Atypical Chemokine Receptors in Cardiovascular Disease

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Thromb Haemost 2019;119:534–541.

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Abstract

Inflammation has been well recognized as one of the main drivers of atherosclerosis development and therefore cardiovascular diseases (CVDs). It has been shown that several chemokines, small 8 to 12 kDa cytokines with chemotactic properties, play a crucial role in the pathophysiology of atherosclerosis. Chemokines classically mediate their effects by binding to G-protein-coupled receptors called chemokine receptors. In addition, chemokines can also bind to atypical chemokine receptors (ACKRs). ACKRs fail to induce G-protein-dependent signalling pathways and thus subsequent cellular response, but instead are able to internalize, scavenge or transport chemokines. In this review, we will give an overview of the current knowledge about the involvement of ACKR1–4 in CVDs and especially in atherosclerosis development. In the recent years, several studies have highlighted the importance of ACKRs in CVDs, although there are still several controversies and unexplored aspects that have to be further elucidated. A better understanding of the precise role of these atypical receptors may pave the way towards novel and improved therapeutic strategies.

Keywords
- atherosclerosis
- cardiovascular diseases
- chemokines
- atypical chemokine receptors

Introduction

Cardiovascular diseases (CVDs) cover a spectrum of conditions that affect the heart and blood vessels, and may manifest in life-threatening events such as myocardial infarction (MI), stroke and aneurysm. The main pathology behind CVDs is atherosclerosis, a lipid-driven, chronic inflammatory disease that impacts arteries.[1] Atherosclerosis is initiated by haemodynamic shear stress-related damage to the endothelium, increasing the endothelial permeability and in turn its susceptibility to lipid invasion. Subsequent modification of lipids in the intima along with the endothelial damage trigger an inflammatory response in which immune cells infiltrate into the sub-endothelial layer.[2] This process results in an on-going plaque development within the arterial wall, which may ultimately occlude the blood vessels or rupture leading to atherothrombosis. Arterial occlusion and the resulting hypoxia of downstream tissues (ischaemia) may progress into severe clinical consequences, such as ischaemic stroke, MI or organ dysfunction.

Current state-of-the-art therapy of CVDs is mostly limited to the mitigation of hyperlipidaemia and management of thrombotic factors, for example, use of statins and aspirin, respectively.[3] In addition to demanding health care procedures causing both economic and social burdens, CVDs still remain the primary cause of mortality worldwide.[4] This clearly signifies the necessity of novel therapeutic measures which specifically address the main mechanisms regulating atherosclerosis development, such as leukocyte infiltration into atherosclerotic lesions. Chemokines and their receptors

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received
October 17, 2018
accepted after revision
November 21, 2018

DOI https://doi.org/10.1055/s-0038-1676988.
ISSN 0340-6245.

are involved in the onset of atherosclerosis and thereby represent promising potential therapeutic targets.

Chemokines and Their Receptors in Atherosclerosis

Chemokines, also known as chemotactic cytokines, were first identified to control immune cell migration in the context of inflammation and later in homeostatic conditions. Inflammatory (induced during inflammation) and homeostatic (constitutively expressed in steady state) chemokines bind to G-protein-coupled receptors (GPCRs). Such chemokine receptors are expressed on all immune cells and their activation by chemokines mediate leukocyte cell migration. However, it is now clear that chemokines can also modulate a plethora of other cellular functions such as proliferation, survival, differentiation, mobilization, cytokine release and phagocytosis in several immune cell populations.[5] Given their immunologically relevant functions, it is not surprising that chemokines and their receptors extensively contribute to various stages of atherosclerosis, such as leukocyte trafficking and influx into atherosclerotic plaques, as well as proliferation, apoptosis and foam cell formation of different cell types within the lesions.[6]

In addition to these 'classical' chemokine receptors, chemokines also bind to atypical chemokine receptors (ACKRs). Four functional ACKRs have been so far assigned: ACKR1 (also known as [aka] Duffy antigen receptor for chemokine [DARC]), ACKR2 (aka D6), ACKR3 (aka CXCR7) and ACKR4 (aka CCRL1). While ACKR1 and ACKR2 bind inflammatory chemokines, ACKR3 and ACKR4 bind homeostatic chemokines (►**Fig. 1**). ACKRs are structurally similar to GPCRs but they do not couple to G proteins due to the absence of the Asp-Arg-Tyr-Leu-Ala-Ile-Val (DRYLAIV) motif in the second intracellular loop.[7,8] As a result, ACKRs fail to induce G-protein-dependent signalling pathways and subsequent cellular responses, such as chemotaxis.[9] Instead, ACKRs can internalize, scavenge, transport or present chemokines and thus regulate the bioavailability of chemokines and thereby chemokine signalling via 'classical' receptors.[10] In contrast to 'classical' receptors, ACKRs are mainly expressed by erythrocytes and non-haematopoietic cells, such as lymphatic and vascular endothelial cells, with the exception of ACKR2 and ACKR3, which are also expressed by some leukocyte subsets.

The rationale behind current research focusing on CVDs is to identify key players in this multifaceted disease to develop suitable therapeutics. Accordingly, ACKRs are of particular interest as they are major regulators of chemokine availability and signalling, thereby potentially contributing to the development of CVDs. In this review, we will discuss the features of each ACKR and their contribution to CVDs, notably in atherosclerosis (►**Fig. 1**).

ACKR1

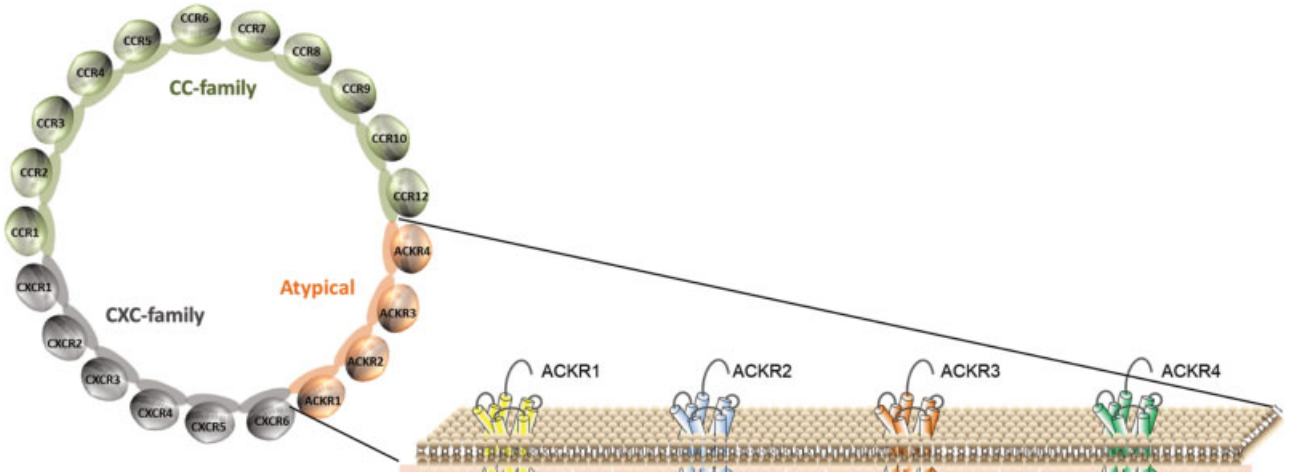
Receptor Characteristics and Signalling

ACKR1, also known as DARC, binds more than 20 different inflammatory CC and CXC chemokines and was ascribed a unique expression profile in erythrocytes, venular endothelial cells and cerebellar Purkinje neurons. On the venular endothelium, ACKR1 can internalize and transport inflammatory chemokines from the tissue onto the luminal endothelial cell surface.[11] This machinery not only protects soluble chemokines from degradation but also allows their presentation at the surface of endothelial cells and consequently leads to the firm adhesion of circulating leukocytes. Notably, ACKR1 expression is up-regulated in post-capillary venules and veins under inflammation,[12] suggesting that endothelial ACKR1 plays a crucial role in leukocyte recruitment in inflammatory diseases.

All sub-Saharan Africans and 70% of African Americans carry the variant rs2814778(G) in the gene encoding *ACKR1* making this variant the most predictive ancestry-informative marker of African origin.[13] The variant corresponds to a single A to G substitution in the promoter region of *ACKR1*, which disrupts the binding site for the GATA1 erythroid transcription factor. As a consequence, individuals who are homozygous for the allele specifically lack ACKR1 expression on erythrocytes but still express ACKR1 on endothelium and cerebellum, causing a Duffy-negative phenotype.[14] We recently found that ACKR1 is highly expressed by nucleated erythroid cells (NECs) in the bone marrow where it regulates the homeostasis of haematopoietic stem and progenitor cells (HSPCs) and controls downstream haematopoiesis.[15] In the absence of ACKR1, the steady-state haematopoiesis is altered; bone marrow HSPCs localize remotely from NECs and give rise to phenotypically distinct neutrophils. Overall, these findings highlight that ACKR1 expression in the erythroid lineage regulates patterns of haematopoiesis and the ultimate phenotype of myeloid cells. The specific properties of the neutrophils produced in Duffy-negative individuals may have a positive impact on innate immune responses against pathogens. On the other hand, a stronger immune response may be detrimental in the context of chronic inflammation and autoimmune disease.

Clinical Significance of ACKR1

Few studies investigated the role of ACKR1 in atherosclerosis. A study by Wan et al suggested that ACKR1 plays a harmful role in atherosclerosis as the absence of ACKR1 (using conventional global knockout) in *Apoe*$^{-/-}$ mice showed a reduction in atherosclerotic plaque size.[16] Interestingly, although *Ackr1* deficiency did not affect plasma cholesterol levels, plaque stability or macrophage content in the atherosclerotic lesions, it was associated with a decreased T cell number in the aorta. Whether this is due to the capacity of ACKR1 to mediate chemokine transcytosis and leukocyte extravasation remains to be further investigated. In line with this, the expression of ACKR1 was up-regulated in the aorta of *Apoe*$^{-/-}$ mice fed a high-fat diet (HFD).[16] As mentioned above, ACKR1 is exclusively expressed on the venular and not arterial (including aorta) vessels. Interestingly, a recent study pointed out that ACKR1 was detected in the *vasa vasorum* around the aorta of wild-type mice, and its expression in these vessels was increased in the aortas of *Apoe*$^{-/-}$ mice with atherosclerotic lesions.[17] It still remains to be defined whether the reduction of T cell infiltration in the aorta of *Ackr1*$^{-/-}$ mice was due to a decrease of T cells in the atherosclerotic plaques or in the



		REF		REF		REF		REF
Alternative names:	DARC, CD234, FY Glycoprotein	21 77-78	D6, CCBP2	21 77-78	RDC1, CXCR7	35 21 77-78	CCRL1, CCR11, CCXCKR	21 77-78
Mainly expressed by:	NEC Erythrocytes Venular endothelial cells Cerebellar Purkinje neurons	15 80 17 79	Lymphatic endothelial cells Some macrophage subsets Innate-like B cells	83 86 86	Endothelial cells Neurons Marginal B cells Mesenchymal cells	89 90 91	Lymphatic endothelial cells Mesenchymal cells Keratinocytes	87-88
Ligands:	CCL2, CCL5, CCL7-8, CCL11, CCL13-14, CCL17, CCL22, CXCL1-3, CXCL5-8, CXCL11, CXCL13	84 85 86	CCL2-5, CCL7-8, CCL11, CCL13-14, CCL17, CCL22	22	CXCL11, CXCL12, MIF, ADM	37 21 77-78	CCL19, CCL21, CCL25, CXCL13	21 77-78
Signaling via:	Not applicable		B-Arrestin	92-93	B-Arrestin	48	B-Arrestin	94
Heterodimer formation with:	CCR5	81	Not applicable		CXCR4	47	CXCR3	82
Homeostatic functions:	- HSPC homeostasis regulation and downstream hematopoiesis - Leukocyte recruitment	15 11	- Development of lymphatic system - Regulating myeloid cell trafficking and differentiation	25 27	- Development of cardiovascular system	33	- Controls chemokine gradient in lymph nodes	74
Evidence for a role in inflammation/CVD:	-Increased expression in vasa vasorum in Apoe-/- mice. -Promotes atherosclerotic lesions - ACKR1 on RBCs controls inflammation, leukocyte migration and endothelial function. -ACKR1-presented CXCL2 enables unidirectional neutrophil diapedesis	17 16 19 95	- Reduces CCL2/CCL3 levels after MI - Decreases migration of monocytes and neutrophils after MI - Decreases risk of cardiac rupture	31 31 31	- Induces cholesterol uptake in AT - Promotes EC proliferation and angiogenesis - Stimulates proliferation and migration of EPCs - Increases vSMC migration - Enhances platelet survival - Increases leukocyte adhesion	44 62 63-64 49 56 70	Not applicable	

Fig. 1 Overview of expression and functions of the atypical chemokine receptors (ACKRs). The circle displays all currently identified chemokine receptors and depicts the 4 ACKRs (orange) that are further highlighted in the table. Appropriate references for each statement are depicted in the REF columns. ADM, adrenomedullin; AT, adipose tissue; CVD, cardiovascular disease; EC, endothelial cell; EPC, endothelial progenitor cell; HSPC, haematopoietic stem and progenitor cells; MI, myocardial infarction; MIF, macrophage inhibitory factor; NEC, nucleated erythroid cells; RBC, red blood cell; vSMC, vascular smooth muscle cell.

artery tertiary lymphoid organs (ATLOs), which are atherosclerosis-associated lymphoid aggregates participating in T and B cell responses against atherosclerosis-specific autoantigens.[18] It would therefore be crucial to determine whether ACKR1 expressed in the *vasa vasorum* around the aorta is involved in the formation of ATLOs and/or the recruitment of T cells in these lymphoid tissues. Further investigation of *Ackr1*$^{-/-}$ mice may shed new light on the role of lymphoid cells in ATLOs which still needs to be clearly defined.

While these studies determined a role of endothelial ACKR1 in atherosclerosis, little is known about erythroid ACKR1 in this context. While it is well-known that HFD induces endothelial dysfunction, a recent study by Unruh et al demonstrated that HFD also affects red blood cell (RBC) function,[19] notably by increasing the levels of CCL2 bound to RBCs, which promotes interactions between leukocytes and endothelial cells. Importantly, this is partly due to ACKR1 expression on RBCs as pro-inflammatory response levels in RBCs were dramatically reduced in the absence of ACKR1. Therefore, this study not only demonstrates that RBCs play a central role in endothelial dysfunction and leukocyte recruitment in a HFD context, but also highlights the importance of ACKR1 on erythroid cells in atherosclerosis.

Future research on the role of ACKR1 in atherosclerosis should focus on dissecting the specific role of both endothelial and erythroid ACKR1 in the initiation, development and

consequences of the disease. What is the function of endothelial ACKR1 in ATLOs and subsequently the effects on atherosclerosis? In contrast, how does the absence of ACKR1 on erythroid cells in the bone marrow and the production of phenotypically distinct myeloid cells, affect atherosclerosis development? Individuals of African ancestry are more susceptible to CVD, stroke and several autoimmune as well as inflammatory diseases.[20] A better understanding of the role of erythroid ACKR1 in the development of CVDs may help to elucidate pathogenic mechanisms and ultimately to develop therapies specifically tailored to tackle CVD in individuals of African ancestry.

ACKR2

Receptor Characteristics and Signalling

ACKR2, also known as D6, was first identified in human lymphatic endothelial cells,[21] with scavenging properties towards the inflammatory CC chemokines.[22] Consequently, the role of the atypical receptor in the resolution of inflammation has been extensively studied.[23,24] ACKR2 has a prominent role in the development of the lymphatic system,[25] regulating the local microenvironment in lymphatic vessels and cell positioning via one of its ligands CCL2.[26] Moreover, ACKR2 deficiency in non-haematopoietic cells causes an increase of CCL2 levels in the serum of these mice and a subsequent increase of circulating myeloid cells.[27] More recently, ACKR2 was also shown to regulate myeloid cell differentiation.[28]

Clinical Significance of ACKR2

Inflammatory CC chemokines and more specifically CCL2 are key mediators of monocyte infiltration after MI.[29,30] Cochain et al evaluated the effect of ACKR2 in a mouse model of MI.[31] In accordance with previous findings, ACKR2 deficiency resulted in elevated levels of CCL2 and CCL3 in the heart of infarcted mice. In addition, deletion of ACKR2 in non-haematopoietic cells enhanced the infiltration of inflammatory monocytes and neutrophils into the heart 5 days after the operation, a process crucial for the healing of the infarcted tissue.[32] Finally, a fourfold increase of cardiac rupture events was noted in *Ackr2*$^{-/-}$ mice.[31] These data underline the importance of the ACKR2 in inflammation, although further research is needed to elucidate the role of this atypical receptor in CVDs.

ACKR3

Receptor Characteristics and Signalling

ACKR3 is highly expressed in the heart, brain, spleen, kidney, lungs and thyroid,[8] especially by endothelial cells, neurons and marginal B cells. It has an indispensable importance in the development of cardiovascular system, as its absence was shown to result in cardiac phenotype defects, such as heart valve malformation leading to perinatal death in mice.[33,34] The receptor was first identified from a dog thyroid and formerly known as RDC1.[35] Later, it was renamed CXCR7 as a member of the CXC chemokine receptor family. Currently, this receptor is classified as ACKR3,[36] which is activated by two chemokine ligands, CXCL12 and CXCL11, which furthermore bind CXCR4 and CXCR3, respectively.[37] However, both ACKR3 and CXCL12 bind each other with greater affinities in comparison to their alternative ligand and receptor, respectively.[38–40] ACKR3 was described to be internalized upon CXCL12 binding, which ultimately leads to the lysosomal degradation of its bound ligand,[39,41–43] indicating a scavenging feature. As such, ACKR3 regulates extracellular CXCL12 concentrations[44,45] and can thereby control CXCR4 activity.[46] ACKR3, like the other ACKRs, is not able to directly mediate G-protein signalling by itself, nevertheless it may indirectly modulate the G-protein signalling by forming heterodimers with CXCR4.[47] Moreover, ACKR3 can also recruit and signal through β-arrestin 2, an adapter protein involved in receptor signalling and desensitization.[48–52] This type of signalling was shown to support cell survival and proliferation via Akt activation.[53] Heinrich et al[54] have moreover confirmed extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation via CXCL12/ACKR3 mediated β-arrestin 2 signalling. In addition to its well-recognized chemokine ligands CXCL11 and CXCL12, macrophage inhibitory factor (MIF) was recently acknowledged to bind to ACKR3[55] and mediate phosphoinositide-3-kinase-Akt signalling.[56] In addition, MIF/ACKR3 interaction has been shown to result in the activation of the ERK1/2 pathway and receptor internalization.[57] Moreover, a vasodilator hormone named adrenomedullin delivering essential support in cardiac development was also proposed as a ligand for ACKR3,[10,58] although functional consequences remain to be further elucidated.

Clinical Significance of ACKR3

Expression of the main ACKR3 ligands, CXCL11 and CXCL12, is reported to be up-regulated under a wide range of pathological conditions; CXCL12 protein expression rises with inflammation, hypoxia as well as ischaemia,[59,60] whereas CXCL11 expression increases during infection.[55] Genome-wide association studies marked a strong association between *CXCL12* gene locus and CVDs, giving ACKR3 a prominent spot in CVD research.[61] Several studies already revealed noteworthy effects of ACKR3 in CVDs. Li et al[44] developed a wire-induced carotid artery injury model in mice with ubiquitous genetic ablation of ACKR3 to study its role in atherosclerosis. Their results showed significant increases in blood cholesterol due to reduced cholesterol uptake by adipose tissue along with advanced atherosclerotic lesions in mice. These findings clearly indicate an atheroprotective role of ACKR3 through lowering blood cholesterol levels and preventing hyperlipidaemia.

Recently, a study by Hao et al[62] demonstrated a protective role of endothelial ACKR3 in vascular and cardiac remodelling after MI on account of its role in endothelial cell proliferation and angiogenesis. The latter complements previously established roles of ACKR3 in the vascular endothelium presented by Dai et al.[63] According to their results, the interaction of both ACKR3 and CXCR4 with CXCL12 similarly accounts for proliferation and transmigration of endothelial progenitor cells (EPCs), although ACKR3 is especially responsible for the survival of EPCs as well as the adhesion of these cells onto the

endothelium. These findings were later confirmed by Yan et al[64] (except for the role of ACKR3 in EPC proliferation). EPCs are fundamental regulators of neovascularization in response to tissue ischaemia.[65] While these and other studies underline a crucial role of ACKR3 in endothelial cells and highlight the therapeutic potential of ACKR3 in angiogenesis,[66,67] other findings demonstrated a function of ACKR3 on vascular smooth muscle cells (VSMCs).

VSMC migration is an important process during atherosclerotic plaque development necessary to initiate fibrous cap formation, which stabilizes plaques and decreases the risk of plaque rupture and subsequent thrombosis. Interestingly, ACKR3 was described to induce VSMC migration in response to CXCL11 as a result of ACKR3 and β-arrestin 2 interaction.[49] This discovery is in sharp contrast to the notion that ACKR3 is not involved in chemotaxis due to its incapacity of G-protein signalling.[49] Hence, a detailed study investigating the role of VSMC-specific ACKR3 in the onset of atherosclerosis would be of great benefit to CVD research. This would also be a significant addition to the novel role of ACKR3 in the management of thrombosis: MIF-mediated Akt signalling through ACKR3 was shown to decrease apoptosis and promote survival in platelets,[56] which could have a crucial impact on CVDs offering an outstanding therapeutic potential.

Although these studies clearly demonstrated a protective role of ACKR3 in CVDs, there are also indications of its potential detrimental effects. A key event driving foam cell formation in atherosclerotic lesions is monocyte to macrophage differentiation. Ma et al detected ACKR3 in the macrophage-positive area of aortic atheroma of *Apoe*$^{-/-}$ mice, but not in healthy aorta.[68] Further research demonstrated influence of ACKR3 on inflammation, a fundamental process aggravating atherosclerosis.[69–71] Finally, ACKR3-driven cell adhesion[38,63,64,72] may be another pro-atherosclerotic event as it might enhance leukocyte adhesion onto the endothelium and thus transmigration and influx into atherosclerotic lesions. These theories yet remain to be elucidated for a better understanding of the specific roles of ACKR3 in CVDs.

The precise impact of ACKR3 in health and disease is a topic under debate due to its wide array of functions. Nevertheless, it is evident that ACKR3 is a significant modulator in CVDs, although a unique function to ACKR3 cannot be assigned, as it has numerous functions in different cell types which reflect great discrepancies depending on the disease model.

ACKR4

Receptor Characteristics and Signalling

ACKR4 binds the homeostatic chemokines CCL19, CCL21, CCL25 and CXCL13 and has been attributed scavenging properties.[73] Few studies investigated the functions of ACKR4 in vivo and it has been proposed that ACKR4 plays a crucial role for the compartmentalization of CCL21 chemokines in lymph nodes. Ulvmar et al reported a selective expression of ACKR4 in lymphatic endothelial cells of the outer wall of lymph node cortex. Such expression establishes a gradient of the chemokine CCL21 between the sub-capsular sinus and the paracortex area.[74] Consequently, CCR7 positive dendritic cells following this CCL21 gradient entered the lymph node parenchyma. These findings suggest a critical role of ACKR4 in cell chemotaxis into lymph nodes.

Clinical Significance of ACKR4

The significance of ACKR4 in CVDs has so far not been investigated. However, given that CCR7 positive cells play an important role in atherosclerosis[6] and that CXCL13 and CCL21 were shown to be highly expressed and important chemokines for lymphocytes clustering in TLOs,[18,75,76] it would be interesting to determine the role of ACKR4 in the formation of ATLOs.

Conclusion

Research focusing on the prevention/treatment of CVDs aims to identify molecular players in this complex and multifaceted disease with the ultimate goal to develop suitable drugs to prevent or treat cardiac diseases. While 'classical' chemokine receptors have been extensively studied in CVDs during the last two decades, the roles of ACKRs in CVDs are still only poorly understood. Therefore, more efforts are needed to better understand ACKRs functions in CVDs, thereby paving the way towards new therapeutic targets.

Note

After the acceptance of the current manuscript, a study by Girbl et al demonstrating a new function for ACKR1 in leukocyte trafficking was published. This study showed that ACKR1, not only is involved in leukocyte adhesion[11], but can also regulate leukocyte transendothelial migration. Indeed, CXCL2 produced by neutrophils is deposited on ACKR1 at endothelial junctions, and ACKR1-presented CXCL2 facilitates unidirectional luminal-to-abluminal migration of neutrophils.[95]

Funding

The authors' research is supported by the DFG (SFB1123 TP A1) to Y.D. and C.W., by the DFG (SFB1123 TP A10) to J.D. and C.W. and by the Alexander von Humboldt Foundation to E.P.C.v.d.V.

Conflict of Interest

None declared.

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