Research Roundup

Motility from self-antigens

T cells get moving with a little self-stimulation, say Ursula Fischer, Elizabeth Ingulli (University of Minnesota, Minneapolis, MN), and colleagues. Interactions with self-ligands activate motility pathways in helper T cells, the new findings reveal.

Helper T cells hunt in the lymph nodes for just the right combination of antigen and its presenting MHC class II molecule (MHCII). But most of the time, they instead find self antigen-MHCII pairs that do not elicit T cell activation.

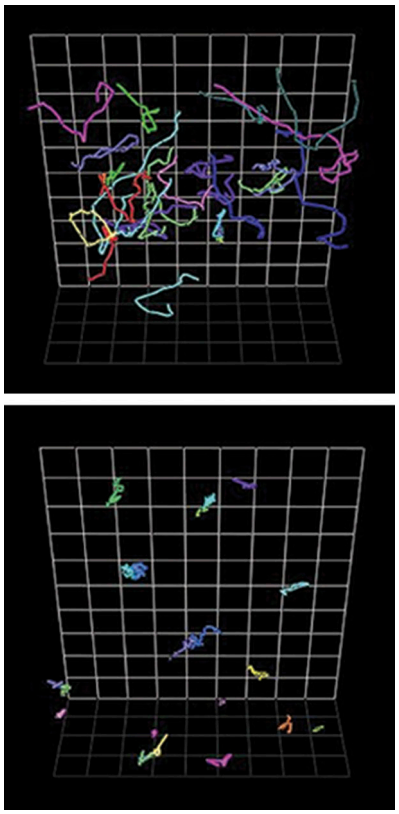
Fischer et al. investigated the role of these persistent self-interactions by studying mice that lack MHCII. They injected these mice with T cells carrying a receptor specific for an ovalbumin peptide. When the mice were then given normal dendritic cells presenting the ovalbumin antigen, the T cells were apathetic–they did not mount their normal immune responses. And the longer the T cells spent in the MCHII-free mice before seeing the antigen, the more apathetic they became.

The authors traced this growing indifference to a failure of the T cells to meet up with cells carrying their antigen. Normally, these two cell populations quickly overlap in the lymph nodes. But in the MHCII-lacking mice, they were more often found apart. And the T cells were unusually lethargic compared with those in normal lymph nodes.

"If the T cells can't move, they can't actively seek out and find their given antigen," says Ingulli. "Crawling across all these self signals, it's what makes the T cells move through the lymph nodes. Then they can peruse the dendritic cells, asking 'who's got my antigen?'"

The slow T cells were lacking in activated Rap1 and Rac–small GTPases that are known for stimulating motility. Ingulli assumes that the GTPases are turned on by interactions between self-ligands/MHCII and the T cell receptors. "It's a little tickling through the T cell receptor," she says. "It creates a baseline signaling, but not enough to get the T cell fully activated." Now she wants to better dissect this signaling pathway. JCB

Reference: Fischer, U.B. et al. 2007. *Proc. Natl. Acad. Sci. USA.* doi:10.1073/pnas.0608299104.



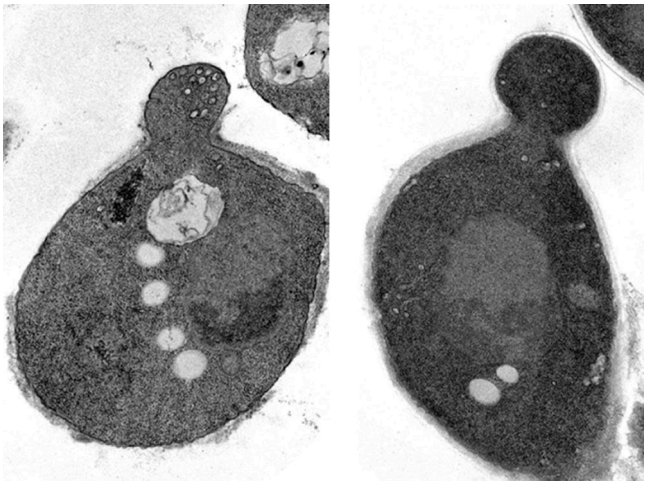
INGULLI/NAS

T cell wanderings (colored lines) are limited if the cells lack contact with self-antigens (bottom).

Linking division and growth

A protein that pushes forward the cell cycle coordinates division with the ensuing growth of the cell surface, according to work from Derek McCusker, Douglas Kellogg (University of California, Santa Cruz, CA), and colleagues.

It's well accepted that progress through the cell cycle depends on cell growth. In contrast, says Kellogg, "general thinking held that growth is continuous and independent of the cell cycle."



KELLOGG/MACMILLAN

Vesicles delivering new surface materials in the growing bud are missing (right) when Cdk1 activity is blocked.

But McCusker et al. now show that Cdk1, which triggers the G1 to S phase transition in budding yeast, also directly promotes the bud's growth. Bud growth quickly stalled upon blocking Cdk1 activity. The stall stemmed from a loss of polarized secretion. Normal cells placed secretory components such as vesicle tethering proteins and a myosin motor at the growing bud tip, but these proteins were rapidly delocalized when Cdk1 was inhibited.

The group then sought targets of Cdk1 that regulated cell surface growth. Several proteins that depended on Cdk1 for phosphorylation during bud growth were found in a complex that included a guanine nucleotide exchange factor and an activating protein for the Cdc42 GTPase, which is required for polarized cell growth. How phosphorylation of proteins in this complex leads to new bud membrane addition is not yet clear. The complex might orient the actin cytoskeleton in the right direction for secretion, although at least one affected secretory protein did not require actin for its polarization. JCB

Reference: McCusker, D., et al. 2007. *Nat. Cell Biol.* doi: 10.1038/ncb1568

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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.

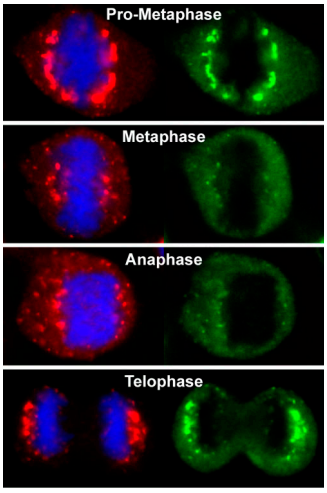
The upshot, says Dennis, is "a principle of how cells regulate the ratio of growth and arrest receptors in a cell-autonomous manner downstream of nutrients. First, an increase in proliferation is accompanied by glucose uptake and increased metabolism." Then when metabolite flux sufficiently increases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

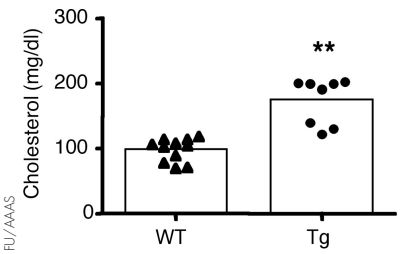
Other stem cells probably also depend on Numb and the Golgi-organized timing of ACBD3 release. And there's no reason to assume that ACBD3 is the only protein that exploits Golgi dynamics. "Golgi fragmentation in lots of vertebrate cells may be doing more than divvying up the organelle," says Zhong. JCB

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.