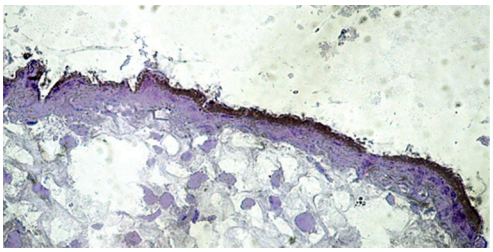
Text by William A. Wells
wellsw@rockefeller.edu


MANTOVANI/NAS

D6 (black) protects placenta from invading chemokines.

Chemokine blockade

A fetus must be sheltered from any inflammatory battle taking place in the mother. Now, Yeny Martinez de la Torre, Alberto Mantovani (University of Milan, Italy), and colleagues report that a decoy receptor in the placenta captures potentially dangerous pro-inflammatory chemokines from the mother. This scavenging suppresses inflammation and prevents fetal loss.

Decoy receptors such as the D6 receptor bind many inflammatory chemokines without activating intracellular signaling. Instead, the receptor and chemokine are internalized and the chemokine is destroyed.

The Italian group confirmed that D6 is expressed in the placenta, specifically on the apical side of syncytial trophoblasts. This is the side looking at the maternal blood and thus "a strategic location at the very interface between mother and fetus," says Mantovani.

To test the function of D6, the team injected pro-inflammatory LPS. The response was greater in mice lacking D6: several inflammatory chemokines built to higher levels in the circulation and placenta; more macrophages and T lymphocytes invaded the placenta; and there was more fetal loss.

Fetal loss may occur after a deadly positive feedback between inflammation and blood clotting in the placenta. In the mice lacking D6, this can be prevented with an infusion of anti-chemokine antibodies. A similar blocking approach may be possible in some humans who suffer from recurrent fetal loss, although it is not yet clear whether changes in D6 function are implicated in any of these individuals. JCB

Reference: de la Torre, Y.M., et al. 2007. *Proc. Natl. Acad. Sci. USA*. doi:10.1073/pnas.0607514104.

Pass the cycloheximide

Worms with reduced protein production capacity live longer, according to Popi Syntichaki, Kostoula Troulinaki, and Nektarios Tavernarakis (IMBB, Foundation for Research and Technology, Heraklion, Greece). The reduction appears to save energy—energy that can be put to work in fixing life-threatening damage.

Protein translation rates decrease with age. Tavernarakis wondered if increased translation might increase turnover of damaged proteins and thus slow aging. But, he says, "what we found was the opposite."

The group knocked down the levels of *IFE-2*, one of the five isoforms of the eIF4E translation initiation factor in worms. The development and eating patterns of the worms were normal, but they had an extended lifespan.

Other longevity-promoting pathways, such as the insulin and caloric restriction pathways, may modulate the eIF4E pathway (e.g., caloric restriction may reduce protein synthesis by down-regulating eIF4E). But *ife-2* knockout was additive with mutation of these other pathways, suggesting that a simple linear relationship is unlikely.

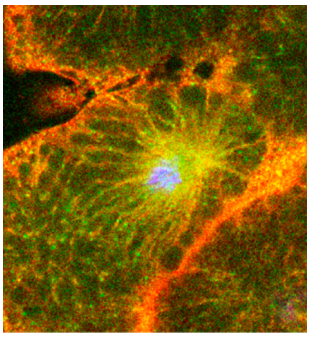
Animals with less eIF4E had higher ATP levels and were more able to resist oxidative damage. "If we reduce the rate of protein synthesis we allow the cell to invest some extra energy in maintenance and repair functions," says Tavernarakis. "By repairing damage the cells can now survive for longer."

This benefit is only relevant in the soma. In the germline, by contrast, translation is already near a minimum and a further reduction in eIF4E activity was lethal. "The germline invests in repair and maintenance but not so much in building," says Tavernarakis. "If we make our soma look a little more like our germline…then we might prolong the life of the soma." JCB

Reference: Syntichaki, P., et al. 2007. *Nature*. doi:10.1038/nature05603.

Motoring to a signaling check-up

The Smad2 signaling protein is shuttled back to the membrane to check up on its receptor, according to Julie Batut, Michael Howell and Caroline Hill (Cancer Research UK, London). The check-ups ensure that intracellular signaling accurately reflects the activation status of the membrane-bound receptor.


HILL/ELSEVIER

Smad2 (green) motors along microtubules (red).

Smad proteins are phosphorylated by and act downstream of TGF-β receptors. Once Smad2 has helped activate transcription, the group previously found, it is shuttled out of the nucleus.

They now discover that this discarded Smad2 is dragged back to the TGF-β receptor by the microtubule motor kinesin. Smad2 phosphorylation and nuclear accumulation was prevented by microtubule poisons and an antikinesin drug, even in the presence of a constitutively activated receptor. This result held true in frog and zebrafish embryos and mammalian cells. Unphosphorylated Smad2 coimmunoprecipitated with a kinesin light chain.

Long-range transport of Smad2 by kinesin has not yet been demonstrated. Hill also hopes to find a motor that transports active Smad2 from receptor to nucleus. Smad and STAT signaling pathways may be particularly suited to undertake such journeys, as in these two cases a single protein first interacts at the membrane and then acts in the nucleus. In these cases, "I think diffusion is never enough," says Hill. "With cells we tend to assume that things are swimming around in a soup, but I think everything is directed." JCB

Reference: Batut, J., et al. 2007. *Dev. Cell.* 12:261–274.