Matrix of death

For most normal mammalian cells, survival depends on attachment. By binding to integrins, many extracellular matrix proteins activate survival pathways that prevent detachment-induced apoptosis. But on page 559 Todorovic et al. reveal a matrix molecule that kills instead.

This death matrix protein, CCN1, is selective in its carnage. Endothelial cells are known to thrive on CCN1, but the group now finds that fibroblasts are not so lucky. Many fibroblasts that attach and spread on a CCN1 matrix die, despite activating the FAK–JNK cell survival pathway.

The different outcomes might lie in the combination of integrins and their coreceptors. Endothelial cells use integrin αvβ3 to activate FAK, which turns on multiple survival signals in various cell types. But fibroblasts are also known to interact with CCN1 via integrin αvβ1. Antibodies that blocked this integrin or its syndecan-4 coreceptor prevented apoptosis.

How this integrin activates death is still fuzzy. Bcl family proteins and p53 were necessary, as were caspases-3 and -9. Detachment-induced apoptosis, by contrast, depends on caspase-8. Caspases-3 and -9 are mediators of stress-induced apoptosis, but the authors do not yet know what, if any, cellular stress CCN1 might be triggering.

After development, CCN1 is primarily expressed during inflammation and wound healing. Wounds are sealed by large numbers of fibroblasts that are then removed to prevent scar tissue formation. With its contrasting outcomes, CCN1 may be both the trigger for this massive death and the support system for the renewing vasculature. During development, CCN1 might create a sharp boundary between tissues, as would any other matrix found to be similarly bipolar, by supporting growth of one cell type while simultaneously killing off those of a neighboring tissue.