Biochemical Pharmacology, Vol. 40, No. 8, pp. 1683–1687, 1990.
Printed in Great Britain.

0006-2952/90 $3.00 + 0.00

COMMENTARY

REGULATION OF THE ADHESION OF NEUTROPHILS TO ENDOTHELIUM

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Neutrophils are an essential cellular component of inflammatory reactions. The importance of neutrophils can be judged by the clinical condition of agranulocytosis in which they are absent. These patients have an abnormal propensity to bacterial infection and, in spite of antibiotic treatment, often die from these infections.

The human bone marrow puts out an average of 2×10^{10} neutrophils each day. Neutrophils normally circulate in blood vessels, lined by a continuous layer of endothelial cells, until programmed senescence when they are removed by the reticulo-endothelial system. There appear to be active mechanisms which ensure that neutrophils do not violate the endothelial cell barrier of the circulation. During infections which usually begin in tissues, it is essential that the normal vascular barriers are altered to allow neutrophils *to migrate from the circulation into the tissues*. The migration of neutrophils into the tissues has two essential components: (a) it is a local event, and (b) it is transient. These two features serve to limit the extent and duration of inflammation. Failure of these controls is thought to lead to generalized vascular plugging or chronic inflammation.

An accurate mechanism that regulates the migration of neutrophils, therefore, is essential. This may be achieved at either the level of *adhesion to endothelial cells* (EC†) or the *subsequent emigration* through these cells. Although the precise understanding of these processes is still in its infancy we shall summarize briefly some of the more interesting features.

ADHESION OF NEUTROPHILS TO ENDOTHELIUM

Character of adhesion

Neutrophils that adhere to glass or plastic undergo a characteristic shape change and become flattened [1]. Several groups have observed that neutrophils adherent to endothelium, or proteins derived from endothelium, fail to undergo this shape alteration [1–3]. This observation may have important implications if the primary role of attachment to endothelium is the transmigration of cells; in this case, it would appear important to ensure that the type of attachment is such as to enable movement to intercellular sites appropriate to transmigration.

An additional consideration is that some form of binding, such as seen to opsonized particles, is an important step in stimulation of neutrophil oxidative burst and degranulation [4]. Production of such toxic materials seems to be an undesirable consequence of attachment to endothelium as damage may ensue. There is no evidence that attachment of neutrophils to endothelium causes degranulation and, in fact, neutrophils bound to endothelium produce less O_2^- in response to exogeneous agents than those stuck to plastic [3]. Attempts at showing damage as a consequence of attachment have failed to demonstrate other than small amounts of endothelial cell lysis, as determined by ^{51}Cr release [3, 5, 6], and suggest that binding to EC is not associated with damage. Nevertheless, certain agents that promote adhesion such as the cytokine tumor necrosis factor-α (TNF-α) also stimulate a limited degree of degranulation [7]. This suggests that endothelial cells are exposed to granule contents and may have special mechanisms to protect from damage. It thus appears that neutrophil adhesion to endothelium is designed to ensure rapid migration and not to cause endoethelial cell damage and to be characterized by a "rounded" rather than a flattened or polarized appearance.

Site of adhesion

Monocytes have been noted [8] to bind preferentially to the intercellular junction of confluent endothelial cells. For neutrophils this is less certain. It seems that the site of primary attachment is random [9], but cells are concentrated at intercellular junctions when stimulated to migrate to extravascular sites. This may be the result of rapid movement to these areas perhaps due to the cell surface near these junctions being more adhesive. This finding may be relevant to the mechanism of migration which takes place through cell–cell junctions [10].

REGULATION OF ADHESION

Neutrophils

Neutrophils "activated" by agents such as f-formyl-methionyl-leucyl-phenylalanine (FMLP) or C5a [11]

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† Abbreviations: EC, endothelial cells; ELAM, endothelial-leukocyte adhesion molecule; FMLP, f-formyl-methionyl-leucyl-phenylalanine; LAI, leukocyte-adhesion inhibitor; PAF, platelet-activating factor; PMN, polymorphonuclear leukocyte; TGF, transforming growth factor; and TNF, tumour necrosis factor.

adhere, to a greater extent, to endothelial cells than to untreated cells. Should these agents be released into the circulation they will cause a generalized change in adhesiveness of cells and thus not be of special significance for local infection. In addition, adhesion stimulated by FMLP appears to be shear sensitive and transient, and does not lead to transmigration [12]. It is interesting to note that these agents, when presented in a system where gradients can be established, are themselves chemoattractants; thus, their physiological role may be primarily as chemoattractants in the extravascular tissues.

Treatment of neutrophils with TNF-α [13] also stimulates the adhesive capacity. This stimulation is rapid, transient [14], does not involve new protein or RNA synthesis [13], appears to be associated with an increased expression of adhesion molecules [15] on the surface of neutrophils, and appears at least in some ways, similar to that caused by FMLP. Granulocyte-macrophage colony-stimulating factor (GM-CSF), although weaker than TNF-α, has a similar effect on neutrophil adhesion [16, 17]. Since neutrophil granules have been shown to be a cytoplasmic store of adhesion proteins [18, 19], the effect of these agents was felt to be due to a limited degranulation-like process associated with fusion of granules with membrane [20]. Subsequently, it was shown that adhesion can be induced without upregulation of receptor numbers and that enhanced adhesion was more likely to be due to conformational changes in adhesion structures [21, 22].

The possibility that platelet-activating factor (PAF) is the final messenger of these adhesion reactions has also been raised since PAF stimulates adhesion [23, 24] and is made in neutrophils in response to some adhesion-stimulating agents [25] and perhaps even in response to endothelial cell ligands [26]. The primary adhesion-stimulating target of PAF, at least in some systems, appears to be the endothelium [27]. Interestingly, although intracellular PAF can be elevated in neutrophils in response to adhesion-promoting substances, little or no secretion has been demonstrated [23]. Nevertheless, PAF antagonists have inhibited adhesive reactions, and PAF may well be one important intermediate product in achieving the adhesive phenotype [26].

Effects on endothelium stimulating adherence

The observation that cytokines TNF and interleukin-1 (IL-1) stimulate endothelial cells to become more adhesive for neutrophils [12, 28] was important in providing a mechanism of *local change in EC* that could initiate the local emigration of cells in inflammation. Both agents need a 4-hr incubation for optimal effect, and their mechanism of action involves new protein and RNA synthesis. Interestingly, the induced adhesiveness for neutrophils is *transient*, becoming less intense by 24 hr; this contrasts with that for lymphocytes for which adherence is also induced but is still intense at 24 hr [29].

Adhesion due to changes in EC is qualitatively different from that induced by treatment of neutrophils with agents such as FMLP. Stimulation of endothelium by TNF and IL-1 induces an adhesion which is shear resistant and leads to active transmigration [11, 30] and, thus, has direct relevance to mechanisms of inflammation.

Effects of endothelium inhibiting adhesion

There is very little information on what, if any, factors operate to keep the EC from becoming adhesive and how the transience of stimulated adhesion is assured.

Two observations appear to have major impact in this area. First, Wheeler *et al.* [31] noticed that IL-1 treated EC transiently made a molecule, called leukocyte-adhesion inhibitor (LAI), that inhibits the capacity of PMN and, to a lesser extent, monocytes, to adhere to EC in a short (10 min) adhesion assay. The duration of this assay may be significant in that the more conventional 30-min assays may allow some cells to migrate through EC and thus be removed from inhibitory influences. This molecule may be responsible for the transience of IL-1 stimulating EC adhesiveness for PMN [13, 28]. The cloning of this molecule will enable a determination of its potency, and antibodies may help define its role *in vivo*. LAI has been cloned and found to be identical to interleukin-8 albeit with an additional six amino acids [32].

The second observation, that TGF-β inhibits EC adhesiveness and the capacity of EC to respond to TNF [33], suggests that TGF-β may have an *in vivo* role in limiting adhesiveness. The effect of TGF-β on transmigration has not been measured, but since it inhibits TNF-mediated adhesion, it would be reasonable to hypothesize that it also inhibits transmigration.

Recently, immunoreactive TGF-β has been observed in vascular tissues such as the heart, and in increased concentrations around sites of myocardial infarction. In these instances TGF-β was seen in regenerating EC (and even in PMN!) [34]. These observations suggest that, especially under conditions of regeneration, TGF-β may ensure that new vessels remain unoccluded. Clearly, these observations suggest that a failure in production of TGF-β could be as important as the elaboration of TNF or IL-1 in stimulating adhesion changes. Since *in vitro* TGF-β needs at least a 9-hr period for its action, it is likely to be more involved in chronic changes.

Another aspect of the effect of TGF-β on endothelium is potentially important. Under certain growth conditions, associated with prolonged *in vitro* culture, EC lose responsiveness to TGF-β [33]. This suggests that in order to develop inflammatory reactions one needs not only the presence of pro-inflammatory cytokines such as TNF-α, but also either the disappearance of TGF-β from the microenvironment or change in EC in which responsiveness to TGF-β is lost. This model is in keeping with the general view that endothelial integrity is actively controlled and needs more than one signal for disintegration.

MOLECULES INVOLVED IN NEUTROPHIL ADHESION

Cell–cell adhesion is mediated, at least to a large part, by interactions between cell surface proteins. The major neutrophil adhesion ligand is recognised

by antibodies against CD11-CD18. This group of molecules (or integrins) consists of a heterodimer of one beta chain (CD18) associated with one of three alpha chains: CD11a marks the LFA-1 heterodimer, CD11b the Mac-1, and CD11c the gp150,95 molecule. A congenital absence or reduction of CD18 results in widespread abnormality of neutrophil adhesion and severe bacterial sepsis and premature death [35, 36]. Similarly, administration of anti-CD18 antibodies to animals inhibits neutrophil adhesion and migration and causes marked susceptibility to several forms of infections [37, 38].

The information on molecules involved in resting adherence is confusing as two groups claim either CD11a [39] or CD11b [40] as being mainly responsible. The discrepancy may be due to resting adhesion being very low and antibody mediated changes being of small amplitude. It is agreed, however, that FMLP-stimulated adhesion involves in approximately equal portions both CD18a and CD18b [39, 40].

The situation is even more complicated when the endothelial counterparts for CD11/18 are investigated. The ligand on EC (and other cell types) for CD11a is ICAM-1 [41]. However, after FMLP stimulation of the neutrophil, CD11b also recognises ICAM-1 [40]. The degree of involvement in adhesion of these neutrophil integrin molecules also changes with the duration of endothelial activation. LFA-1 and Mac-1 predominate in early adhesion with gp150,95, becoming involved in more chronic adhesion [39].

There are at least two other ligands involved in adhesion to endothelium. ICAM-2 has now been cloned; it binds to LFA-1, but its role in adhesion is not yet defined [42]. The endothelial-leukocyte adhesion molecule (ELAM) is a molecule on EC, transiently expressed after TNF and IL-1 treatment [43, 44]. This molecule is responsible for a part of the increased adhesion seen after TNF-α or IL-1 treatment of EC. It belongs to the "lectin-epidermal growth factor-complement" (LEC) class of cell adhesion molecules (CAM) [45], is responsible for a major portion of the adhesion in patients lacking CD18, and is likely to be involved as the alternative adhesion momecule in anti-CD18-treated models. The receptor on neutrophil for ELAM is not known.

The adhesion of PMN to thrombin or leukotriene C_4 (LTC_4) stimulated EC is, to a large extent, CD18 independent and does not appear to involve ELAM expression over the time periods of stimulation. Thus, these observations provide a presumptive basis for a third, non-CD18 non-ELAM, set of adhesion molecules [46].

As mentioned earlier, evidence is mounting that adhesive phenotype is not explicable merely by a quantitative alteration of adhesion proteins but rather that conformational changes [47] or aggregation in the membrane [48] is responsible.

MIGRATION OF NEUTROPHILS THROUGH ENDOTHELIUM

Although this is the critical step in inflammation, relatively little about neutrophil migration is understood clearly. Chemotactic agents when presented on the abluminal side of endothelial monolayers undoubtedly stimulate transmigration [9, 49]. On the other hand, in examining influences directly on the neutrophil or EC, it appears that migration is not an inevitable consequence of attachment. For example, FMLP-stimulated neutrophils showing increased attachement do not transmigrate significantly. (This effect is not to be confused with the chemoattractant role of FMLP.) By contrast, TNF or IL-1 treatment of EC promotes both attachment and transmigration [12], highlighting the critical role of EC in this phenomenon. It appears that the same antibodies that inhibit attachment also inhibit transmigration—hardly surprising in view of the sequence of events. Interestingly, anti-CD18 antibodies in rabbits and mice [38] inhibit neutrophil accumulation only to some pathogens, suggesting that an alternative set of molecules can serve to attach and transmigrate neutrophils. Although ELAM–ELAM receptor appears the logical choice as the second system controlling transmigration, no evidence for the role of ELAM in this process has been reported.

FUTURE PROSPECTS

The prospect of understanding the molecular basis of inflammation is exciting. This will involve:

(a) a full understanding of molecules involved in neutrophil adhesion and transmigration and of the growth factors that regulate their function.
(b) examination of tissues in sites of (chronic) inflammation and delineation of expression of adhesion molecules and growth factors, with a special view to finding abnormalities that predispose or propagate chronic inflammation.
(c) development of agents to interfere with these processes and the testing of these in animal models.

Acknowledgements—We thank Mrs. Mari Walker for typing the manuscript and Drs. A. Lopez and W. Smith for helpful discussion.

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BP 40:8-B