UvA-DARE (Digital Academic Repository)

Neutrophil adhesion molecules and MOF

van Deventer, S.J.H.; Pajkrt, D.

DOI

[10.1007/s001340050362](https://doi.org/10.1007/s001340050362)

Publication date

1997

Published in

Intensive Care Medicine

[Link to publication](#)

Citation for published version (APA):

van Deventer, S. J. H., & Pajkrt, D. (1997). Neutrophil adhesion molecules and MOF. *Intensive Care Medicine*, 23, 487-488. <https://doi.org/10.1007/s001340050362>

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

S. J. H. van Deventer
D. Pajkrt

Neutrophil adhesion molecules and MOF

Received: 28 January 1997
Accepted: 3 February 1997

S. J. H. van Deventer (✉) · D. Pajkrt
Laboratory for Experimental Internal Medicine,
Academic Medical Center, Meibergdreef 9,
1105 AZ Amsterdam, The Netherlands
FAX: +31 (20) 697 7191
e-mail: s.j.van.deventer@amc.uva.nl

Normal neutrophil function is necessary for a successful host immune response in infectious diseases, but a large body of evidence has implicated uncontrolled neutrophil activation in the pathogenesis of organ damage in sepsis and ischemia–reperfusion injury. Because the pulmonary endothelium represents a vast surface area, and the diameter of pulmonary capillaries is relatively small, the lungs are particularly vulnerable to granulocyte-mediated tissue injury, and activated neutrophils are considered to have an important role in the pathogenesis of the adult respiratory distress syndrome (ARDS). Specific adhesion of neutrophils to the vascular endothelium is a multistep process that depends on the interactions of adhesion molecules and the activity of small cytokines with chemoattractant properties, known as chemokines. Under shear stress conditions, inflammatory stimuli, such as endotoxin and various cytokines, induce rapid upregulation of “sticky” molecules, such as P-selectin and in later stages E-selectin, on the luminal surface of the endothelium, which by interacting with neutrophil L-selectin causes the neutrophil to slow down and “roll” over the endothelium. While rolling, the neutrophil becomes activated by platelet-activating factor and interleukin-8, which are present at the endothelial surface, and this results in shedding of L-selectin and a rapid increase in the expression of $\beta 2$ -integrins, in particular CD11b/CD18.

CD11b/CD18 is the ligand for endothelial cell-expressed intercellular adhesion molecule 1 (ICAM-1), and this interaction causes the tight adhesion that is necessary for transmigration into the inflamed tissue. Although these mechanisms have been very well characterized in models using endothelial cell monolayers and in animal models [1–3], the evidence implicating neutrophil-mediated tissue injury in sepsis or ischemia–reperfusion injury is indirect, because reliable techniques for quantitating neutrophil activation and adhesion in critically ill patients do not exist. Most studies have used either fluorescent-activated cell scan (FACS) analysis to measure expression of various adhesion molecules on neutrophils or enzyme-linked immunosorbent assays to quantitate the concentration of soluble adhesion molecules that are shed from endothelial cells or neutrophils. For example, soluble E- and P-selectin plasma concentrations are increased in patients with sepsis and acute lung injury [4, 5], but sL-selectin levels are lower in patients at risk who subsequently develop ARDS [6]. Although the latter observation seems paradoxical, it has been interpreted to represent a reflection of increased binding of sL-selectin to the activated endothelium. In the present issue of *Intensive Care Medicine*, Botha et al. present data on the expression of the integrins CD11a, CD11b and CD18 by circulating neutrophils in injured patients at risk for multiple organ failure (MOF) [7]. The expression of CD11b by neutrophils, but not of CD18 or CD11a, was shown to be consistently increased in this patient population. These data are in accordance with findings in endotoxin-challenged volunteers, where CD11b (and not CD18) upregulation is also the major cause of increased expression of CD11b/CD18 by neutrophils [8]. The present report is one of few studies that have attempted to characterize the adhesive properties of neutrophils in MOF, and, as is often the case with novel findings, raises several questions.

First, in order to be able to bind to ICAM-1, CD11b needs to be activated, and most monoclonal antibodies

used for FACS analysis (including the antibody used in the present study) do not specifically recognize activated CD11b [9]. Hence, the present data do not necessarily indicate that neutrophils from patients at risk for MOF display an increased ability to bind to ICAM-1. On the other hand, many of the stimuli that are necessary for activation of CD11b are presumed to be present in patients at risk for MOF. Another potential confounder in FACS studies on circulating neutrophils in sepsis is the fact that this methodology does not provide information on the status of adherent neutrophils, nor on the ability of neutrophils to transmigrate into tissues. In future studies, such data could be obtained by combining FACS analysis with quantification of neutrophils in bronchoalveolar lavage fluid or with dynamic scintiscanning using Tc-labeled neutrophils. A stepwise multivari-

ate analysis using CD11b as the dependent variable showed a significant correlation only with base deficit. These data may suggest a relationship between these two variables but certainly do not prove causality. Potential explanations for this finding include the possibility that both CD11b expression and base deficit reflect severity of sepsis, or increased neutrophil adherence to the endothelium may result in reduced tissue perfusion and acidosis.

Finally, data such as those presented by Botha et al. may provide a rationale for novel therapeutic interventions, because monoclonal antibodies and "designer" molecules that target neutrophils have experimentally shown potential for reducing end-organ damage in sepsis and ischemia reperfusion injury [10–13].

References

- Kelly KJ, Williams WW Jr, Colvin RB, Meehan SM, Springer TA, Gutierrez-Ramos JC, Bonventre JV (1996) Inter-cellular adhesion molecule-1-deficient mice are protected against ischemic renal injury. *J Clin Invest* 97: 1056–1063
- Mizgerd JP, Meek BB, Kutkoski GJ, Bullard DC, Beaudet AL, Doerschuk CM (1996) Selectins and neutrophil traffic: margination and *Streptococcus pneumoniae*-induced emigration in murine lungs. *J Exp Med* 184: 639–645
- Soriano SG, Lipton SA, Wang YF, Xiao M, Springer TA, Gutierrez-Ramos JC, Hickey PR (1996) Inter-cellular adhesion molecule-1-deficient mice are less susceptible to cerebral ischemia-reperfusion injury. *Ann Neurol* 39: 618–624
- Katayama M, Handa M, Ambo H et al (1992) A monoclonal antibody-based enzyme immunoassay for human GMP-140/P-selectin. *J Immunol Methods* 153: 41–48
- Sakami F, Ishizaka A, Handa M, et al (1995) Soluble form of P-selectin in plasma is elevated in acute lung injury. *Am J Respir Crit Care Med* 151: 1821–1826
- Donnelly SC, Haslett C, Dransfield I, Robertson CE, Carter DC, Ross JA, Grant IS, Tedder TF (1994) Role of selectins in development of adult respiratory distress syndrome. *Lancet* 344: 215–219
- Botha AJ, Moore FA, Moore EE, Peterson VM, Goode AW (1997) Base deficit after major trauma directly relates to neutrophil CD11b expression: a proposed mechanism of shock-induced organ injury. *Intensive Care Med* 23: 504–509
- Pajkrt D, Doran JE, Koster F, Lerch P, Arnet B, van der Poll T, ten Cate JW, van Deventer SJH (1996) Antiinflammatory effects of reconstituted high density lipoprotein during human endotoxemia. *J Exp Med* 184: 1601–1608
- Binnerts ME, van Kooyk Y, Edwards CP, Champe M, Presta L, Bodary SC, Figdor CG, Berman PW (1996) Antibodies that selectively inhibit leukocyte function-associated antigen 1 binding to intercellular adhesion molecule-3 recognize a unique epitope within the CD11a I domain. *J Biol Chem* 271: 9962–9968
- Mulligan MS, Varani J, Dame MK, Lane CL, Smith CW, Anderson DC, Ward PA (1991) Role of endothelial-leukocyte adhesion molecule 1 (ELAM-1) in neutrophil-mediated lung injury in rats. *J Clin Invest* 88: 1396–1406
- Ridings PC, Windsor ACJ, Jutila MA, et al (1995) A dual-binding antibody to E- and L-selectin attenuates sepsis-induced lung injury. *Am J Resp Crit Care Med* 152: 247–253
- Lee WP, Gribbling P, De Guzman L, Ehsani N, Watson SR (1995) A P-selectin-immunoglobulin G chimera is protective in a rabbit ear model of ischemia-reperfusion. *Surgery* 117: 458–465
- Kelly KJ, Williams WW Jr, Colvin RB, Bonventre JV (1994) Antibody to inter-cellular adhesion molecule 1 protects the kidney against ischemic injury. *Proc Natl Acad Sci USA* 91: 812–816