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Endothelial cell regulation of leukocyte infiltration in inflammatory tissues

A. Duperray,[1,CA] A. Mantovani,[2,3] M. Introna[2] and E. Dejana[1]

[1]CEA, Laboratoire d'Hématologie, INSERM U 217 DBMS CEN-G, Grenoble, France; [2]Istituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy and [3]Section of General Pathology, Dept of Biotechnology, Università di Brescia, Italy

[CA]Corresponding Author

ENDOTHELIAL cells play an important, active role in the onset and regulation of inflammatory and immune reactions. Through the production of chemokines they attract leukocytes and activate their adhesive receptors. This leads to the anchorage of leukocytes to the adhesive molecules expressed on the endothelial surface. Leukocyte adhesion to endothelial cells is frequently followed by their extravasation. The mechanisms which regulate the passage of leukocytes through endothelial clefts remain to be clarified. Many indirect data suggest that leukocytes might transfer signals to endothelial cells both through the release of active agents and adhesion to the endothelial cell surface. Adhesive molecules (such as PECAM) on the endothelial cell surface might also 'direct' leukocytes through the intercellular junction by haptotaxis. The information available on the molecular structure and functional properties of endothelial chemokines, adhesive molecules or junction organization is still fragmentary. Further work is needed to clarify how they interplay in regulating leukocyte infiltration into tissues.

Key words: Adhesion molecules, Chemokines, Cytokines, Diapedesis, Endothelium, Extravasation, Inflammation, Leukocytes.

Introduction

Circulating leukocytes migrate from the vessels and enter tissues under normal or pathological conditions. Whereas monocytes, lymphocytes and natural killer cells exhibit a significant spontaneous migration through resting endothelial cells (EC), neutrophils and eosinophils require chemotactic stimuli and/or endothelial cell activation.[1–3] Cell migration across endothelial monolayers involves leukocyte adherence to the endothelium, crawling on the endothelial surface and penetration between endothelial clefts.

Endothelial cells can actively regulate leukocyte infiltration in inflammatory tissues through different mechanisms such as vasodilatation, release of chemotactic cytokines, expression of adhesion molecules and opening of interendothelial junctions (Fig. 1).[1,2,4–6]

All these reactions act in concert in localizing leukocytes and in facilitating their passage through the interendothelial junctions. Inflammatory stimuli are able to activate endothelial cells inducing their functional reprogramming toward a 'proinflammatory' phenotype.[5] Interleukin-1 (IL-1) or tumour necrosis factor (TNF) induce production of the vasodilatatory mediators such as prostacyclin and nitric oxide,[5,7,8] as well as the synthesis of a large series of adhesive molecules[1] and chemokines[5], and cause endothelial increase in permeability and alteration of junction organization.[6,9,10] In addition to 'classic' inflammatory agents, stimuli associated with the development of atherosclerotic plaques (such as minimally oxidized low-density lipoprotein [LDL]) can also modify endothelial cell reactivity and induce monocyte and lymphocyte infiltration into the vessel wall.[11] In a general sense atherosclerotic plaque evolution presents many similarities with inflammatory reactions.

In this review we will focus concisely on the role of endothelial cells in promoting leukocyte infiltration in tissues. In particular, we will consider chemokine production, expression of adhesive molecules and regulation of junction organization. Previous reviews of this rapidly expanding area of research provide the background and framework for this contribution.[1,6,10,12,13]

Chemokines

The proinflammatory chemokines are a family of 16 homologous low molecular weight (8–10 kDa) proteins. They activate different leuko-

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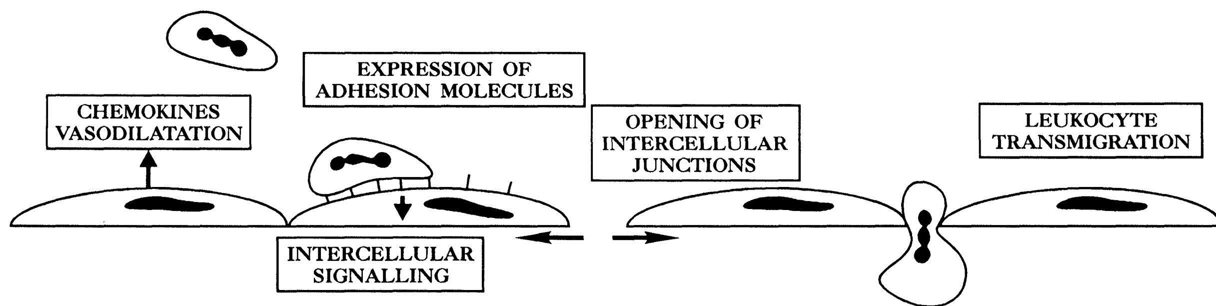

FIG. 1. Leukocyte extravasation as a multistep process regulated by the endothelium.

Table 1. The chemokine family

α-chemokines (C–X–C)	β-chemokines (C–C)
IL-8	RANTES
GRO-α-β,-γ	MCP-1,-2,-3
IP-10	MIP-1α
ENA-78	MIP-1β
MGSA	
NAP-2	

For details see References 14 and 15.

cyte subtypes inducing a large set of responses including change in cell shape, release of enzymes, formation of bioactive lipids, respiratory burst and most importantly activation of adhesive molecules and chemotaxis.[14,15] One of their characteristics is the presence of four cysteines, conserved in all members of the family. They can be subgrouped in α-chemokines (Table 1) when the first two cysteines are interrupted by one amino acid (C–X–C) and β-chemokines when they are together (C–C). α-Chemokines act on neutrophils, β-chemokines activate monocytes, eosinophils and basophils.[14,15]

In vitro studies: Endothelial cells produce various chemokines in response to signals representative of inflammatory reactions, immunity and thrombosis.[5] Inflammatory cytokines (IL-1 and TNF) and bacterial endotoxins induce expression and release of IL-8 and GROα.[16–23] Induction of IL-8 expression is associated with and depends on gene transcription.[20] IL-4 and IL-13 are weak inducers of IL-8 expression and amplify induction by inflammatory cytokines.[24,25–28] Histamine induces IL-8 production in EC.[29] Hypoxia has recently been shown to induce IL-8 and MCP-1 expression in EC, a finding potentially relevant for pathological conditions in which activation and recruitment of leukocytes may amplify tissue damage.[30,31] Platelets contain IL-1 and, when they interact with vascular EC, induce IL-8 gene expression.[32]

As a result of proteolytic cleavage, IL-8 versions with a different NH_2 terminus and length can be produced.[14] It has been suggested that EC release predominantly a 77-amino acid version of IL-8, which is a less active species at activating leukocytes than the most common 73-residue form.[23,33] The proteolytic conversion to smaller versions of the molecule can be catalysed by thrombin.[33]

The influence of IL-8 on the interaction of polymorphonuclear cells with vascular EC has been the object of seemingly conflicting observations, which seem now to reflect different experimental protocols and, most interestingly, different functions exerted by this cytokine under different pathophysiological conditions. IL-8 increased the adhesiveness of normal polymorphonuclear leukocytes for normal EC.[34] In apparent contrast with these findings, EC-derived IL-8 was reported to inhibit binding of the polymorphonuclear leukocytes to activated EC.[23] Although it elicits polymorphonuclear leukocyte extravasation when given locally, IL-8 inhibits recruitment if administered systematically by the i.v. route.[35,36] The seemingly paradoxical anti-inflammatory effects of high levels of systemic IL-8, possibly dependent upon the action of a reverse chemotactic gradient and leukocyte deactivation, may represent a feedback mechanism to control tissue damage.

The role of IL-8 produced locally by vascular cells was reexamined using reconstructed vessel wall models.[37] Unequivocal evidence was obtained for the importance of IL-8 in transendothelial migration induced by inflammatory cytokines.[37,38]

EC of postcapillary venules bind IL-8, possibly via heparin-like molecules.[39] EC of postcapillary venules in kidney and other tissues express the promiscuous chemokine receptor present also on erythrocytes and known as Duffy antigen.[40,41] This receptor is present on EC of both Duffy+ and Duffy− individuals and may serve to present chemokines to circulating leukocytes. Solid phase IL-8 elicits haptotactic migration.[42] Thus, locally

produced IL-8 may be retained on the surface of EC and activate adhesive interactions and migration.[39]

EC activated *in vitro* by inflammatory cytokines express GROα, which according to one report, could in turn act on EC.[17] It has been suggested that EC-bound GROα may promote monocyte adhesion.[43]

IP10, a member of the C–X–C family but unique in that it attracts monocytes, is expressed in certain endothelia of mice exposed *in vivo* to IFNγ or to lipopolysaccharides (LPS).[44,45] There are no reports on *in vitro* expression of this chemokine in EC.

EC produce substantial amounts of the C–C chemokine MCP-1.[21,22] The proinflammatory signals IL-1, TNF and, to a lesser extent, endotoxin are potent stimuli for MCP-1 production.[21,22] IL-4 and IL-13 are active, though less potent inducers of MCP-1 expression.[25–27] IFNγ was recently shown to induce MCP-1 in human microvascular EC.[46] M-CSF was reported to induce MCP-1, though we did not detect the M-CSF receptor c-fms in EC by Northern analysis.[47] Given the role that lipids and monocytes play in the natural history of atherosclerosis, it is of interest that minimally modified LDL induce MCP-1 production in EC and smooth muscle cells.[48] Thrombin was recently found to induce expression of MCP-1 in monocytes and, less prominently, in EC.[49] The C–C chemokine RANTES was produced by EC exposed to TNF and IFNγ.[50]

The molecular basis of stimulation of chemokine expression in EC has been studied to a limited extent. Induction by inflammatory signals and thrombin is protein synthesis independent in EC, but, interestingly, not in monocytes.[49] Direct demonstration of enhanced gene transcription was obtained for MCP-1 and IL-8 by nuclear run off analysis.[20,21]

In vivo studies: EC at sites of delayed type hypersensitivity reactions and kidney allograft rejection express the C–C chemokine RANTES.[51,52] *In vivo* studies on chemokines in vessel wall pathology have largely been restricted to atherosclerosis. MCP-1 expression has been detected in atheromatous lesions of rabbits, primates and man.[53–56] IL-8 and MCP-1 mRNA have been detected in increased amounts of aortic aneurisms.[57] Chemokine gene expression has been detected in various cellular elements, including smooth muscle cells, EC and mononuclear phagocytes, with somewhat different results in different studies. In the only study with mAb,[53] cell populations positive for MCP-1 were different in lesions representative of different stages of the natural history of atherosclerosis. EC staining was prominent in diffuse intimal thickening and in fatty streaks, whereas it was weak in atheromatous lesions. Subendothelial macrophages were strongly positive for MCP-1 in fatty streak lesions and in atherosclerotic plaques. In plaques, a few intimal smooth muscle cells stained for MCP-1. These results suggest that EC and macrophages are the major source of MCP-1 in early atherosclerotic lesions.[53] Monocyte adhesion and infiltration is an early event in the natural history of atherosclerosis.[13,11] Mononuclear phagocyte infiltration is also a prominent feature of vasculitis.[58] Locally produced MCP-1 may play an important role in regulating extravasation of leukocytes, of monocytes in particular, in vessel wall pathology.

Endothelial adhesive molecules

The recruitment of leukocytes into sites of inflammation involves a cascade of sequential events controlled by the interaction between adhesion molecules expressed by leukocytes and by the endothelium. This multi-step process is a cell to cell adhesive reaction that involves specific binding of membrane receptors on one cell to counter-receptor structures on the other cell. Several adhesion receptors belonging to different families including integrins, selectins, and immunoglobulin-like molecules have been shown to participate in this mechanism.[1,2] In the current model, selectins are implicated in the initial rolling, while adhesion receptors from the integrin family and the immunoglobulin superfamily are involved in the firm attachment, flattening and extravasation of leukocytes.[1,2,59,60] Leukocytes have to adhere to the endothelium before transmigrating, and it is difficult to distinguish between adhesion molecules involved only in adherence and proteins involved in the transmigration process. However, several studies have shown that intercellular cell adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), platelet endothelial cell adhesion molecule 1 (PECAM-1) and selectins are important for leukocyte diapedesis between endothelial cells.

Selectins: The selectin family comprises three proteins: E-selectin (CD62E), L-selectin (CD62L) and P-selectin (CD62P).[59,61] They all contain a lectin domain, an epidermal growth factor domain, and a variable number of short consensus repeats of 60 amino acids present in the complement regulatory proteins. The three selectin genes are located on chromosome 1.[62,63]

E- and P-selectins are expressed on endothelial cells, while L-selectin expression is restricted to leukocytes. Selectins bind to carbohydrate ligands via their lectin domains. It has been shown that tetrasaccharides sialyl Lewis X and sialyl Lewis A (sLeX, sLeA) have a ligand activity for all the three selectins.[61,64] The role of selectins in leukocyte transmigration is still debated.

E-selectin. E-selectin (CD62E) is a 115 kDa glycoprotein, only expressed on EC after activation by IL-1, TNF-α,[65] or bacterial endotoxin such as LPS.[66] After EC stimulation, newly synthesized E-selectin is rapidly detected with a maximal surface expression after 3–6 h and a return to basal levels within 24 h.[65,67] This rapid down-regulation, although not completely understood, has been explained by the release of a soluble form of E-selectin,[68,69] and internalization of the molecule.[70] This regulation of E-selectin expression might be crucial to control leukocyte accumulation in inflammatory responses. Several ligands for E-selectin have been identified on leukocytes, but have not yet been cloned.[71,72] Monoclonal antibodies specific for E-selectin have been shown to inhibit leukocyte transmigration.[73–76] It has been suggested that binding of leukocytes to E-selectin on activated endothelium upregulates CD11b (Mac-1) on the leukocytes, and induces an increased adhesion through an ICAM-1/Mac-1 interaction.[73,77,78]

P-selectin. P-selectin (CD62P), previously termed PADGEM or GMP-140, is a single-chain glycoprotein of 140 kDa, expressed in platelets and endothelial cells. In platelets, P-selectin is stored in α-granules,[79] whereas in endothelial cells it is found in Weibel–Palade bodies.[80,81] After activation, P-selectin is mobilized to the external plasma membrane within minutes. This increase in P-selectin expression is transient, and the protein is rapidly internalized inside the cell, where it is degraded or recycled.[82,83] P-selectin is also upregulated transcriptionally by TNF-α.[67] Two ligands has been identified: the P-selectin glycoprotein ligand-1 (PSGL-1), expressed on various leukocytes[84] and a 120 kDa ligand expressed only on myeloid cells.[85] P-selectin deficient mice have been shown to be deficient in leukocyte extravasation.[60]

IgG superfamily:

ICAM-1. In general, interaction of leukocytes with ICAM-1 seems to be necessary for their extravasation. ICAM-1 (CD54) is a single chain membrane glycoprotein of 80–115 kDa, with five Ig-like repeats in its extracellular domain.[86] ICAM-1 is moderately expressed on resting endothelial cells, but release of cytokines at sites of inflammation and immune response such as TNF-α, IL-1 or IFNγ results in augmented cellular expression of ICAM-1.[87,88] The expression of ICAM-1 has also been demonstrated on lymphocytes, monocytes and other non-haematopoietic cells, like fibroblasts, epithelial cells and mucosal cells.[87,89] ICAM-1 is a ligand for CD11a/CD18 (LFA-1)[90] and for CD11b/CD18 (Mac-1).[91] The primary binding site for CD11a/CD18 is located in the NH_2-terminal first Ig-like domain of ICAM-1, with domain 2 also involved in this interaction,[92] while the one for CD11b/CD18 is localized to the third Ig-like domain.[93] ICAM-1 is also a receptor for the major group of rhinoviruses[94,95] and the malaria trophozoite *Plasmodium falciparum*,[96] the binding site for both ligands, though distinct from the LFA-1 binding site, is located in the first two domains of the ICAM-1 molecule.[92,97] In addition, ICAM-1 is a receptor for CD43[98] and hyaluronan.[99] The interaction between Mac-1/LFA-1 (CD11a,b/CD18) and endothelial ICAM-1 is a well documented adhesion pathway, important in the adhesion and extravasation of leukocytes.[73,74,100–102] It has been shown recently that fibrinogen (Fg) is a ligand for ICAM-1, and that Fg binding to ICAM-1 results in enhanced adhesion of leukocytes to EC monolayers,[103] and an increase in their transendothelial migration.[104] These results suggest that Fg must act as a bridging molecule: for monocyte and polymorphonuclear leukocyte adhesion, it could bind to leukocyte CD11b/CD18[105] and to endothelial cell ICAM-1, while for lymphocyte adhesion it could interact with two ICAM-1 molecules on opposing cells. This interaction between Fg and ICAM-1 was inhibited by a commercially available mAb specific for ICAM-1, LB2, epitope-mapped to the first immunoglobulin domain of ICAM-1,[97] suggesting that this domain is involved in the Fg interaction with ICAM-1. However, the inhibition obtained with LB2 on Fg-dependent adhesion was only partial, even at a high mAb concentration. This limited inhibition might reflect the fact that LB2 is not reacting with the exact binding site of Fg on ICAM-1, but rather with a nearby site. Alternatively, an unidentified Fg receptor present at the surface of endothelial cells could contribute to Fg-mediated adhesion of leukocytes. Both Fg-mediated leukocyte adhesion and transendothelial migration could be inhibited by a peptide from the fibrinogen γ chain.[106]

VCAM-1. VCAM-1 (CD106) is a transmembrane glycoprotein of 110 kDa expressed only on

cytokine-activated endothelium.[107,108] A protein containing six Ig-like domains was initially cloned (6D VCAM-1),[109] but this form arises from an alternative splicing of a seven Ig-like domain of VCAM-1 (7D VCAM-1), which is the dominant form on activated endothelium.[110–112] VCAM-1 is a ligand for $\alpha4\beta1$ (VLA-4) and $\alpha4\beta7$ integrins.[113–116] VLA-4 binds VCAM-1 through the first and the fourth Ig domain.[117,118] Using monoclonal antibodies, several studies have shown that VCAM-1 is involved in the transmigration of monocytes and eosinophils,[74,75] but its involvement in lymphocyte transendothelial migration remains to be clarified.[119,120]

PECAM-1. PECAM-1 (CD31) is a 130 kDa glycoprotein expressed on endothelial cells, platelets and some leukocytes.[121] CD31 is constitutively expressed on endothelial cells, and its expression is not increased by cytokines.[122] Molecular cloning studies have shown that CD31 is composed of six extracellular Ig-like domains, a short transmembrane region, and a relatively long cytoplasmic tail of 118 amino acid-containing potential sites for posttranslational modifications.[122–125] Alternative splicing of the cytoplasmic tail can generate multiple CD31 isoforms that may regulate phosphorylation, cytoskeletal association and ligand affinity of the protein.[126] CD31 is heavily glycosylated and glycosylation accounts for 40% of the mass of CD31.[123] PECAM-1 appears to be able to interact both with itself in a homophylic interaction and with other molecules in a heterophylic interaction.[125,127] In endothelial cells, CD31 is localized at intercellular junctions,[122,125] and plays an important role in adhesion of endothelial cells.[125] The high level of constitutive expression of PECAM-1 in endothelial cells suggests that its function might be regulated, and phosphorylation of the cytoplasmic domain has been demonstrated.[128] PECAM-1 is directly involved in the process of leukocyte diapedesis between endothelial cells, as demonstrated by inhibition studies using anti-PECAM-1 monoclonal antibodies and soluble recombinant PECAM-1.[129] Leukocytes blocked in transmigration by anti-PECAM-1 antibodies remained attached to the endothelium, clearly implicating PECAM-1 in diapedesis rather than in adhesion.[129]

Regulation of endothelial cell-to-cell junctions

Circulating cells infiltrate into tissues migrating through intercellular junctions. These organelles are formed by a complex network of transmembrane proteins linked to a well developed plasmalemmal undercoat.[130–132] One of the typical characteristics of endothelial junctions is their dynamic organization. Endothelial cells are able to rapidly change the architecture of the junctions to allow the passage of circulating blood cells. This effect, in most cases, is quickly reversible and the endothelium is able to disorganize/reorganize its intercellular junctions within minutes. Interendothelial junctions present a different degree of complexity along the vascular tree responding to different functional requirements.[133] For instance, they are well organized and numerous in large arteries or in the blood vessels of the brain where the control of permeability must be strict, whereas they are very primitive in the post-capillary venules, where cell extravasation and exchange of plasma constituents need to be particularly efficient.[133]

On the basis of morphological and functional characteristics at least four types of junctions have been described in endothelial cells. These are: tight junctions (TJ),[134–136] adherence junctions (AJ),[132] gap junctions[137] and syndesmos.[138]

Although there is a great deal of information regarding the molecules that mediate leukocyte adhesion to the endothelium, the mechanisms by which leukocytes trigger the opening of endothelial cell junctions is still obscure. In many conditions the passage of leukocytes through endothelial junctions is a non-toxic process that does not increase endothelial permeability *per se* or cause vascular damage.[139]

Chemoattractants and adhesive molecules stimulate neutrophils to secrete oxygen free radicals, lipid metabolites and proteases, each of which is a potential agonist of endothelial permeability.[131] However, experimental evidence suggests that these reactive agents are not necessary for neutrophil extravasation.

In patients with chronic granulomatous disease leukocytes are unable to make oxygen metabolites but can extravasate and infiltrate in areas of inflammation and form pus.[139]

Inhibitors of proteases do not affect neutrophil extravasation in different experimental conditions.[139] In addition, the possibility that leukocyte passage through the endothelium requires protease digestion of membrane proteins seems unlikely in view of the very rapid, within seconds, closure and reorganization of the junctions after leukocyte diapedesis.

These observations, however, do not exclude the possibility that oxygen free radicals and proteases might act as contributing factors in leukocyte extravasation, inducing endothelial cell damage and mediating oedema during sustained inflammatory reactions.

The question of how leukocytes pass through endothelial clefts remains open. An interesting possibility is that leukocyte adhesion to endothelial cells could cause a cascade of events that resembles that induced by soluble agonists of endothelial permeability. In particular, leukocyte ligation to endothelial adhesive molecules (such as selectins, VCAM or ICAM-1) could generate intracellular signals similar to those induced by permeability increasing agents. It has been found[140] that endothelial cells respond to neutrophil contact and migration by increasing intracellular calcium. Similarly, inhibitors of intracellular Ca^{2+} block neutrophil transmigration. In addition, ICAM-1 activation by specific antibodies leads to cortactin phosphorylation.[141] This or other signals could induce changes in cleft molecular organization (see above), leading to the opening of gaps between endothelial cells. According to this hypothesis endothelial cells would not only play an important role in regulating leukocyte attachment to their surface but also actively modulate their extravasation.

Leukocytes might find preferential pathways for their passage through the interendothelial clefts. As discussed above, TJ and AJ comprise a system of discrete ion selective pores rather than an absolute seal around the cells.[134] In endothelial cells, the presence of areas of junctionless clefts that regulate the transendothelial transport of high molecular weight proteins has been described.[142] Leukocytes might be directed to these pores through the concentration gradient of specific adhesive molecules such as PECAM. Their passage would require them to squeeze through the pores accompanied by a rearrangement of the endothelial cell cytoskeleton organization around these structures.

There might be differences comparing the modalities of leukocyte extravasation for different types of vessels, for example lymphatic versus large vessels, where the clefts present different levels of complexity. There might also be distinct mechanisms regulating the passage of the different types of leukocytes or of other types of cells.

Concluding remarks

We begin now to understand that leukocytes and endothelial cells are able to communicate and reciprocally modulate their responses. Following inflammatory stimulation endothelial cells attract and localize leukocytes through the release of chemokines and expression of adhesive molecules. Leukocytes in turn might transfer signals to the endothelium releasing soluble mediators, such as cytokines, oxidation products and lytic enzymes. Adhesion of leukocytes to endothelial adhesive molecules might also cause endothelial cell activation facilitating leukocyte passage through interendothelial clefts. Leukocyte extravasation is not always accompanied by endothelial cell damage and an increase in permeability. In contrast, it seems that the opening of endothelial junctions is a well regulated process that is frequently reversible. Future work is required to fully understand how we might modulate the cross-talk between endothelial cells and leukocytes. This appears to be a difficult task considering the complexity and the number of soluble and membrane bound molecules which involved interplay.

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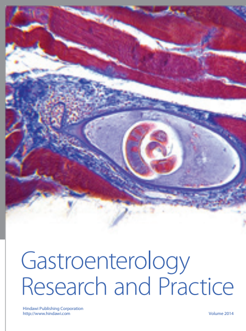

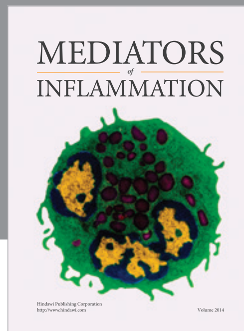

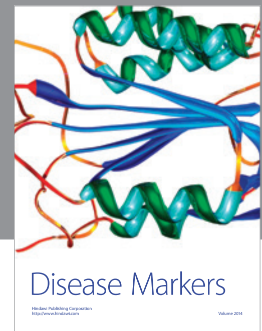

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