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Endogenous Modulators of Inflammatory Cell Recruitment

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Abstract

Leukocyte recruitment is a central immune process. Multiple factors have been described to promote leukocyte infiltration into inflamed tissues, but only recently has evidence for endogenous negative modulators of this inflammatory process emerged. The discovery of several locally produced modulators has emerged into a new field of endogenous inhibitors of leukocyte extravasation. Recent findings from several inflammatory disease models show that tissues can self-regulate the recruitment of inflammatory cells, suggesting that local tissues may have a greater “regulatory say” over the immune response than previously appreciated. Here, we propose that locally produced modulators of leukocyte recruitment may represent local homeostatic mechanisms that tissues and organs may have evolved for protection against the destructive potential of the immune system.

Leukocyte recruitment

All inflammatory processes involve or depend upon leukocyte recruitment to the inflamed tissue. Inflammatory or infectious stimuli trigger the extravasation of initially circulating neutrophils—and in some cases of monocytes— that are crawling on the endothelial cell surface and patrolling the vasculature, from the vessel into the parenchymal tissue [1–7]. This initial inflammatory wave is followed by the recruitment of monocytes and inflammatory lymphocytes [1–6]. Leukocyte recruitment is orchestrated by different tissue-derived stimuli, such as chemokines or cytokines, and is perpetuated by further leukocyte-derived inflammatory stimuli [1–6,8].

A tightly regulated cascade of low- and high-affinity binding and adhesive interactions between the inflammatory cells and the endothelium that lines the vascular bed of the inflamed tissue coordinates leukocyte extravasation [4,6]. Specifically, leukocyte adhesion to the endothelium involves the following steps: 1) The initial contact between leukocytes and the endothelium is mediated by the tethering and rolling of leukocytes on the endothelial cell surface. Rolling interactions only take place under flow conditions, are transient and are dependent on the binding of P- or E-selectin on the endothelial cell surface to their leukocyte glycoprotein ligands, such as P-selectin glycoprotein ligand-1 (PSGL-1) [4,9]; 2) Subsequently, the velocity of the rolling leukocytes is reduced, resulting in slow rolling,

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which is considered an independent step, as it is mediated by both selectin- and integrin-dependent adhesive interactions [4]; 3) Leukocytes then firm arrest on the endothelium. This step of firm adhesion to the endothelium and the subsequent step of slow locomotion (or crawling) on the endothelial cell surface, during which leukocytes seek an appropriate site for transmigration, are mediated by leukocyte integrins, such as VLA-4 ($\alpha 4\beta 1$), LFA-1 ($\alpha L\beta 2$; CD11a/CD18) or Mac-1 (CD11b/CD18) that interact with endothelial ligands, including VCAM-1, ICAM-1, ICAM-2, or RAGE [4,5,10–12]. The integrin-dependent adhesive interactions involve a complex activation of the avidity of integrins that can thereby bind stronger to their endothelial ligands; activation of integrins can take place either at the level of the affinity of the single integrin receptor for its ligand involving conformational changes, or via clustering of the integrins, usually induced by ligand binding [1,4,13,14]; and 4) Finally, the step of diapedesis or transmigration of leukocytes through the endothelial monolayer mostly occurs via passing through endothelial junctions and involves the participation of several adhesion receptors, such as integrins, Junctional Adhesion Molecules (JAM), PECAM-1 or CD99, capable of interacting in a heterophilic or homophilic manner [1,4,5,10,15]. These different steps of leukocyte extravasation can be modulated by cytokines or chemokines: Whereas tissue-derived cytokines can upregulate endothelial adhesion molecule expression, tissue-derived chemokines present on the apical endothelial cell surface can trigger conformational changes on leukocyte integrins leading to their activation [4,5,8].

Multiple chemokine and adhesion receptors (>20) have been identified to promote leukocyte recruitment, by acting on the various steps of the leukocyte adhesion cascade. More recently, several endogenous negative regulators of leukocyte extravasation have been identified. Here we consider the idea that as tissue-derived chemokines and cytokines trigger leukocyte extravasation and inflammation, these tissues may also possess mechanisms to homeostatically control this inflammatory process. These mechanisms may involve local tissue production of appropriate inhibitors or local release of such inhibitors by the recruited leukocytes upon their interaction with the endothelium.

Endogenous inhibitors of leukocyte recruitment

Pentraxin-3 (PTX-3)

Recently, PTX-3 was identified as inhibitor of the first step of the leukocyte adhesion cascade, *i.e.*, leukocyte-endothelial rolling [16]. Pentraxins constitute a conserved family of soluble pattern-recognition molecules characterized by a radial pentameric structure [17]. Whereas serum amyloid P or C reactive protein belong to the short pentraxins, PTX-3 is a prototypic member of the long pentraxin subfamily [17]. The expression of PTX-3 can be induced by Toll-like receptor ligation in immune or stromal cells [17]. In neutrophils, PTX3 is constitutively stored in the specific granules and can be released locally at the leukocyte-endothelial cell interface by several stimuli including Toll-like receptor agonists [18]. PTX3 participates in various aspects of the innate immune response, such as pathogen recognition, opsonization, and regulation of complement function [19,20].

The anti-inflammatory activity of PTX-3 was inferred by early studies of PTX-3-deficient mice that displayed elevated cardiac tissue damage associated with higher inflammation in the course of ischemia-reperfusion injury of the heart [21]. More recently, it was demonstrated that PTX-3 binds to P-selectin present on endothelial cells, thereby interfering with the interaction of P-selectin with its leukocyte ligand, PSGL-1 (Figure 1) [16]. PTX-3 thereby potently inhibits neutrophil rolling on the endothelium under shear stress. Glycosylation of PTX-3 was required for mediating binding to P-selectin, which is in keeping with the preference of selectins for carbohydrate ligands, such as PSGL-1 [16,22]. The regulatory function of PTX-3 in leukocyte extravasation was demonstrated in mouse

models of inflammation, where PTX-3-deficient mice displayed elevated neutrophil recruitment as compared to PTX-3-sufficient controls. In particular, in a model of pleural inflammation and acid-induced acute lung injury, neutrophil infiltration was higher in mice deficient in PTX-3 as compared to PTX-3-sufficient mice [16]. In bone marrow chimera experiments, hematopoietic-specific deficiency of PTX-3 led to increased inflammation showing that PTX-3 is leukocyte-derived [16].

In addition to its role in leukocyte rolling, PSGL-1 binding to P-selectin mediates leukocyte-platelet interactions [3,23], which additionally involve the binding of leukocyte Mac-1 to JAM-C or glycoprotein Ib on platelets [24,25]. The leukocyte-platelet interaction is involved in several inflammatory processes, including autoimmunity or acid-induced acute lung injury [26,27]. Interestingly, blocking P-selectin-dependent neutrophil-platelet aggregation reverses lung injury [27]. Therefore, PTX-3 may antagonize inflammatory reactions mediated by leukocyte-platelet aggregates. Taken together, PTX-3 is a specific inhibitor of the PSGL-1/P-selectin interaction and can thereby interfere with leukocyte rolling or other PSGL-1-dependent functions of leukocytes.

Galectins

Galectins comprise a family of β -galactoside-binding lectins with at least one carbohydrate-recognizing domain. They interact with host carbohydrate ligands in embryogenesis and development but can also function as immunomodulatory pattern-recognition molecules that can, for instance, interact with glycans on microbial surfaces [28]. Additionally, certain galectins are implicated in the regulation of leukocyte recruitment and inflammation. For instance, endothelial galectin-1 inhibits neutrophil rolling and adhesion under flow in vitro and neutrophil recruitment in vivo. The underlying mechanism may involve downregulation of expression of adhesion molecules, such as CD11b, on neutrophils [29,30]. Consistent with this, neutrophil recruitment was enhanced in galectin-1-deficient mice in a model of IL-1 β -induced inflammation of the vascular bed of the cremaster muscle [29]. The anti-inflammatory role of recombinant galectin-1 has been demonstrated in different mouse models of autoimmunity [31,32]. In contrast, galectin-3, expressed in neutrophils and macrophages among other cell types, seems to have a proinflammatory action [33,34]. Moreover, galectin-3 may promote eosinophil rolling and adhesion [35]. However, galectin-3 has also been reported as a negative regulator of LPS-induced inflammation in mice [36], implying that the regulatory effects of galectin-3 (and possibly other galectins) on inflammation may be context- and/or tissue-dependent.

Developmental endothelial locus-1 (Del-1)

Del-1, also known as EGF-like repeats and discoidin I-like domains 3 (EDIL3) is an endothelial cell-expressed 52-kDa glycoprotein, originally described for its role in vascularization [37]. Although secreted by endothelial cells, Del-1 can become associated with the endothelial cell surface by binding to surface proteoglycans or to integrin $\alpha v \beta 3$ by means of an Arg-Gly-Asp (RGD) motif on the second EGF-like repeat [1,38]. More recently, Del-1 was shown to be a novel ligand for the LFA-1 integrin but, unlike ICAM-1, it antagonizes LFA-1-dependent leukocyte adhesion onto the vascular endothelium (Figure 1) [39]. Importantly, at equimolar amounts, Del-1 outcompetes ICAM-1 for binding to LFA-1 on leukocytes and thereby inhibits the adhesion and diapedesis of neutrophils [39]. These findings suggest that Del-1 acts homeostatically to regulate local inflammation. This concept was demonstrated in an animal model of periodontitis [40], a chronic inflammatory disease, which leads to the destruction of the tissues that surround and support the teeth (periodontium) and constitutes a risk factor for systemic diseases (*e.g.*, atherosclerosis, rheumatoid arthritis, adverse pregnancy outcomes, diabetes, and aspiration pneumonia) [41–46].

The role of Del-1 in periodontal homeostasis was established in distinct models. Del-1 expression is diminished in gingival tissue in old age, correlating with excessive neutrophil recruitment and IL-17-dependent inflammatory bone loss, the hallmark of periodontitis [40]. Consistent with this, Del-1-deficient mice develop spontaneous inflammatory bone loss at young age accompanied by heavy neutrophil infiltration in the gingiva, and inflammation is dependent on LFA-1 and the IL-17 receptor. Whereas Del-1 inhibits LFA-1-dependent neutrophil recruitment and IL-17 production, IL-17 downregulates Del-1 expression in endothelial cells and thereby promotes neutrophil recruitment [40]. Therefore, Del-1 and IL-17 are reciprocally cross-regulated and, moreover, the inhibition of Del-1 by IL-17 is a novel mechanism by which IL-17 can facilitate neutrophil recruitment to sites of inflammation. Other, previously established mechanisms include the capacities of IL-17 to orchestrate granulopoiesis and neutrophil mobilization and chemotaxis [47–49]. The inverse expression of Del-1 and IL-17 is also observed in human gingival biopsy samples, with Del-1 dominating in healthy gingiva and IL-17 in inflamed gingiva [40]. Moreover, human Del-1 inhibits LFA-1-dependent transendothelial migration of human neutrophils in vitro [40].

These findings indicate that Del-1 serves as a mechanism whereby a tissue can locally self-regulate persistent inflammation associated with chronic recruitment of neutrophils. This concept may be exploited therapeutically. Proof-of-concept was established by showing that local periodontal treatment with soluble Del-1 in old mice inhibits IL-17 production, LFA-1-dependent neutrophil infiltration, and bone loss [40].

GDF-15

Growth differentiation factor-15 (GDF-15), a member of the TGF β superfamily, is another local tissue-expressed inhibitor of leukocyte extravasation. GDF-15 is upregulated in cardiomyocytes upon myocardial infarction [50]. This is likely a protective homeostatic mechanism in myocardial infarction, as GDF-15 restrains the recruitment of neutrophils and thereby attenuates the inflammatory response in the heart leading to reduced infarct size [51]. Conversely, GDF-15-deficient mice exhibit increased myocardial rupture and mortality after infarction [51]. The inhibition of neutrophil recruitment by GDF-15 is dependent upon its ability to interfere with leukocyte integrin activation. Specifically, GDF-15 blocks chemokine-induced activation of β 2-integrin affinity and clustering, thereby preventing neutrophil adhesion to ICAM-1 and transendothelial migration [51]. Mechanistically, the inhibitory effect of GDF-15 on integrin activation is mediated through regulation of small GTPases, involving activation of Cdc42 and deactivation of Rap1 (Figure 1) [51]. Therefore, GDF-15 upregulation in cardiomyocytes upon myocardial infarction appears to be a local tissue mechanism to attenuate inflammation and myocardial damage.

In contrast to the direct mechanism of GDF-15 action (Figure 1), other cytokines such as IL-4, IL-10, and TGF β exert indirect and complex effects to regulate inflammatory cell recruitment, including transcription regulation of molecules that promote or inhibit endothelial cell-leukocyte interactions [52,53]. Therefore, at least in principle, the different mechanisms of action of these regulators could be exploited for complementary therapeutic approaches to inflammatory diseases.

Endogenous pro-resolving agents

It is now well established that resolution of inflammation is an active process mediated by specific pro-resolving agonists of endogenous origin. Such agonists include small lipid molecules, such as lipoxins, resolvins, and protectins, which are derived from arachidonic acid and other polyunsaturated fatty acids [54]. In contrast to Del-1, which at the

endothelial-leukocyte interface is produced by endothelial cells [39,40], lipid mediators involved in the resolution of inflammation are generated through transcellular biosynthesis involving both endothelial cells and leukocytes [55]. For instance, endothelial cells can act as donor cells that convert a precursor compound (*e.g.*, eicosapentaenoic acid) into an intermediate product (18*R*-hydroxyeicosapentaenoic acid) that is converted into the final active compound (resolvin E1) by activated 5 lipoxygenase in neutrophils, which act as acceptor cells when they interact with endothelial cells within the vasculature [55]. When generated within the vascular lumen, lipoxins and resolvins (derived from docosahexaenoic acid [D series] or eicosapentaenoic acid [E series]) arrest neutrophil diapedesis and recruitment into the tissues. The underlying mechanisms involve primarily modulation of adhesion receptor expression in both neutrophils and endothelial cells. For example, lipoxin A₄ inhibits leukotriene- or peptidoleukotriene-induced neutrophil adhesion and transmigration by inhibiting the expression of P-selectin on endothelial cells and of β 2 integrin (CD11b/CD18) on neutrophils [56,57]. Other activities by lipoxins or resolvins that inhibit the extravasation of neutrophils include inhibition of L-selectin shedding and of ICAM-1 expression, and upregulation of endothelium-expressed nitric oxide, an established anti-adhesive factor [58,59].

In addition to resolvins, resolving exudates from various models of inflammation also contain a biochemically distinct family of docosahexaenoic acid-derived pro-resolving mediators termed protectins [55]. Recently, it was shown that D series resolvins (RVD1 and RVD5) and protectin D1 are temporally and differentially regulated in the course of bacterial infections and collectively enhance phagocytosis, downregulate proinflammatory mediators and, moreover, lower the antibiotic requirements for bacterial clearance [60].

In contrast to their inhibitory effects on neutrophils, pro-resolving lipid mediators actually promote the recruitment and activation of monocytes, albeit for nonphlogistic phagocytosis of apoptotic neutrophils by activated monocyte-derived macrophages [61,62]. These and other anti-inflammatory or pro-resolving actions of lipoxins, resolvins, and protectins explain their protective role in several models of inflammatory diseases, including colitis, peritonitis, periodontitis, ischaemia-reperfusion injury, and asthma [54].

Concluding remarks: Local tissue in control of inflammation

Tissues may have greater control, than traditionally appreciated, over the initiation and type of the immune response by virtue of their capacity to communicate with the immune system via tissue-derived signals (*e.g.*, cytokines, chemokines, antimicrobial peptides, and growth factors) [63,64]. In this context, tissues may not be passive recipients of immune protection since tissue-derived “alarm” signals can educate and appropriately activate antigen-presenting cells to promote a certain effector class of host response [63]. Conversely, when no longer needed, the host response can be downregulated by local “health” signals (*e.g.*, resolvins) to promote resolution of inflammation and tissue regeneration [54,63,64].

These notions for proactive involvement of the tissues in immune regulation is consistent with evidence that immune-privileged sites, such as the brain and the eye, have built-in mechanisms to favor the appropriate class of immune response that may protect the tissue against infection without destructive inflammation [63,65,66].

The hypothesis that tissues may have a “regulatory say” over the immune response is strongly supported by the recent advancements on the locally released endogenous modulators of the leukocyte adhesion cascade. It is now clear that tissues can locally regulate the recruitment of inflammatory cells [39,40,51,59]. In fact, the spontaneous periodontal inflammatory phenotype of Del-1–deficient mice suggests that Del-1–expressing tissues may have greater control over the local host inflammatory response than the immune

system itself. Intriguingly, immune-privileged tissues/organs, such as the eye and brain, display abundant expression of Del-1 at significantly higher levels than peripheral tissues, such as the lung or the gingiva [39,40]. This suggests that these tissues may “prefer to take their chances” with infection rather than inflammation. Although Del-1 is not expressed in the heart [39], as discussed above local inflammation is regulated through increased expression of GDF-15 in cardiomyocytes [51]. Hence, distinct mechanisms at different tissues may be employed to self-regulate local inflammatory responses. Understanding the tissue-specific promoters and inhibitors of leukocyte recruitment and their regulation becomes therefore imperative and warrants further research (Box 1). We propose that the above discussed and other, yet to be identified, inhibitors of the leukocyte adhesion cascade may represent local homeostatic mechanisms that tissues and organs may have evolved for protection against the destructive potential of the immune system.

Box 1

Outstanding questions

- What is the tissue specificity and relative abundance of the various endogenous modulators of inflammatory cell recruitment? Is there a correlation between their expression levels and the immune privilege or susceptibility of a tissue or an organ?
- Is the expression of these endogenous modulators regulated by signals derived from the recruited inflammatory cells in a negative feedback loop?
- Is there a crosstalk or cooperation between different classes of endogenous modulators, *e.g.*, do resolvins or lipoxins regulate Del-1 or GDF-15 expression?
- Does aging adversely affect the expression of endogenous modulators? If so, can local treatment reverse or mitigate age-associated inflammatory conditions? By the same rationale, can endogenous modulators be used locally to treat inflammatory diseases affecting tissues that do not normally express them?

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References

1. Chavakis E, et al. Novel aspects in the regulation of the leukocyte adhesion cascade. *Thromb Haemost.* 2009; 102:191–197. [PubMed: 19652868]
2. Luster AD, et al. Immune cell migration in inflammation: present and future therapeutic targets. *Nat Immunol.* 2005; 6:1182–1190. [PubMed: 16369557]
3. Langer HF, Chavakis T. Leukocyte-endothelial interactions in inflammation. *J Cell Mol Med.* 2009; 13:1211–1220. [PubMed: 19538472]
4. Ley K, et al. Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat Rev Immunol.* 2007; 7:678–689. [PubMed: 17717539]
5. Vestweber D. Adhesion and signaling molecules controlling the transmigration of leukocytes through endothelium. *Immunol Rev.* 2007; 218:178–196. [PubMed: 17624953]
6. Nourshargh S, et al. Breaching multiple barriers: leukocyte motility through venular walls and the interstitium. *Nat Rev Mol Cell Biol.* 2010; 11:366–378. [PubMed: 20414258]

7. Auffray C, et al. Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. *Science*. 2007; 317:666–670. [PubMed: 17673663]
8. Shamri R, et al. Lymphocyte arrest requires instantaneous induction of an extended LFA-1 conformation mediated by endothelium-bound chemokines. *Nat Immunol*. 2005; 6:497–506. [PubMed: 15834409]
9. McEver RP, Zhu C. Rolling cell adhesion. *Annu Rev Cell Dev Biol*. 2010; 26:363–396. [PubMed: 19575676]
10. Chavakis T. Leucocyte recruitment in inflammation and novel endogenous negative regulators thereof. *Eur J Clin Invest*. 2012; 42:686–691. [PubMed: 22577952]
11. Schenkel AR, et al. Locomotion of monocytes on endothelium is a critical step during extravasation. *Nat Immunol*. 2004; 5:393–400. [PubMed: 15021878]
12. Phillipson M, et al. Intraluminal crawling of neutrophils to emigration sites: a molecularly distinct process from adhesion in the recruitment cascade. *J Exp Med*. 2006; 203:2569–2575. [PubMed: 17116736]
13. Abram CL, Lowell CA. The ins and outs of leukocyte integrin signaling. *Annu Rev Immunol*. 2009; 27:339–362. [PubMed: 19302044]
14. Carman CV, Springer TA. Integrin avidity regulation: are changes in affinity and conformation underemphasized? *Curr Opin Cell Biol*. 2003; 15:547–556. [PubMed: 14519389]
15. Woodfin A, et al. The junctional adhesion molecule JAM-C regulates polarized transendothelial migration of neutrophils in vivo. *Nat Immunol*. 2011; 12:761–769. [PubMed: 21706006]
16. Deban L, et al. Regulation of leukocyte recruitment by the long pentraxin PTX3. *Nat Immunol*. 2010; 11:328–334. [PubMed: 20208538]
17. Garlanda C, et al. Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. *Annu Rev Immunol*. 2005; 23:337–366. [PubMed: 15771574]
18. Maina V, et al. Coregulation in human leukocytes of the long pentraxin PTX3 and TSG-6. *J Leukoc Biol*. 2009; 86:123–132. [PubMed: 19389798]
19. Cotena A, et al. Complement dependent amplification of the innate response to a cognate microbial ligand by the long pentraxin PTX3. *J Immunol*. 2007; 179:6311–6317. [PubMed: 17947708]
20. Bottazzi B, et al. The long pentraxin PTX3 as a prototypic humoral pattern recognition receptor: interplay with cellular innate immunity. *Immunol Rev*. 2009; 227:9–18. [PubMed: 19120471]
21. Salio M, et al. Cardioprotective function of the long pentraxin PTX3 in acute myocardial infarction. *Circulation*. 2008; 117:1055–1064. [PubMed: 18268142]
22. McEver RP. Selectins: lectins that initiate cell adhesion under flow. *Curr Opin Cell Biol*. 2002; 14:581–586. [PubMed: 12231353]
23. Gawaz M, et al. Platelets in inflammation and atherogenesis. *J Clin Invest*. 2005; 115:3378–3384. [PubMed: 16322783]
24. Chavakis T, et al. High molecular weight kininogen regulates platelet-leukocyte interactions by bridging Mac-1 and glycoprotein Ib. *J Biol Chem*. 2003; 278:45375–45381. [PubMed: 12952972]
25. Santoso S, et al. The junctional adhesion molecule 3 (JAM-3) on human platelets is a counterreceptor for the leukocyte integrin Mac-1. *J Exp Med*. 2002; 196:679–691. [PubMed: 12208882]
26. Langer HF, et al. Platelets contribute to the pathogenesis of experimental autoimmune encephalomyelitis. *Circ Res*. 2012; 110:1202–1210. [PubMed: 22456181]
27. Zarbock A, et al. Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation. *J Clin Invest*. 2006; 116:3211–3219. [PubMed: 17143330]
28. Vasta GR. Galectins as pattern recognition receptors: structure, function, and evolution. *Adv Exp Med Biol*. 2012; 946:21–36. [PubMed: 21948360]
29. Cooper D, et al. Novel insights into the inhibitory effects of Galectin-1 on neutrophil recruitment under flow. *J Leukoc Biol*. 2008; 83:1459–1466. [PubMed: 18372340]
30. Gil CD, et al. Effect of exogenous galectin-1 on leukocyte migration: modulation of cytokine levels and adhesion molecules. *Int J Clin Exp Pathol*. 2010; 4:74–84. [PubMed: 21228929]

31. Offner H, et al. Recombinant human beta-galactoside binding lectin suppresses clinical and histological signs of experimental autoimmune encephalomyelitis. *J Neuroimmunol.* 1990; 28:177–184. [PubMed: 1694534]
32. Toscano MA, et al. Galectin-1 suppresses autoimmune retinal disease by promoting concomitant Th2- and T regulatory-mediated anti-inflammatory responses. *J Immunol.* 2006; 176:6323–6332. [PubMed: 16670344]
33. Nieminen J, et al. Galectin-3 interacts with naive and primed neutrophils, inducing innate immune responses. *J Leukoc Biol.* 2005; 78:1127–1135. [PubMed: 16260586]
34. Kuwabara I, Liu FT. Galectin-3 promotes adhesion of human neutrophils to laminin. *J Immunol.* 1996; 156:3939–3944. [PubMed: 8621934]
35. Rao SP, et al. Galectin-3 functions as an adhesion molecule to support eosinophil rolling and adhesion under conditions of flow. *J Immunol.* 2007; 179:7800–7807. [PubMed: 18025226]
36. Li Y, et al. Galectin-3 is a negative regulator of lipopolysaccharide-mediated inflammation. *J Immunol.* 2008; 181:2781–2789. [PubMed: 18684969]
37. Penta K, et al. Del1 induces integrin signaling and angiogenesis by ligation of alphaVbeta3. *J Biol Chem.* 1999; 274:11101–11109. [PubMed: 10196194]
38. Hidaï C, et al. Discoidin domain of Del1 protein contributes to its deposition in the extracellular matrix. *Cell Tissue Res.* 2007; 330:83–95. [PubMed: 17701220]
39. Choi EY, et al. Del-1, an endogenous leukocyte-endothelial adhesion inhibitor, limits inflammatory cell recruitment. *Science.* 2008; 322:1101–1104. [PubMed: 19008446]
40. Eskin MA, et al. The leukocyte integrin antagonist Del-1 inhibits IL-17-mediated inflammatory bone loss. *Nat Immunol.* 2012; 13:465–473. [PubMed: 22447028]
41. Pihlstrom BL, et al. Periodontal diseases. *Lancet.* 2005; 366:1809–1820. [PubMed: 16298220]
42. Genco RJ, Van Dyke TE. Prevention: Reducing the risk of CVD in patients with periodontitis. *Nat Rev Cardiol.* 2010; 7:479–480. [PubMed: 20725103]
43. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. *Nat Rev Endocrinol.* 2011; 7:738–748. [PubMed: 21709707]
44. Tonetti MS, et al. Treatment of periodontitis and endothelial function. *N Engl J Med.* 2007; 356:911–920. [PubMed: 17329698]
45. Jeffcoat M, et al. Periodontal infection and preterm birth: successful periodontal therapy reduces the risk of preterm birth. *BJOG.* 2011; 118:250–256. [PubMed: 20840689]
46. Lundberg K, et al. Periodontitis in RA-the citrullinated enolase connection. *Nat Rev Rheumatol.* 2010; 6:727–730. [PubMed: 20820197]
47. Kolls JK, Linden A. Interleukin-17 family members and inflammation. *Immunity.* 2004; 21:467–476. [PubMed: 15485625]
48. Stark MA, et al. Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. *Immunity.* 2005; 22:285–294. [PubMed: 15780986]
49. Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol.* 2009; 9:556–567. [PubMed: 19575028]
50. Kempf T, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. *Circ Res.* 2006; 98:351–360. [PubMed: 16397141]
51. Kempf T, et al. GDF-15 is an inhibitor of leukocyte integrin activation required for survival after myocardial infarction in mice. *Nat Med.* 2011; 17:581–588. [PubMed: 21516086]
52. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. *Circ Res.* 2012; 110:159–173. [PubMed: 22223212]
53. Carlos TM. Leukocyte recruitment at sites of tumor: dissonant orchestration. *J Leukoc Biol.* 2001; 70:171–184. [PubMed: 11493608]
54. Serhan CN, et al. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol.* 2008; 8:349–361. [PubMed: 18437155]
55. Serhan CN, Petasis NA. Resolvins and protectins in inflammation resolution. *Chem Rev.* 2011; 111:5922–5943. [PubMed: 21766791]

56. Papayianni A, et al. Lipoxin A4 and B4 inhibit leukotriene-stimulated interactions of human neutrophils and endothelial cells. *J Immunol.* 1996; 156:2264–2272. [PubMed: 8690917]
57. Fiore S, Serhan CN. Lipoxin A4 receptor activation is distinct from that of the formyl peptide receptor in myeloid cells: inhibition of CD11/18 expression by lipoxin A4-lipoxin A4 receptor interaction. *Biochemistry.* 1995; 34:16678–16686. [PubMed: 8527441]
58. Spite M, Serhan CN. Novel lipid mediators promote resolution of acute inflammation: impact of aspirin and statins. *Circ Res.* 2010; 107:1170–1184. [PubMed: 21071715]
59. Spite M, et al. Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. *Nature.* 2009; 461:1287–1291. [PubMed: 19865173]
60. Chiang N, et al. Infection regulates pro-resolving mediators that lower antibiotic requirements. *Nature.* 2012; 484:524–528. [PubMed: 22538616]
61. Godson C, et al. Cutting edge: lipoxins rapidly stimulate nonphlogistic phagocytosis of apoptotic neutrophils by monocyte-derived macrophages. *J Immunol.* 2000; 164:1663–1667. [PubMed: 10657608]
62. Schwab JM, et al. Resolvin E1 and protectin D1 activate inflammation-resolution programmes. *Nature.* 2007; 447:869–874. [PubMed: 17568749]
63. Matzinger P, Kamala T. Tissue-based class control: the other side of tolerance. *Nat Rev Immunol.* 2011; 11:221–230. [PubMed: 21350581]
64. Stout RD, Suttles J. Immunosenescence and macrophage functional plasticity: dysregulation of macrophage function by age-associated microenvironmental changes. *Immunol Rev.* 2005; 205:60–71. [PubMed: 15882345]
65. Niederkorn JY, Stein-Streilein J. History and physiology of immune privilege. *Ocul Immunol Inflamm.* 2010; 18:19–23. [PubMed: 20128645]
66. Streilein JW. Ocular immune privilege: therapeutic opportunities from an experiment of nature. *Nat Rev Immunol.* 2003; 3:879–889. [PubMed: 14668804]

Figure 1. Endogenous modulators of leukocyte recruitment

(a) Leukocyte-derived PTX-3 binds to endothelial P-selectin thereby inhibiting the PSGL-1/P-selectin-dependent rolling. (b) GDF-15 counteracts the chemokine-induced activation of β 2-integrins by targeting both affinity (involving conformational changes in a single integrin receptor resulting in higher binding to its ligand) and valency (involving the clustering of more integrin receptors). The inhibitory action of GDF-15 on integrin activation is mediated via upregulation of Cdc42-GTPase activity that antagonizes the activity of Rap1-GTPase. (c) Finally, endothelial cell-associated Del-1 inhibits LFA-1-dependent leukocyte adhesion. The adhesive interactions between LFA-1 on leukocytes and ICAM-1 on endothelial cells constitute a major mechanism mediating firm leukocyte arrest on the endothelium and the subsequent transmigration process.