Mechanisms of neutrophil-mediated injury

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The interaction of neutrophils with endothelial cells results in damage or killing of the latter. This outcome requires alteration of the endothelial cells such that adhesive interactions between neutrophils and endothelial cells are enhanced. In addition, neutrophil stimulation must also occur. To date, the most important adhesion promoting molecules appear to involve either P-selectin or E-selectin as well as intercellular adhesion molecule-1 (ICAM-1). The 'counter-receptors' for these endothelial adhesion molecules are oligosaccharides (sialyl Lewis^x) presumably present on neutrophils in some sort of glycoconjugate as well as the β2 integrins of the neutrophil (CD11a/CD18, CD11b/CD18, CD11c/CD18). Engagement of these adhesion molecules results in close physical contact between neutrophils and their targets, the endothelial cells. Activated neutrophils release two important types of products involved in endothelial cell injury: proteases and oxygen products. With respect to the former, human leukocytic elastase apparently gains entry to the endothelial cell cytoplasm where it induces limited cleavage of xanthine dehydrogenase, converting this enzyme to xanthine oxidase (x.o.) [1]. The major oxygen product from the activated neutrophil is H_2O_2, which readily diffuses into the endothelial cells. In turn, H_2O_2 causes breakdown of endothelial cell ATP, ultimately to form xanthine and hypoxanthine, substrates for x.o. [2]. Interactions of these substrates with x.o. results in generation of superoxide anion (O_2^-). The availability of iron in the endothelial cell appears to be critical to the outcome of endothelial cell injury, since inadequate availability of iron will block neutrophil-mediated injury of endothelial cells [3]. The requirement for iron has been shown by the use of iron chelators (deferroxamine) or by the use of late passage endothelial cells which show iron depletion [4]. In vitro repletion of intracellular iron by exogenously administered iron restores susceptibility to neutrophil-mediated killing. It appears that the key role of intracellularly generated O_2^- is to reduce the storage form of iron, Fe^{3+}, to its transition state, Fe^{2+}. The latter then reacts with H_2O_2 to cause a single electron addition, producing the hydroxyl radical (HO•). HO• appears to be the toxic oxygen product responsible for endothelial cell injury [3]. The requirement for intracellular O_2^- in neutrophil mediated killing of endothelial cells has been shown by causing the endothelial cell levels of superoxide dismutase (SOD) to increase approximately 10 fold by exogenous addition of SOD [5]. Under these conditions, neutrophil-mediated killing of endothelial cells is greatly attenuated. Thus, the ability of neutrophils to kill endothelial cells requires products both from neutrophils as well as from endothelial cells.

The cytokine, tumor necrosis factor α (TNFα), accentuates neutrophil-mediated killing of endothelial cells by at least four mechanisms. Firstly, TNFα can 'prime' neutrophils for accentuated production of H_2O_2. Secondly, TNFα has powerful effects on upregulation of endothelial adhesion molecules, E-selectin and ICAM-1 [6]. Thirdly, TNFα is an agonist for endothelial cells and can directly induce endothelial cell generation of O_2^- [7]. This pathway of endothelial cell activation appears to be independent of involvement of g-protein, as determined by lack of effects of pertussis toxin pretreatment of endothelial cells. Finally, under special conditions TNFα is directly toxic to endothelial cells although the mechanism related to this toxicity remains to be determined [8].

It is also important to point out that endothelial cells are responsive to a variety of inflammatory mediators that have different effects. Certain mediators will cause conversion of xanthine dehydrogenase to x.o. These include C5a, formyl chemotactic tripeptide and TNFα but not IL-1. In addition, TNFα and C5a can directly cause generation of O_2^- [9]. It is apparent that each of these mediators will also cause priming or direct activation of neutrophils. These data underscore the complexity of neutrophil-mediated killing of endothelial cells and the several mediators that will affect and alter both endothelial cells and neutrophils, the outcome of which is enhanced damage of endothelial cells.

References

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The fate of the neutrophil in vasculitis

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The neutrophil polymorphonuclear granulocyte is the archetypal inflammatory leucocyte. It is a terminally differentiated cell and does not divide once it has left the bone marrow, usually remaining within the blood for several hours before being removed by poorly understood mechanisms by macrophages in the liver and spleen. However, should infection or injury of a tissue generate inflammatory mediators, the neutrophil is usually the first type of leucocyte to leave the blood and migrate to the perturbed site in order to defend the host. The arsenal of the neutrophil is impressive - membrane systems which generate reactive oxygen intermediates and secretory granules containing potent degradative enzymes and toxic cationic proteins ('defensins'). Unfortunately these weapons can inflict 'friendly fire' injury on the