In this issue

Syndecan-4 regulates wound repair in vivo

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Cell surface heparan sulfate proteoglycans (HSPG) can be divided generally into two gene families: syndecans and glypicans. While the glypicans are GPI-anchored, the syndecans are transmembrane-anchored with distinct ectodomains and short cytoplasmic tails. Syndecans bind a range of soluble ligands including growth factors as well as insoluble ligands such as the extracellular matrix protein fibronectin. Indeed, in combination with β1 integrins, syndecan-4–dependent interactions with fibronectin lead to the assembly of focal adhesions and actin stress fibers. Given the fact that syndecan-4 is upregulated in endothelial cells and fibroblasts during wound healing, it has been speculated that this cell-surface HSPG might participate in tissue repair. Echtermeyer and colleagues provide the first characterization of wound repair in syndecan-4 knockout mice. Interestingly, homozygotes as well as heterozygotes for the disrupted gene display marked defects in wound repair and angiogenesis. Of some surprise, in vitro analysis of syndecan-4–deleted fibroblasts demonstrate normal focal adhesion assembly, stress fiber formation and contractility. Likewise, the cells respond to FGF-2 normally despite the ability of syndecan-4 to act as a co-receptor for the growth factor. The –/– cells do, however, display a reduced role of migration in vitro, but in contrast to the in vivo state, only the –/– fibroblasts (and not the +/– fibroblasts) are affected. More telling defects in cell-matrix and growth factor interactions may be compensated for by other members of the syndecan family. These studies not only highlight the importance of syndecan-4 in wound repair, but also underscore the limited ability of in vitro analyses to predict complex behavior in vivo.

Immunoprivilege has its disadvantages

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Increasing interest continues to focus on the possibility that viral infection of the vessel wall can initiate and maintain human vascular disease. While virus is usually cleared from most affected sites, Del Canto and colleagues now report that viruses may evade the immune system by establishing themselves in a protected niche provided by the elastic media of large arteries. Chronic infection then leads to a destructive arteritis associated with a neutrophilic infiltrate. Of note, immunoprivilege arises as a counterproductive consequence of the ability of the elastic media to specifically exclude infiltrating T cells and macrophages. The means by which mononuclear cells, but not neutrophils, are prevented from invading the media remains to be determined, but experiments performed in either interferon-γ (IFNγ)-depleted or IFNγ-receptor-deleted mice clearly establish a role for the cytokine in disease progression. Bone marrow transplants into wild-type or IFNγ-receptor knockout mice further demonstrate that IFNγ limits medial infection as well as disease severity by affecting somatic as well as hematopoietic cell function. Given reports emphasizing the ability of IFNγ to promote vascular pathology in other settings such as arteriosclerosis, this cytokine has recently been considered as a new target for therapeutic intervention. However, as demonstrated in the current study, attempts to intercept IFNγ must be considered carefully as vessel wall disease could be exacerbated depending on the underlying initiating event.

Clearing the way for lipopolysaccharide

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The rapid initiation and execution of a host response to pathogens is critical. In the case of Gram-negative bacteria, lipopolysaccharide (LPS), a major constituent of the outer membrane, provokes a potent, generalized inflammatory response in the infected host by virtue of its ability to bind membrane factors present on the surface of macrophages and other cells crucial to host defense. LPS also binds to circulating plasma proteins such as the LPS binding protein (LBP). However, once the response to Gram-negative bacteria is initiated, there is a need to eliminate LPS from the circulation to minimize potential deleterious effects of an unregulated response. The primary means of eliminating LPS is by its incorporation into lipoproteins. Again, LBP plays a role by catalyzing the transfer of LPS from micelles into lipoproteins. In fact, consistent with the role of LBP and lipoproteins in LPS clearance, among the changes seen in the acute phase response are substantial increases in the circulating levels of LBP and serum lipid and lipoproteins. In this issue, Vreugdenhil et al. offer additional insights into LPS clearance, showing that circulating LBP and LPS are predominantly complexed with apoB-associated lipoproteins — i.e., low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) — in normal and septic individuals. While LBP will bind in vitro to apoA-I, a component of HDL, the basis for the preferential in vivo association of LBP with LDL and VLDL appears to result in part from the considerably greater affinity of LBP for apoB than for apoA-I. Furthermore, LBP, when complexed with LDL and VLDL, appears to enhance LPS binding to these lipoproteins. Additional studies of the interactions of LBP and LPS with apoB, apoE, and perhaps other LDL- and VLDL-associated factors should further understanding of specific mechanisms that regulate LPS levels in infection and inflammation.