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.

Transformed fusions

The occasional accidental fusion between somatic cells is probably harmless to an organism, as the resulting cell generally does not divide. But viruses have the ability to create proliferative fused cells, according to Duelli et al. (page 493). The authors wonder whether viruses might thus contribute to carcinogenesis.

The authors were studying human fibroblasts expressing the E1A oncogene when they noticed that the cells fused with normal fibroblasts. The fusogenic activity derived from a contaminating retrovirus, Mason-Pfizer monkey virus (MPMV), in the oncogenic cell line. Exosome-like infectious MPMV particles caused fusion between these cells and the normal fibroblasts. It is not known how the virus causes fusion, although the authors show that exosomal tetraspanins are required.

Virus-instigated fusion is not new, but the products of these fusions were oddly proliferative. The group determined that this ability stemmed from the presence of one of several oncogenes and the ability of the virus to fuse two rather than many cells. Fused cells did not proliferate unless one of the partners expressed an oncogene, such as E1A or c-Myc. Mutant p53 tumor suppressor activity in one fusion partner also led to proliferation of fused cells.

Fusion potentially combines the properties of very different cell types, making the behavior of the resulting hybrid highly unpredictable. Their duplicated centrosomes also make them prone to aneuploidy, which is a common feature of cancer cells. Indeed, recent studies showed that tetraploid cells with mutations in a tumor suppressor generated cancerous aneuploid cells (Fujiiwa et al. 2005. Nature. 1043–1047).

Whether viruses create proliferative fused cells in an organism is not yet known, but a virus that provides the machinery for both fusion and deregulated cell cycles might be especially dangerous. Therapeutic treatments that involve either viral vector sequences (as in gene therapy) or cell fusion (as in stem cell treatments) should thus be carefully examined for potential cancer-causing side effects.
Stuck on a channel

Active Ca\textsuperscript{2+} channels, according to Hudmon et al. (page 537), get their own dedicated Ca\textsuperscript{2+} sensors that cause well-used channels to open with gusto.

Some Ca\textsuperscript{2+} channels, including voltage-gated L-type channels, let through more Ca\textsuperscript{2+} per opening when they are used frequently. This positive feedback, known as facilitation, allows fast-beating cardiac cells, for instance, to beat harder (as during exercise). The new findings reveal that local retention of a Ca\textsuperscript{2+}/calmodulin-dependent kinase, CaMKII, is behind this ability.

CaMKII is activated by autophosphorylation in response to Ca\textsuperscript{2+}/calmodulin. The authors find that CaMKII then tethers itself to the pore-forming \( \alpha_{1C} \) subunit of the L-type channel, which is abundant in heart muscle. Even upon dephosphorylation, CaMKII lingers at the channel.

From this position, the kinase can up-regulate channel activity when Ca\textsuperscript{2+} influx is frequent. The authors show that active CaMKII phosphorylates two regions of \( \alpha_{1C} \) that were previously found to regulate channel activity. Unlike NMDAR-bound CaMKII, which is constitutively active, \( \alpha_{1C} \)-bound CaMKII still depends on Ca\textsuperscript{2+}/calmodulin. This difference might explain why NMDARs are up-regulated for the long term by a brief stimulus, whereas full activity of voltage-gated channels requires repeated activation.

Tethering to \( \alpha_{1C} \) is necessary for facilitation, even though the channel can be phosphorylated by free kinase. The close proximity may allow the kinase to outdo channel-defacilitating phosphatases. Only when Ca\textsuperscript{2+} influx is frequent, and CaMKII activity is repeatedly high, can CaMKII win the fight.

G proteins live in excess

On page 517, Elia et al. show how fly photoreceptors achieve their exquisite sensitivity to a single photon of light. The key is not the number of photoreceptor-activating proteins but the ratios of their components.

Photoreceptor sensitivity depends on extremely low levels of spontaneous activity in the dark. This activity, spontaneous or otherwise, depends on a G protein coupled to the rhodopsin receptor. Rhodopsin activation induces the G protein’s \( \alpha \) subunit to exchange its bound GDP for GTP, dissociate from its binding partner, \( \beta\gamma \), and initiate downstream signaling. The group now finds that excess \( \beta\gamma \) ensures that \( \alpha \) is not activated in the dark.

Wild-type photoreceptors had over twofold more \( \beta\gamma \) than \( \alpha \) and low background activity. Mutants with less \( \beta\gamma \) had much more spontaneous activity. This defect was corrected by simultaneously reducing \( \alpha \) levels in the mutant (thus restoring the \( \beta\gamma \) excess).

Spontaneous activity was actually higher in cells with moderate rather than extreme reduction in \( \beta\gamma \). The authors explain this finding by showing that \( \beta\gamma \) was needed to bring \( \alpha \) to the rhodomere, from which \( \alpha \) signals. Thus, in stronger \( \beta\gamma \) mutants, there was less \( \alpha \) able to signal and hence less spontaneous activity.

The group must now determine how the excess \( \beta\gamma \) limits \( \alpha \) activity. Perhaps it either accelerates GTP hydrolysis on \( \alpha \) to block the downstream cascade or prevents the unsolicited exchange of GDP for GTP on \( \alpha \).

Cadherin rules microvilli

A cadherin in flies concentrates not on sticking cells together, say D’Alterio et al. (page 549), but on controlling the extension of microvilli.

Microvilli are actin-filled apical protrusions on epithelial cells. Actin bundling and polymerizing proteins are the usual suspects regulating microvilli length. But the new results reveal that a plasma membrane protein, a cadherin family member called Cad99C, is also necessary.

Female flies lacking Cad99C had short, misshapen microvilli on their follicle cells, which secrete the material used to make egg shells. Overexpression of Cad99C, by contrast, resulted in abnormally long microvilli.

Mutations in a related vertebrate cadherin, called protocadherin 15 (PCDH15), cause deafness associated with abnormal cochlear microvilli. Scientists have generally guessed that PCDH15 links and aligns microvilli similar to the classical cadherin involvement in adherens junctions. But this might not be the case, based on the new findings. Follicle cell microvilli were too far apart for Cad99C to link them, and Cad99C overexpression created large microvilli that fanned out rather than clumping together.

The transmembrane and extracellular domains of Cad99C were sufficient to control its microvilli function. The authors hypothesize that several Cad99C molecules might interact in cis to stiffen the membrane of a growing microvillus. As another possibility, Cad99C might sense extracellular molecules and transmit their signals to nearby membrane proteins that control actin reorganization.

Excess G\( \beta\gamma \) in normal (left) rhodomeres silences G\( \alpha \) (black). Weak G\( \beta\gamma \) mutants (middle) have enough G\( \alpha \) to create spontaneous activity; strong G\( \beta\gamma \) mutants (right) do not.