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EDITORIAL

Imaging Vascular Endothelial Activation

Keelan and colleagues exploit some of the recently acquired knowledge in molecular biology, particularly the fundamentally important mechanisms of leukocyte-endothelial adhesion in the inflammatory reaction (*1*). A brief summary of this subject (*2–5*) follows for the stout-hearted (others, please skip the next paragraph).

Of all leukocyte integrin adhesion molecules, only neutrophils activated in inflammatory lesions by local specific chemotactic cytokines such as interleukin-8 (IL-8) possess significant numbers of the surface glycoprotein complexes designated CD11b/CD18 or Mac-1. These complexes interact with endothelial intercellular adhesion molecule-1 (ICAM-1). Another leukocyte integrin, LFA-1, predominantly in lymphocytes but also in neutrophils, has an affinity for endothelial ICAMs (*5*). Other adhesion molecules include three selectins: L-selectin or leukocyte endothelial cell adhesion molecule 1 (lymphocyte homing receptor, MEL-14, gp 90, LAM-1 or Leu 8) is expressed on the surface of neutrophils; E-selectin or endothelial leukocyte adhesion molecule (ELAM-1), expressed on the surface of activated endothelial cells (as described by the authors), interacts with L-selectin, leading to cell margination which is followed by adhesion as a result of the interaction between the neutrophil integrin and ICAM-1; and P-selectin, granule membrane protein-140 (GMP-140) or platelet activation-dependent granule to external membrane (PADGEM, CD62) is released from platelets and endothelial cells, promoting further adhesion of neutrophils and platelets. Thus, adhesion is a multistep process involving multiple alternative receptor-ligand pairs (*5*), and all of the players have not been identified as yet.

In this preliminary paper, Keelan et al. describe an intriguing idea for imaging foci of inflammation with a radiolabeled monoclonal antibody (Mab) specifically for E-selectin expressed on the surface of activated endothelial cells. So far, they have provided quantitative data only in the form of localization ratios of inflamed versus contralateral normal extremities in pigs. Information on the absolute concentration of radioactivity in different inflammatory lesions, including abscesses, also would be important. How would these concentrations compare with those obtained with leukocytes labeled in vitro after their reinjection? To assess the value of this agent, we need to know its distribution in the major visceral organs to judge its efficacy in detecting inflammatory lesions in the torso. Some information on the cardiac, hepatic and skin activity, and plasma disappearance is provided in the companion paper (author's reference 9). Immunohistological studies in this earlier publication showed that the only normal tissue expressing E-selectin was the vascularity of the dermis.

This imaging approach unavoidably introduces the well-known disadvantages of murine Mabs such as the likelihood of HAMA formation. The plasma clearance of the large IgG_1 molecules will be slow. Hence, optimal imaging will probably be seen at 24 hr instead of providing definitive images within a few hours. However, Keelan et al. found that the plasma clearance was faster with the specific Mab than with nonspecific IgG, probably because of better localization in the inflammatory lesion and extraction by the dermal vasculature. Could specific antibody Fab, Fab_1 or $F(ab)_2$ fragments reduce the time interval for optimal imaging?

Many other questions remain to be answered. Is traumatized endothelium activated by mechanisms similar to those of inflammatory lesions? The pathology literature (summarized in companion paper reference 9) indicates that E-selectin expression occurs in many lesions, including chronic dermatoses, "collagen vascular" diseases, allergies, transplant rejection and even lymphoid malignancies. Will leukocytes attracted and bound to activated endothelial E-selectin receptors compete with the binding of specific Mab molecules?

Despite these unknowns, this new approach looks exciting. Hence, further experimental work and subsequent clinical trials appear very worthwhile.

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