IN THE NEWS

The final research frontier?

2001 may be the start of a space odyssey for cell biology research. A collaboration has been set up between NASA's Center for Computational Astrobiology and Fundamental Biology (NCCAFB) and Stanford's Center for Biomedical Computation (CBMC) to conduct research and development in computational biology (Wired News, 30 October 2001). Their goal is to develop new computational methods and apply them to explain how cells function, evolve and are affected by diseases, both on Earth and in space.

"Biological research has always been earthbound, but recent Shuttle experiments made NASA realize that in space, some cellular functions behave differently than they do on Earth," reported Wired News. "For example, one Shuttle experiment showed that human kidney tissue can be grown in space, even though the tissue refuses to grow properly in terrestrial laboratories." Other studies have shown that ovarian cancer cells grow in three dimensions under low gravity conditions, giving a more biologically representative *in vitro* model of a tumour *in vivo*.

The initial research will focus on cell metabolism, using both healthy and diseased cells cultured from studies on Earth and in space. In the future, the scientists hope to simulate the interactions between molecules in a cell.

"This is just the first step", said Dr. Andrew Pohorille, director of NCCAFB, based at NASA's Ames Research Center. "I hope we will eventually grow and involve other institutions to bring all of these minds together to develop a whole infrastructure for biocomputation."

Simon Frantz

CELL ADHESION

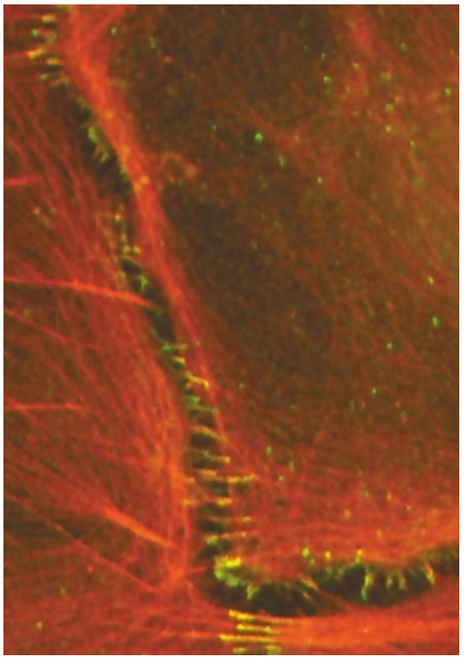
Neighbourhood watch

We often aim to form, maintain and strengthen tight bonds with our neighbours, and our cells are no different. Reporting in the December issue of *Nature Cell Biology*, Elaine Fuchs and colleagues investigated how such bonds are formed, and provide evidence for the essential role of desmoplakin in this process.

Desmoplakin is a cytoskeletal-linker protein that is largely restricted to specialized cell–cell adhesion structures called desmosomes, which are abundant in epidermal cells. Desmosomal cadherins interact through molecules, such as desmoplakin, to link with the intermediate-filament network. As a rare human skin condition has been linked to haploinsufficiency of desmoplakin (that is, a loss of one of the two desmoplakin alleles), this protein seems to be essential for skin formation. Because of this, Fuchs and colleagues generated a conditional knockout of the gene to probe the functions of the desmoplakin protein.

The authors found that mice with this conditional knockout have severe epidermal defects — any stress applied to the skin causes intercellular separation and the skin peels away from the affected pups. At a cellular level, desmosomes lack any interactions with keratin filaments and have an altered composition. In addition, the lower layers of the epidermis have a weakend state of adhesion, which is evident in the splitting of desmosomes after trauma. In desmoplakin-null keratinocytes placed in tissue culture, the overall number of desmosomes is reduced and epidermal-sheet formation is defective.

Most surprisingly, these desmoplakin-null epidermal keratinocytes and epidermal cells from the conditional-knockout pups have a reduced number of adherens junctions. Adherens junctions are adhesion complexes composed of E-cadherins (green in the figure) and catenins. They are distinct from desmosomes, and are linked to the actin cytoskeleton. Recent work has indicated that these two adhesion complexes might interact.



CELL ADHESION

A life or death situation?

Integrins, as cell-adhesion receptors, are usually associated with promoting cell survival, by encouraging cells to attach to appropriate substrata. Indeed, anoikis — death due to cell detachment from the substrate — is thought to exist to prevent anchorage-independent cell growth, a hallmark of tumour cells. However, an integrin antagonist can induce endothelial cell death in otherwise adherent cells, thereby blocking angiogenesis; whereas development can occur normally in integrin-knockout mice. Now, Cheresh and colleagues have reported data in the *Journal of Cell Biology* that help reconcile these findings, describing how fully adherent cells undergo apoptosis when their integrins exist in a unligated state, in a process they have coined 'integrin-mediated death', or IMD.

Cheresh and colleagues studied T24E carcinoma cells in a three-dimensional collagen matrix and found that cells expressing $\alpha v\beta 3$ started to die (by apoptosis) within 48–72 hours in culture. By contrast, T24E cells selected for the absence of $\alpha v\beta 3$ showed increased survival in a collagen matrix, and re-introduction of $\alpha v\beta 3$ into these cells accelerated cell death. Extending the studies to different cell types showed a correlation between cell death and the presence of unligated $\alpha v\beta 3$ which could be suppressed by reducing the levels of endogenous unligated receptor.

To test whether the cytoplasmic domain of integrins mediates this death, the authors expressed chimaeras comprising the extracellular domain of the interleukin receptor CD25 with the cytoplasmic domain of either $\alpha 5$, $\beta 1$ or $\beta 3$ in COS cells. Both the $\beta 1$ and $\beta 3$ chimaeras, but not the $\alpha 5$ chimaera, induced IMD. A series of truncations made in the cytoplasmic domain of CD25–$\beta 3$ showed that a minimal sequence — different from a critical motif known to be involved in 'classical' integrin signalling — conferred the ability of cells to exclude propidium iodide from their nuclei and to cleave poly-ADP ribose polymerase (both are used to indicate apoptosis).