with the inhibitory effect of PTX-3 on leukocyte rolling, PTX-3-deficient mice display increased leukocyte recruitment in a model of acute lung injury (Deban et al., 2010; Hajishengallis and Chavakis, 2013).

Growth Differentiation Factor (GDF)-15 is a member of the transforming growth factor (TGF)-β superfamily. Its tissue expression is increased upon sterile inflammation during ischemic injury and it acts as an inhibitor of leukocyte extravasation limiting myocardial tissue damage (Kempf et al., 2006). Moreover it was shown that coronary artery ligation in Gdf15-deficient mice led to enhanced recruitment of neutrophils into the infarcted myocardium and an increased incidence of cardiac rupture, while, infusion of recombinant GDF-15 repressed neutrophil recruitment. The regulatory role of GDF-15 on leukocyte recruitment is mediated by activation of Cdc42 GTPase and inhibition of Rap1 GTPase, thus blocking chemokine-induced activation of β2-integrins (Kempf et al., 2011). It remains to be addressed in more detail, whether factors, such as PTX-3 or GDF-15 could be therapeutically engaged in preclinical and clinical inflammatory settings.

Additional endogenous molecules have been described that influence leukocyte recruitment. Galectin-1 has been demonstrated to down-regulate neutrophil expression of PSGL-1, CD11b and L-selectin induced by platelet-activated factor *in vitro* and neutrophil adhesion to endothelial cells under flow. In turn, increased leukocyte adhesion was observed in the cremaster model in galectin-1 deficient mice, using intravital microscopy (Cooper et al., 2008, Herter and Zarbock, 2013).

Annexin 1, a Ca^{2+} and phospholipid binding protein, is another potent endogenous regulator of inflammation (Gerke et al., 2005). Annexin 1 is abundant in neutrophils and it is released upon neutrophil activation (Perretti and Flower, 2004). Several peptides deriving from its N-terminal domain potently inhibit neutrophil recruitment (Perretti et al., 2002). Upon exposure to the cell surface, annexin 1 interacts with the formyl peptide receptor (FPR), the high affinity receptor of fMLP, as well as the lipoxin A4 receptor (ALX or FPR-like receptor) (El Kebir et al., 2008; Perretti and Flower, 2004; Perretti et al., 2002; Perretti, 2003). Glucocorticoids promote annexin 1 synthesis, and annexin 1 is thereby thought to mediate many of the anti-inflammatory effects of these steroids (Perretti and Flower, 2004).

Its important role in the regulation of neutrophil recruitment was demonstrated in mice deficient for annexin 1, which display augmented and prolonged inflammatory reaction and partial resistance to the anti-inflammatory effect of dexamethasone, during acute or chronic inflammation (Hannon et al., 2003; Perretti and Flower, 2004). Combined treatment with aspirin-triggered lipoxins and annexin-1-derived peptides significantly limits neutrophil infiltration (Perretti et al., 2002).

Conclusion

Leukocyte integrins constitute major players in inflammatory cell recruitment into sites of infection and/or tissue injury. Preclinical studies in animal models of inflammation have indicated that integrin blockade or deficiency may significantly modulate disease initiation and/or progression. These findings led to the development of antibodies against leukocyte integrins, which are used in clinical practise for the treatment of patients with severe inflammatory disorders. However, patients treated with such agents may experience immunosuppression, and rarely, may suffer from severe infections, including PML. The identification of endogenous inhibitors, which homeostatically regulate leukocyte recruitment to inflammatory sites, may have fewer side effects and thus may prove beneficial as a therapeutic alternative in the treatment of inflammatory syndromes.

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Abbreviations

(BBB)	Blood-brain barrier
(CCL)	CC-chemokine ligand
(CAMs)	cell adhesion molecules
(CNS)	central nervous system
(CD)	Crohn's disease
(CXCL)	CXC-chemokine ligand
(DCs)	dendritic cells
(Del-1)	Developmental endothelial locus-1
(EGF)	epidermal growth factor
(EAE)	experimental autoimmune encephalomyelitis
(GDF)	Growth Differentiation Factor
(GALT)	gut-associated lymphoid tissue
(IBD)	inflammatory bowel diseases

(LAD-I)	I leukocyte adhesion deficiency
(ICAM-1)	intercellular cell-adhesion molecule 1
(JAM)	Junctional Adhesion Molecule
(LFA-1)	lymphocyte function-associated antigen 1
(Mac-1)	macrophage-1 antigen
(MAdCAM1)	mucosal vascular addressin cell-adhesion molecule 1
(MS)	multiple sclerosis
(PTX-3)	pentraxin-3
(PECAM-1)	platelet/endothelial-cell adhesion molecule 1
(PML)	progressive multifocal leukoencephalopathy
(PSGL-1)	P-selectin glycoprotein ligand-1
(RAGE)	receptor advanced glycation end products
(Treg)	regulatory T cells
(RA)	rheumatoid arthritis
(TLRs)	Toll-like receptors
(UC)	ulcerative colitis
(VCAM)	vascular cell-adhesion molecule
(VLA)	very late antigen

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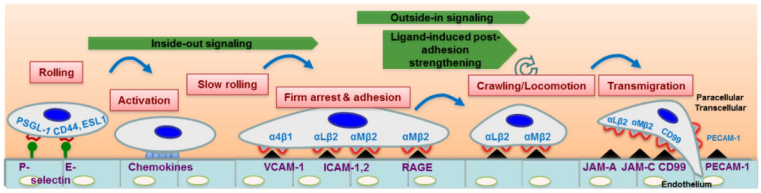

Figure 1. The multistep model of leukocyte recruitment

The sequential steps of the leukocyte adhesion cascade and the adhesive interactions between endothelium and leukocytes are shown. The cascade is initiated with leukocyte capturing and rolling on the endothelium, followed by chemokine-induced leukocyte activation, slow rolling, firm leukocyte adhesion/arrest, adhesion strengthening induced by integrin ligation, crawling and leukocyte transmigration. Essential molecular players involved in the adhesive processes include: selectins and their glycoprotein ligands, chemokines and their receptors, integrins and adhesion receptors of the immunoglobulin-superfamily. α4- and β2-integrins play a critical role in the course of the cascade. Integrin activation occurs upon chemokine triggered signaling (inside-out signaling) in cooperation with selectin-activated pathways. Activated integrins contribute to slow rolling, firm adhesion, crawling and to transendothelial migration.

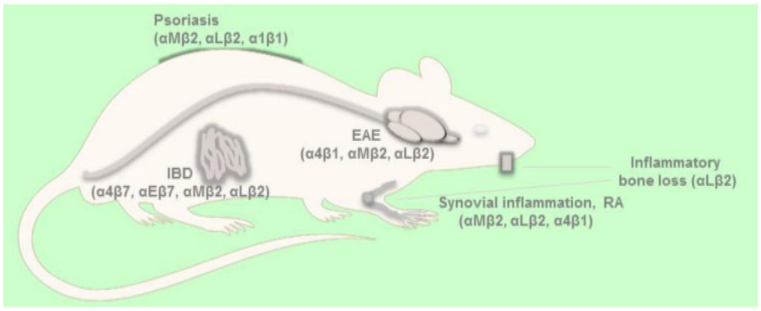

Figure 2. Leukocyte integrin targeting in animal inflammatory models

The role of the β2 integrins αMβ2 and αLβ2 has been studied in several animal models of inflammatory disorders. In autoimmune encephalomyelitis (EAE), a rodent model resembling multiple sclerosis, either treatment with an antibody against CD11b or CD11a or deficiency in one of these integrins leads to reduced EAE disease severity. Administration of anti-CD11b or anti-LFA-1 antibodies limits skin manifestations and inflammation in psoriatic models. In addition, deficiency in the β2 subunit CD18 protects animals from arthritis development and combined inhibition of CD11b and CD11a leads to significantly decreased neutrophil recruitment. CD11a blockade has also been linked to decreased bone loss in inflammatory arthritis models, whereas mice lacking CD11a demonstrate bone loss in a periodontitis model. Regarding the inflammatory bowel diseases (IBD), CD11b inhibition leads to reduced inflammatory cell infiltration and less mucosal damage in a model of colitis.

In addition, β1 integins serve as targets for interevention in inflammatory disease models. Blockade of α4β1 prevents disease development in an EAE model. Furthermore, T cell recruitment to the synovium is dependent on α4β1-integrin as shown in a model of arthritis. Besides α4β1, the inhibition of α1β1-integrin has been shown to be beneficial by inhibiting disease development in a psoriatic model. In addition, α4β7 blockade attenuates T cell homing to Peyer's patches, a main component of gut-associated lymphoid tissue (GALT). Moreover, treatment with antibodies against either αEβ7 or β7 reduces inflammation in a model of colitis.

Table 1

Therapeutic targeting of leukocyte integrins in clinical use.

Disease	Integrin	Drug	Target	Treatment
Multiple Sclerosis	α4β1	Natalizumab	humanized monoclonal IgG4 antibody against the α4 integrin subunit	Approved for the treatment of relapsing-remitting multiple sclerosis
Psoriasis	αLβ2	Efalizumab	humanized monoclonal IgG1 antibody against the alpha chain (CD11a) of αLβ2 integrin	Effective in the treatment of psoriasis (withdrawn in 2009)
Inflammatory Bowel Disease	α4β7, αEβ7	Natalizumab	humanized monoclonal IgG4 antibody against the α4 integrin subunit	Approved for the treatment of medium to severe Crohn's disease under restrictive distribution program (USA)
		Vedolizu-mab	humanized IgG1 monoclonal antibody against α4β7-integrin	Approved for the treatment of moderate to severe Crohn's disease and ulcerative colitis
		Etrolizumab	humanized IgG1 monoclonal antibody against the β7 subunit of α4β7- and αEβ7-integrins	Effective in the treatment of moderate to severe ulcerative colitis (clinical trials)