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PLEIOTROPIC EFFECT OF INTERLEUKIN-1 ON ENDOTHELIAL CELLS. E. Dejana (1), F. Breviario (1), F. Bussolino (2), L. Mussoni (1) and A. Mantovani (1). Istituto Mario Negri, Via Eritrea 62, Milano (1) and Università di Torino, Istituto di Igiene, via Santena 5bis, Torino, Italy.

Inflammatory processes are often associated with pathological alteration of the vessel wall and sometimes with local or disseminated thrombotic phenomena. Interleukin-1 (IL-1), a monokine produced by activated cells of the monocyte/macrophage lineage and responsible of most of the changes associated with the inflammatory acute phase response, appears to dramatically modify several endothelial cell (EC) functions. Some groups including ours (for review 1) have shown that IL-1 stimulates prostacyclin (PGI_2), platelet activating factor (PAF), plasminogen activator inhibitor (PAi), thromboplastin (PCA) synthesis by cultured human EC in vitro. In addition IL-1 can act directly on EC to increase neuthophil and other leukocyte adhesion on their surface (2). All these effects, in contrast to previously described inducers, require a long time of interaction (30 min to 4 hours) of IL-1 with EC to be apparent and then last for several hours (4 to 12 hours). The IL-1 effects are concentration dependent (minimal active concentration being about 1 unit/ml) and require protein and RNA synthesis. To better define the structural requirement for IL-1 induced modification of EC functions we compared the activity of different IL-1 molecular species. Our approach is based on the observation that IL-1 is indeed a family of polypeptides biochemically different(3). At least two dissimilar gene products have been cloned with very limited homology (denominated α and β). These molecules, though biochemically different, share common activities and possibly the same receptor in different cell types. On EC we investigated whether the α and β IL-1 forms have similar biological activities (4). All the IL-1 preparations used were active on thymocyte costimulatory assay and comparison was made on the basis of the concentrations of these agents equally active on this assay. Human recombinant IL-1α and β (hr IL-1α and hr IL-1β) were both active in stimulating PGI_2, PCA, PAi production and in increasing neutrophil adhesion to EC. In contrast PAF synthesis was stimulated by hr IL-1α but not by hr IL-1β. Murine recombinant IL-1 (mr IL-1α) highly homologous with hr IL-1α, at concentrations able to maximally activate thymocytes was inactive on PGI_2, PCA and in increasing neutrophil adhesion to EC. In contrast, mr IL-1α was equally effective on PAF production as hr IL-1α. A short peptide fragment of hr IL-1β (fragment 167-171) was synthesized on the basis of its predicted exposure on the surface of the molecule (5). This peptide is also located in a region (150-186) of high homology between hr IL-1α and β sequences. While the peptide showed high thymocyte activation capacity it was inactive on EC activities. Overall these results indicate that the α and β forms of human IL-1 elicit largely but not completely overlapping patterns of response in EC. In addition they suggest that the structural requirement for activation by IL-1 is not identical for thymocytes and EC. These results might provide some clues to novel strategies for modulation of IL-1 vascular and immunological activities.

1. Mantovani A. and E. Dejana (1987) Biochem. Pharm. 36:301.
2. Bevilacqua M. et al. (1985) J. Clin. Invest. 76:2003
3. Dinarello C.A. (1985) J. Clin. Immunol. 5:287.
4. Dejana E. et al. (1987) Blood 69:695.
5. Antoni G. et al. (1987) J. Immunol. (in press).

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INTERACTION OF POLYMORPHONUCLEAR LEUKOCYTES AND ENDOTHELIAL CELLS : FUNCTIONAL CONSEQUENCES. T.J. Williams (1), M. Rampart (2), S. Nourshargh (1), P.G. Hellewell (1), S.D. Brain (1) and P.J. Jose (1). Vascular Biology, MRC Clinical Research Centre, Harrow, Middx HA1 3UJ, U.K. (1) and Dept of Experimental Pharmacology, B-2610 Wilrijk, Belgium (2).

The mechanisms involved in the accumulation of polymorphonuclear leukocytes (PMNs) in an inflammatory reaction are complex. A key phase in this process is the attachment of the PMN to the microvascular (venular in most tissues) endothelial cell, initiated by the extravascular generation of a chemical mediator. Experiments in vitro suggest that mediators, such as C5a, may act in vivo by stimulating the increased expression of the CD18 complex on the surface of the PMN within the venule lumen (1), whereas IL-1 may act by causing the expression of an adhesive molecule on the endothelial cell (2). In vitro the former process is rapid whereas the latter is slow in onset. We have measured the local accumulation of intravenously-injected ^{111}In-PMNs in response to intradermally-injected mediators in the rabbit, in order to investigate possible mechanisms in vivo. PMN accumulation was found to be rapid in onset in response to C5a, the rate of accumulation falling progressively to low levels by 4 hours. In contrast PMN accumulation in response to IL-1 was slow in onset, reaching a peak rate at 3-4 hours. Intradermal injection of the vasodilator prostaglandins PGI_2, PGE_2 and the neuropeptides VIP and CGRP caused a marked potentiation of the rate of leukocyte accumulation. PMN accumulation induced by C5a was associated with increased microvascular permeability, as indicated by the leakage of intravenously-injected ^{125}I-albumin with a time-course in parallel with the rate of PMN accumulation enhanced by intradermally-injected vasodilators. Depletion of circulating PMNs abolishes these responses to C5a (3). In contrast, leukocyte accumulation induced by IL-1 was associated with little plasma protein leakage, even in the presence of intradermal vasodilators. This observation indicates that PMN emigration itself does not lead to increased microvascular permeability. C5a, but not IL-1, may stimulate emigrating PMNs to secrete an endogenous factor that increases permeability by an action on endothelial cells (3). This factor does not appear to be the phospholipid PAF (4). In contrast to the enhancing effects of local PGI_2, intravenously-infused PGI_2 inhibited PMN accumulation induced by C5a and IL-1, and plasma protein leakage induced by C5a (5). This effect is probably mediated by elevation of cyclic AMP in intravascular PMNs. We have shown that C5a stimulation of PMNs in contact with endothelial cells in vitro induces endothelial cell PGI_2 secretion (6). Thus, PGI_2 may be part of a negative feedback system in vivo to control interactions between PMNs and endothelial cells.

These observations provide some clues to the intricacies of mechanisms of leukocyte accumulation in vivo.

References

1. Wallis, W.J., Hickstein, D.D., Schwartz, B.R., June, C.H., Ochs, H.D., Beatty, P.G., Klebanoff, S.J. & Harlan, J.M. (1986). Monoclonal antibody defined functional epitopes on the adhesion-promoting glycoprotein complex (CDw18) of human neutrophils. Blood, 67, 1007-1013.
2. Bevilaqua, M.P., Pober, J.S., Wheeler, M.E., Cotran, R.S. & Gimbrone, M.A. (1985). Interleukin-I acts on cultured human vascular endothelium to increase the adhesion of polymorphonuclear leukocytes, monocytes and related leukocyte cell lines. J. Clin. Invest., 76, 2003-2011.
3. Wedmore, C.V. & Williams, T.J. (1981). Control of vascular permeability by polymorphonuclear leukocytes in inflammation. Nature, 289, 646-650.
4. Hellewell, P.G. & Williams, T.J. (1986). A specific antagonist of platelet-activating factor suppresses oedema formation in the Arthus reaction but not oedema induced by leukocyte chemoattractants in rabbit skin. J. Immunol., 137, 302-307.
5. Rampart, M. & Williams, T.J. (1986). Polymorphonuclear leukocyte-dependent plasma leakage in rabbit skin is enhanced or inhibited by prostacyclin, depending on the route of administration. Am. J. Pathol., 124, 66-73.
6. Rampart, M., Jose, P.J. & Williams, T.J. (1985). Leukocytes activated by C5a des Arg promote endothelial prostacyclin (PGI_2) production via release of oxygen species in vitro. Agents & Actions, 16, 21-22.