Meeting Report

A testing time for angiogenesis

Cancer biology covers many hot-button topics—from cell cycle to metastasis to apoptosis—but this year it was angiogenesis that was filling the halls of The Moscone Center to bursting. Ever since Jim Watson’s stamp of approval hit the front page of The New York Times, angiogenesis has been the field to watch. But in recent months, some watchers have been quick to broadcast the early failures of antiangiogenic therapies in humans.

Angiogenesis researchers at the meeting noted several potential explanations for these failures. For starters, said Roy Herbst (M.D. Anderson Cancer Center, Houston, TX), “expectations were too high.” Angiogenesis inhibitors are expected to arrest tumors not shrink them: they should prevent further growth of blood vessels into a tumor rather than dissolve existing blood vessels. Sure enough, even in mouse models there was significant tumor growth after antiangiogenic therapies were started, and before those therapies began to reverse tumor growth. That pattern may be tolerable in a mouse, which can apparently withstand a tremendous tumor burden, but not in a human. Most patients, because of standard selection criteria, enter antiangiogenic trials with late-stage disease and only a few months to live.

But patient selection is only part of the story. Many investigators have now shown that different angiogenic factors are produced by different tumors at different times, in a way that is largely unpredictable even within a single tumor type or even single individual. Thus, a therapy that neutralizes only one angiogenic pathway is unlikely to be effective against many tumors.

This makes the work presented by Douglas Hanahan (University of California, San Francisco, CA) all the more interesting. Hanahan first showed that a standard antiangiogenic treatment (an inhibitor of a VEGF receptor [VEGF-R]) was highly effective only when it was used against early stage disease. But he also found that a different inhibitor, named SU6668, was moderately effective against late stage disease, and highly effective when used in combination with the standard anti–VEGF-R treatment.

SU6668 is better at shutting down the PDGF receptor (PDGF-R) than the VEGF-R. Hanahan suggested that it was preventing a signaling event between endothelial cells and neighboring pericytes—signaling that is needed not for angiogenesis but to maintain the integrity of the newly established endothelium.

Other combination therapies were also mentioned at the meeting. Mike O’Reilly (Harvard Medical School, Boston, MA), the codiscoverer of the famous angiostatin, said that antiangiogenic therapies are now seen more as adjuvants to standard chemotherapies. “Angiogenesis inhibitors,” he said, “should not be considered the magic bullet.”

Reference: Hellström, M., et al. 2001. J. Cell Biol. 153:543–554.

An integrin that keeps it together

When it comes to cancer prognosis, adhesion molecules are generally classified as either good cadherins or bad integrins. The cell–cell adhesion mediated by cadherins sticks potentially metastatic cells together so that they cannot spread, whereas the cell–extracellular matrix (cell–ECM) adhesion provided by integrins helps those same cancer cells to pull away from the pack and search out new sites for growth. But new results from Elizabeth Robinson, Siobhan Corbett, Ramsey Foty, and colleagues (University of Medicine and Dentistry New Jersey, New Brunswick, NJ) indicate that some integrins weigh in on the good side.

Robinson already had clues from clinical studies that expression of the integrin α5β1 was associated with a more positive prognosis. So she overexpressed the integrin in tissue culture cells, and measured its ability to stick cells together. The stickiness test involved measuring the resistance of cell aggregates to compression. Cells making α5β1 were, she found, even more resistant to compression than cells expressing a cadherin.

This effect was dependent on the presence of the α5β1 substrate fibronectin, but was not dependent on expression of a high level of cadherins. The α5β1 is unique amongst the integrins in its ability to organize fibronectin into a matrix. This ability may allow it to convert multiple cell–ECM links into indirect cell–cell connections that can resist both compression forces and metastatic signals.

Reference: Foty, R.A., et al. 1996. Development. 122:1611–1620.
Amoebas on the move

Even complete inhibition of a standard pathway for cancer cell movement might not be enough to prevent metastasis, according to Peter Friedl (University of Würzburg, Würzburg, Germany). He finds that cells inhibited for adhesive migration resort to an amoeboid movement that might be just as good at dispersing cancer cells.

This is not Friedl’s first indication that cancer cells have more than one migration strategy. He has seen cells moving in a variety of configurations—as solid strands, single files, cell clusters, and single cells—suggesting that a variety of mechanisms may be at work. Clustered cells, for example, “behave as a social unit,” he says, with adhesive integrins clustered and sometimes expressed only at the leading edge of the front-most cells.

This sociability can be blown apart with an anti-β1-integrin antibody. The clusters lose polarity, and cells detach and initiate an amoeboid form of crawling that resembles the movement strategy of human T cells. Rather than blazing a path through extracellular matrix, the cells squeeze through the tiny holes present in the intact matrix.

Friedl saw a similar form of amoeboid crawling after treatment of cancer cells with a cocktail of protease inhibitors. Most cancer cells move by chewing a path through the dense extracellular matrix, and Friedl can visualize the destruction that such cells leave in their wake. Many of the drugs that inhibit matrix metalloproteases are aimed at disrupting this process. But when Friedl completely disrupted this process with a cocktail of protease inhibitors, the cells merely switched to the amoeboid form of movement.

Clinical studies were already making it clear that inhibiting a single matrix metalloprotease might not be enough. As Friedl stated, cancer cells “have scissors, they have knives, they have saws, they have swords maybe, and it doesn’t make sense just to take away the scissors.” But now his work suggests that even the perfect inhibitor—one that takes away all those sharp implements—may not suffice.

Reference: Hegerfeldt, Y., et al. 2002. Cancer Res. 62:2125–2130.

The Rb pretenders

As a model for human disease, mice lacking a copy of the Rb tumor suppressor are a distinct failure. For starters, they don’t get retinoblastoma. Even patches of eye cells that lack both copies of Rb don’t become tumors.

Tyler Jacks (Massachusetts Institute of Technology, Cambridge, MA) wondered if the Rb-related proteins p107 and p130 were filling in for Rb. This was consistent with the work of Anton Berns (Netherlands Cancer Institute, Amsterdam, Netherlands), who showed that mice lacking both Rb and p107 developed retinoblastomas. Perhaps the mouse versions of p107 and p130 were better than the human versions when it came to filling in for Rb and acting as tumor suppressors.

But Jacks’ recent experiments suggest another solution. When Jacks eliminated Rb abruptly in adult mice, using an inducible recombinase to flip the gene out of the chromosome, the mice rapidly developed retinoblastomas. Thus, it seems that p107 and p130 (and perhaps other proteins) can fill in for Rb, but only if Rb is absent throughout the life of the mouse.

Here’s one clear example of reprogramming following knockout,” said Jacks. Only when the cells lose Rb acutely, he said, is there insufficient time for compensation, allowing the immediate function of Rb to become apparent.

Reference: Sage, J., et al. 2000. Genes Dev. 14:3037–3050.

Coming back to life

Senescent cells can be revived, according to results presented by Tyler Jacks (Massachusetts Institute of Technology, Cambridge, MA) and Christian Beausejour (Lawrence Berkeley National Laboratory, Berkeley, CA). Furthermore, says Beausejour, the ease with which cells can be revived depends on how far they have entered into the senescent program.

Beausejour, working with Judith Campisi, studied human fibroblasts that had shut down because repeated replication cycles had shortened their telomeres to a critical length. For some cells—those that had recently become senescent—all they needed to get going again was inactivation of the p53 tumor suppressor. The primacy of this pathway is not surprising, as shortened telomeres are a form of DNA damage, and p53 is known to be an expert at detecting other forms of DNA damage.

If cells remained senescent for longer, however, then inactivating p53 was not enough. In this case, Beausejour had to turn off the Rb tumor suppressor pathway as well, suggesting that this pathway gets induced later in senescence. Jacks found that shutting off the Rb pathway was sufficient to reverse the senescence of mouse cells. Senescent mouse cells may not induce the p53 pathway, said Beausejour, because their telomeres are much longer than those of human cells.

Reference: Campisi, J. 2001. Trends Cell Biol. 11:527–531.