all aircraft and at multiple sites on the surface. And better spectral resolution will pin down which spectral regions are doing the absorbing, something which the satellite and surface radiometers used by Cess's and Li's groups couldn't tell us.

'Enhanced cloud absorption' is a difficult pill for the atmospheric solar radiation field to swallow. Its theoretical models, on which large application programmes in remote sensing and climate modelling are based, have been impugned. Now it must backtrack and fill gaping potholes in fundamental knowledge, including: unscrambling the effects of three-dimensional inhomogeneity from true absorption effects; doing spectroscopy in real and artificially generated clouds; and finding out why shortwave models cannot even agree with one another. Accelerated development of promising new tools to map out the internal water structure of clouds is needed, to provide input to three-dimensional radiation modelling. Only with much greater attention to such basics can we begin to close this gaping uncertainty in current models. □

Warren J. Wiscombe is in the Laboratory for Atmospheres, NASA Goddard Space Flight Center, Greenbelt, Maryland 20771, USA.

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LEUKOCYTE ADHESION

Missing link in angiogenesis

Napoleone Ferrara

A FUNDAMENTAL feature of inflammation is the orderly adhesion of white blood cells to the endothelium of postcapillary venules and their subsequent ingress into affected tissues. Leukocyte recruitment may be followed by the formation of new blood vessels (angiogenesis), which happens in a variety of inflammatory disorders including rheumatoid arthritis. In this disease, the new blood vessels play a central pathogenic role as they confer on the inflamed synovium (pannus) the ability to proliferate rapidly and destroy the articular cartilage[1]. Until now, leukocyte/endothelial adhesion and angiogenesis were often considered to be separate processes.

But the discovery of a molecular link is described on page 517 of this issue[2]: Koch *et al.* report that two mediators of leukocyte/endothelium adhesion, E-selectin and vascular cell adhesion molecule-1 (VCAM-1), when tested in their soluble forms, are potent inducers of endothelial-cell chemotaxis *in vitro* and angiogenesis in an *in vivo* model, the rat cornea. They also show that a large portion of the chemotactic and angiogenic activity of synovial fluid derived from patients with rheumatoid arthritis can be neutralized by specific antibodies against E-selectin or VCAM-1. Previous work had shown that the levels of both adhesion molecules are significantly raised in rheumatoid synovial fluid.

Two distinct sets of adhesive, receptor/ligand-like interactions between white blood cells and vascular endothelium have been identified. One involves the integrin family (for example, VLA4) and their ligands (for example, VCAM-1)[3]; the other involves lectin-containing molecules known as selectins, and their carbohydrate ligands immobilized on mucin-like scaffolds[4]. The frequent existence of multiple ligands for each receptor emphasizes the molecular complexity and potential biological diversity of such interactions[4]. Many agents have been identified as mediators of angiogenesis[5], including interleukin-8, TNF-α and the growth factors aFGF, bFGF, VEGF, angiogenin, TGF-α and -β, and HGF.

An earlier report suggested a role for E-selectin and its ligand sialyl Lewis-X/A in bovine capillary morphogenesis *in vitro*[6], but so far any link between leukocyte/endothelial adhesion and angiogenesis has remained hidden. The findings described by Koch *et al.*[2] are important not only because they identify E-selectin and VCAM-1 as potential mediators of the two processes, but also because they provide the first evidence for their involvement in the neovascularization associated with a major inflammatory disorder such as rheumatoid arthritis.

The authors propose the following sequence of events: after binding of leukocytes to vascular endothelial cells, VCAM-1 and E-selectin expressed on the cell surface of endothelial cells are cleaved and shed in a soluble form and are then free to activate and recruit adjacent endothelial cells. Koch *et al.* also explore the mechanism of the endothelial cell chemotactic action of E-selectin and VCAM-1 and show that such an effect is largely mediated by their conventional ligands, sialyl Lewis-X and VLA-4, respectively. A recent study demonstrates that one of the possible ligands for E-selectin is a variant of a receptor for fibroblast growth factor (FGF)[7], a known angiogenic mediator[5]. This finding suggests that E-selectin has the potential to participate in the signal transduction pathways of a conventional angiogenic factor and emphasizes the remarkable biological versatility of the selectin family.

An important question is: do soluble adhesion molecules fully account for the neovascularization that takes place in rheumatoid arthritis? The answer is almost certainly no, considering that rheumatoid synovial fluid contains large amounts of several 'classical' angiogenic cytokines. In particular, previous work[8–10] has shown that interleukin-8, TNF-α, VEGF and HGF, produced primarily by macrophages and synovial-lining cells, may contribute significantly or even substantially to endothelial-cell recruitment and angiogenesis in rheumatoid arthritis. A possible key to this perplexing redundancy is that the actions of these various agents on the endothelium may be, at least in part, temporally and spatially segregated. For example, endothelial-cell-derived E-selectin, which is expressed very early in the inflammatory process[4], may be important in triggering angiogenesis in the initial stages of the disease when neutrophil adhesion is prominent. In contrast, angiogenic factors released by macrophages or synovial lining cells are likely to be important in maintaining angiogenesis in more advanced phases of the disease.

The findings described by Koch *et al.*[2] add to our understanding of the complexity of the regulation of angiogenesis. Validation of these findings would be warranted in animal models of arthritis, where their significance could be investigated free of the high variability inherent in human specimens. Also, it would be interesting to know whether the same mechanism operates in other clinically important conditions such as wound repair and tumour growth, in which leukocyte adhesion and angiogenesis are temporally related. □

Napoleone Ferrara is in the Department of Cardiovascular Research, Genentech, South San Francisco, California 94080, USA.

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