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Mechanisms of the adult respiratory distress syndrome: selectins

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Introductory article

Role of selectins in development of adult respiratory distress syndrome

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The acute lung injury of adult respiratory distress syndrome (ARDS) is characterised by inflammatory cell accumulation and activation in the lung. Selectins are a family of adhesion molecules implicated in leucocyte-endothelial adhesion, whose receptors can exist in a cleaved, soluble form. We investigated whether circulating soluble selectin adhesion molecules, obtained from ARDS at-risk patients, were associated with subsequent ARDS development. Eighty two patients, at risk of ARDS, were enrolled from three well-defined groups (multiple trauma, pancreatitis, perforated bowel). Plasma samples were obtained on hospital presentation and soluble L, E, and P, selectins were quantified with a sandwich enzyme-linked immunosorbent assay (ELISA). Fourteen patients subsequently developed ARDS. Initial plasma soluble L-selectin (sL-selectin) levels were significantly lower in patients who progressed to ARDS compared to those who did not ($p=0{\cdot}0001$; 95% CI for mean in ARDS patients as percent of that in non-ARDS patients, 27–61%). Moreover concentrations were lower than in 62 normal volunteers (range 0·37–6·55, median 1·83 μg/mL, $n=62$), suggesting that a selective reduction of sL-selectin correlates with susceptibility. In addition, a significant correlation was found between low values of sL-selectin and indices of subsequent lung injury including requirement for ventilation ($p=0{\cdot}0001$) and degree of respiratory failure ($p=0{\cdot}0001$). A significant correlation was also found between low values of sL-selectin and patient mortality ($p=0{\cdot}002$). These results elucidate the inflammatory cell endothelial interactions in the early stages of ARDS and may be of prognostic value. (*Lancet* 1994;**344**:215–9)

Early in the course of the adult respiratory distress syndrome (ARDS) – that is, one or two days after the manifestation of respiratory failure – the lung parenchyma is not significantly abnormal and the predominant histological findings are pulmonary oedema and accumulation of polymorphonuclear leucocytes (PMNs) in the pulmonary circulation, interstitium, and alveolar spaces.[1–5] The current paradigm by which PMNs are thought to migrate across the vascular endothelial barrier is a multistage process which begins with a loose attachment of endothelial or cell surface molecules (selectins) to receptors on PMNs or on the endothelium resulting in the phenomenon known as PMN "rolling".[6] This is followed by a more firm adherence between other cell adhesion molecules (integrins) and their specific ligands that is triggered by various factors including interleukin (IL)-8, platelet activating factor, bacterial wall components, complement products, and, possibly, E (endothelial)-selectin.[7–9] Recently, platelet endothelial adhesion molecule (PECAM)-1, another cell adhesion molecule from the immunoglobulin superfamily, has also been linked to PMN transmigration.[10 11]

Donnelly *et al*[12] have recently measured circulating selectin fragments in the blood of patients at risk for ARDS and found that the level of soluble L-selectin was lower in those who progressed to ARDS than in those who did not. This review focuses on selectins and how the observation of Donnelly *et al* might fit into the pathophysiology of ARDS and/or the sepsis syndrome (also known as the multiple organ dysfunction syndrome and the systemic inflammatory response syndrome).

Table 1 Selectin adhesion molecules (from McEver, 1994)[14]

	L-selectin	E-selectin	P-selectin
Synonyms	CD62L LAM-1 LECAM-1 Leu-8 MEL-14	CD62E ELAM-1	GMP-140 PADGEM
Expression	PMNs Monocytes Lymphocyte subsets	Cytokine-activated ECs	Thrombin-activated platelets Thrombin-activated ECs Cytokine-activated ECs
Targets	Activated ECs High endothelial veins	PMNs Monocytes Eosinophils Lymphocyte subsets Some tumour cells	PMNs Monocytes Eosinophils Lymphocyte subsets Some tumour cells

PMN = polymorphonuclear leucocyte; EC = endothelial cell.

Additional information regarding discovery, structure, function, expression, and ligands is available in a review by Bevilacqua and Nelson.[13]

Selectin organisation, expression, and binding

Selectins are composed of a Ca^{2+}-dependent lectin domain at the amino terminal end, an epidermal growth factor-like motif, a series of repeating domains similar to those found in complement regulatory proteins, a transmembrane domain, and a cytoplasmic tail. The lectin domain mediates cell:cell interaction by binding with specific carbohydrates – for example, sialylated, fucosylated lactosaminoglycans (sialyl Lewis X, sLE^x), phosphorylated monosaccharides, and sulphated or phosphorylated polysaccharides. L (leucocyte)-selectin (and other glycoproteins) seem to be important in determining how these carbohydrate moieties are presented to E- and P (platelet)-selectin. PMN rolling under the shear forces that occur in the venous circulation is thought to depend on stable binding of the cytoplasmic domain of the selectins to higher affinity glycosolyted ligands than to sLE^x.[14–16]

L-selectin is constitutively expressed on most circulating PMNs and lymphocytes, and is shed when these cells become activated (table 1).[17–23] Accordingly, L-selectin-dependent adhesion probably requires upregulated ligand expression on the endothelium. Recent data indicate that several non-steroidal anti-inflammatory drugs rapidly decrease L-selectin expression on PMNs.[24]

E-selectin is neither stored in, nor constitutively expressed on, endothelial cells but is synthesised and transported to the cell surface after activation by various cytokines – for example, tumour necrosis factor (TNF)α, IL-1 – or inflammatory stimuli – for example, lipopolysaccharide (LPS). Since expression requires transcription and new protein synthesis, E-selectin expression does not occur until several hours after stimulation.

P-selectin is not constitutively expressed but is stored in Weibel-Palade bodies in endothelial cells and in α granules in platelets, and mobilises to the cell surface minutes after the cells are stimulated by various mediators including histamine, hydrogen peroxide, and thrombin.[18 19 25 26] Upregulated E- and P-selectin expression subsequently diminishes via a process of internalisation (endocytosis).[14] Regulation of the processes by which both upregulation and downregulation of selectin expression occur probably contributes to the extent and duration of the local inflammatory response.

Role of selectins in inflammation

Two unrelated patients with a disorder of fucose metabolism have recently been reported.[27] PMNs from these patients did not express sLE^x and did not adhere to E-selectin or roll on mesenteric venules.[28] Both patients suffered from recurrent bacterial infections (in addition to being of short stature and mentally retarded).

Monoclonal antibodies against E-selectin and L-selectin inhibit TNFα-induced PMN migration into the skin, and thioglycolate-induced PMN migration into the peritoneum, respectively.[20 29] Endothelial P-selectin has been associated with shear- and histamine-induced PMN adhesion.[30 31] PMN recruitment to some, but not all, areas of inflammation is markedly reduced in mice deficient in P-selectin.[32 33] Monoclonal antibodies against L- or P-selectin, or a P-selectin-IgG chimera, decrease the tissue necrosis resulting from ischaemia reperfusion.[34–36]

Although selectins are not thought to activate cells directly, they probably facilitate activation by other molecules by immobilising PMNs on the endothelial surface.[14] Weyrich and colleagues[34] have recently reported that adherence of monocytes to endothelial cells via P-selectin (along with exposure to a second stimulus such as platelet activating factor or bacterial lipopolysaccharide) upregulates TNFα and monocyte chemotactic protein-1 generation through NF-κB signalling (NF-κB is a transcription factor that binds to the regulatory regions of numerous cytokine, adhesion protein, and growth factor/receptor genes containing the appropriate binding site in their regulatory regions). Accordingly, endothelial:monocyte adherence via P-selectin may be a critical step in amplification of the inflammatory response.

Role of selectins in ARDS

Studies in rats indicate that some, but not all, selectins participate in the inflammatory response associated with various PMN-dependent models of acute lung injury (table 2).[33 37–41] Models of lung injury that are PMN-independent also seem to be selectin-independent.

Carden and colleagues found that a monoclonal antibody directed against P-selectin prevented the increase

Table 2 Role of selectins in various models of acute lung injury

	Dependent	*Independent*
PMN-dependent		
IV *Pseudomonas aeruginosa*	E-selectin and/or L-selectin	
Cobra venom factor	P-selectin L-selectin	E-selectin
IT IgG immune complexes	E-selectin L-selectin	P-selectin
Hind limb ischaemia reperfusion	E-selectin	P-selectin
	L-selectin	
IT *Staphylococcus pneumoniae*		P-selectin
PMN-independent		
IT IgA immune complexes		L-selectin P-selectin E-selectin

IV = intravenous; IT = intratracheal.

in pulmonary vascular filtration coefficient that occurred in response to intestinal ischaemia reperfusion, but did so without diminishing the considerable pulmonary sequestration of PMNs that occurred in this lung injury model.[42] This finding suggests that P-selectin might not be responsible for PMN sequestration in the lung, or that it might activate PMNs or modulate transvascular fluid exchange via a non-PMN-dependent mechanism – for example, by altering platelet adhesion.

The function of selectins seems to be organ-specific (as has been shown with the β_2 integrins), as PMN accumulation in the peritoneum in response to *Staphylococcus pneumoniae* instillation is reduced in mice with genetic deletions of intercellular adhesion molecule 1 (ICAM-1) *or* P-selectin and eliminated in those with deletions of ICAM-1 *and* P-selectin, while recruitment to the lung is not affected in either mutant.[33] These data also suggest that the roles of P-selectin and the β_2 integrin adhesion molecules are neither sequential nor completely independent (as implied in the paradigm for PMN transmigration described above).

Possible explanations for organ specificity are that (1) PMNs transmigrate into the lung from capillaries (rather than postcapillary venules, as is the case in the mesentery and skin), and the smaller diameter of lung capillaries, together with the reduced deformability of activated PMNs, suggests that the phenomenon of rolling might be less necessary and less likely to occur in the lung[33 43 44]; and (2) upregulation of endothelial adhesion molecule ligands in response to inflammatory stimuli and/or endothelial proteoglycan expression and resultant cytokine retention may vary from organ to organ,[9 45 46] as well as in different parts of the vascular bed.[33 37] Hypoxia may also contribute to organ specificity of selectin-mediated adhesion as it induces IL-1 production from endothelial cells which, in turn, upregulates endothelial E-selectin and ICAM-1 expression.[47]

The role of L-selectin in PMN rolling in the pulmonary circulation has been questioned by the recent observation that removal of L-selectin from the surface of PMNs by trypsinisation has no effect on PMN sequestration in the lung in response to activation by intravascular complement.[44]

Circulating forms of selectins

Soluble P-selectin has been found in the plasma of normal subjects in a concentration that is sufficiently high to alter PMN:endothelium adhesion by binding to P-selectin receptors on the PMN.[48–50]

After endotoxin-mediated upregulation of E-selectin surface expression decreases, concurrent with the transient (<24 hours) appearance of soluble E-selectin in the plasma.[51] Soluble selectin receptors have also been found in blood as a result of enzymatic cleavage and/or from activation-related shedding. The level of soluble E-selectin increases after endotoxin challenge of human subjects, but the levels are not thought to be high enough to inhibit selectin-dependent PMN adhesion.[51]

L-selectin is cleaved from activated PMNs and has been found in the serum of normal human subjects.[52] High levels of soluble L-selectin inhibit binding of PMNs to endothelial cells and may, therefore, downregulate the inflammatory response.[53]

Soluble L-selectin binds to venular endothelium in regions of inflammation.[22] Reduced levels of soluble L-selectin are consistent with the hypothesis that patients who progress to ARDS have more diffuse upregulation of endothelial L-selectin ligand expression, implying a more severe systemic inflammatory response, than those who do not. This suggestion is supported by the additional finding of Donnelly and colleagues that low levels of soluble L-selectin were also associated with a greater organ failure score. Additionally, the downregulation of PMN:endothelial binding by soluble L-selectin would be diminished.

It would seem more reasonable to link the reduced levels of soluble L-selectin found by Donnelly *et al* in an at-risk population to patients with a more severe form of the sepsis syndrome than to those having ARDS specifically. This distinction could be particularly important in lieu of the observations summarised above which suggest that the selectins, and the associated phenomenon of PMN rolling, might contribute to PMN transmigration in the lung, given the pattern with which solid elements of the blood move through the pulmonary microcirculation.

LEARNING POINTS

* **L-selectin is expressed on circulating polymorphonuclear leucocytes (PMNs).**
* **L-selectin has a role in PMN recruitment to sites of inflammation.**
* **Low circulatory levels of L-selectin reflect more severe or diffuse endothelial damage.**
* **In the context of ARDS, low circulatory levels of L-selectin may be a marker of disease severity.**

Conclusion

Selectins have been clearly linked to (1) PMN rolling in vitro and in situ, and (2) PMN recruitment to sites of inflammation in the skin, peritoneum, and bowel. Data pertaining to PMN-dependent acute lung injury are conflicting, perhaps on a model-specific basis, but the role of selectins in PMN recruitment to the lung has recently been questioned from several aspects.

Low levels of soluble L-selectin probably reflect more severe, or more diffuse, damage to the endothelium in the setting of systemic inflammation rather than being a specific marker of ARDS. Accordingly, as Donnelly *et al* suggest, patients with low levels of L-selectin appear to be at high risk for developing severe disease and it would therefore seem quite appropriate to target this group for new types of anti-inflammatory therapy as they become available.

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