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Glycan growth switch

Those sugary glycan moieties that adorn cell surface receptors are more than decoration. Their ability to prevent receptor endocytosis is well established. Now, Ken Lau, James Dennis (University of Toronto, Canada), and colleagues show that differences in receptors' glycan decorations time a cell's transition from growth to arrest.

Receptors that promote growth generally have more sites for glycan addition than do receptors that halt growth and start differentiation. The authors found that these receptor groups responded differently to changes in metabolite status, which determines the complexity of the added glycans (more sugar-nucleotides means more intricately branched glycans are created in the Golgi).

With their many glycans, growth receptors were cross-linked by sugar-binding galectins and retained on the surface even in stringent growth conditions. Receptors that promote differentiation required higher sugar-nucleotide levels before their fewer glycans gained enough galectin-binding branches to counter their loss by endocytosis.

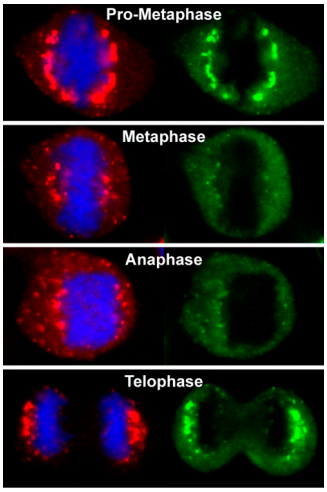
The upshot, says Dennis, is "a principle of how cells regulate the ratio of growth and arrest receptors in a cell-autonomous manner downstream of nutrients. First, an increase in proliferation is accompanied by glucose uptake and increased metabolism." Then when metabolite flux sufficiently increases sugar-nucleotides and the branched glycans, differentiation receptors can accumulate, turning off proliferation. JCB

Reference: Lau, K.S., et al. 2007. *Cell.* 129:123-134.

Cell fate depends on Golgi

The Golgi hides the partner of a stem-cell fate protein, according to results from Yan Zhou, Weimin Zhong (Yale University, New Haven, CT), and colleagues. Only when its partner is briefly freed during Golgi disassembly can Numb defend the undifferentiated state.

Numb has a paradoxical role in cell fate: when a neuronal progenitor divides, Numb keeps one daughter in the progenitor state by inhibiting Notch. Yet Numb is also needed for neuronal differentiation. To solve this mystery, Zhong's group fished for Numb's binding partners. They found a Golgi protein called ACBD3 whose brief cytosolic appearances during mitosis turned Numb into a supporter of the progenitor fate.



ZHONG/ELSEVIER

Escape of ACBD3 (green) from fragmented Golgi (red) allows it to bind Numb during mitosis.

During progenitor division, Numb is sent to one daughter, where it carries on the progenitor fate. The authors found that Numb's binding to ACBD3 was required for this progenitor maintenance. This binding was only possible during mitosis, when the Golgi disassembled and ACBD3 was released into the cytosol to meet Numb. Given this narrow window of opportunity, Zhong figures, "fate must be determined before cells are even finished dividing. After that, it might be just maintenance."

The lack of Numb in the other daughter allowed for Notch-orchestrated neuronal differentiation. But later, this neuron's survival depended on newly made Numb and its ACBD3-free activity. Forcing ACBD3 to remain in the cytosol inhibited neurogenesis.

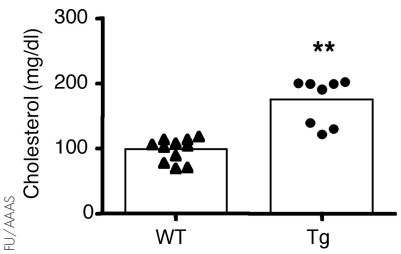
Other stem cells probably also depend on Numb and the Golgi-organized timing of ACBD3 release. And there's no reason to assume that ACBD3 is the only protein that exploits Golgi dynamics. "Golgi fragmentation in lots of vertebrate cells may be doing more than divvying up the organelle," says Zhong. JCB

Reference: Zhou, Y., et al. 2007. *Cell.* 129:163-178.

Immunity raises cholesterol

Our immune system is trying to give us a heart attack. Findings from James Lo, Yugang Wang, Godfrey Getz, Yang-Xin Fu (University of Chicago, IL), and colleagues reveal that T cells hinder the liver's ability to remove cholesterol from the blood.

The immune system and the liver were previously linked by a mouse model of inflammation that causes the animals to have enlarged livers. These mice express high levels of proinflammatory molecules called LIGHT and LT on their T cells. The authors now find that LIGHT-expressing T cells bump up triglyceride and cholesterol levels in the mouse bloodstream.



FU/AAAS

Mice with LIGHT-expressing T cells (right bar) have high cholesterol.

These lipids are normally broken down by the liver. But T cells carrying LIGHT caused liver cells to make less hepatic lipase, which hydrolyzes triglycerides and phospholipids. Interfering with LIGHT's ability to bind to its LTβR receptor on liver cells lowered cholesterol levels, even in mice that did not have high LIGHT levels to begin with.

High cholesterol is also caused by genetic diseases linked to the loss of the low-density lipoprotein receptor. The group found that mice lacking this receptor also benefit from the blockade of LIGHT signaling. A practical means to thwart LIGHT in humans has not yet been devised. Whether the high risk of heart disease associated with autoimmune diseases is also caused by LIGHT remains to be seen. JCB

Reference: Lo, J.C., et al. 2007. *Science.* 316:285-288.