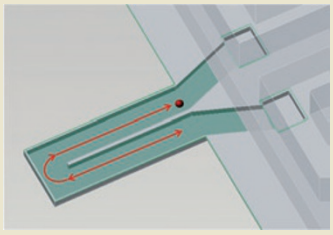
Weighing in on single cell growth rates



Manalis and colleagues monitor the growth of single cells in real time by developing a fluidic control system for a previously described suspended microchannel resonator. By trapping a cell in the channel and then continuously alternating the direction in which fluid flows through the device, they are able to repeatedly measure over time the cell's buoyant mass, a parameter analogous to its dry mass. The high mass precision achieved by the resonator enables growth rates to be measured over intervals much shorter than the cell division time (typically ~5 min for *Escherichia coli*, *Bacillus subtilis* and *Saccharomyces cerevisiae*, and ~20 min for mouse lymphoblasts). For all four of these cell types, heavier cells grow faster than lighter ones and there is substantial variation in the 'instantaneous' growth rate, even for cells of similar mass. Coupling this approach with fluorescent reporters of molecular and cellular activities and/or transgenes encoding products of biotechnological interest may provide insights into disease mechanisms or the modes of action of drugs. (*Nat. Methods*, published online 11 April 2010; doi:10.1038/nmeth.1452) *PH*

RNA-binding site mapping

Cellular RNAs are bound by a variety of RNA binding proteins. Identifying the targets of these proteins and determining the functional consequences of RNA-protein interactions have been the focus of intensive research. Tuschl and colleagues now present a method that enables efficient isolation of RNAs bound to a specific protein and high-resolution mapping of the interaction sites within each RNA species. The method is based on the incorporation of the thymidine base analog 4-thiouridine, which can be covalently cross-linked to proteins by UV light. After immunoprecipitation of the protein of interest, the bound RNAs are identified by Illumina sequencing. As cross-linked 4-thiouridine is detected as cytosine in the sequencing reaction, regions of an RNA with high frequency of T to C conversion indicate sites where protein binds. The authors use this technology, termed PAR-CLIP, to map sites targeted by miRNAs and RNA-binding proteins. Surprisingly, 50% of the miRNA target sites occur within the coding regions of mRNAs, although coding sequence target sites appear to be less efficient in destabilizing mRNAs than more traditional 3′ untranslated region sites. The data also suggest that RNA-binding proteins and miRNAs bind to a large percentage of the total cellular RNA species (5–30%), providing the basis for a complex combinatorial mode of post-transcriptional regulation of gene expression. (*Cell* **141**, 129–141, 2010) *ME*

Single tomato gene linked to yield

Crops with superior agricultural traits can often be created by crossing different varieties, but few examples exist of single genes that determine the genetic basis of this effect, known as heterosis. These so-called single-gene overdominant loci are highly desirable in plant breeding as they would facilitate rational design of hybrid lines. By examining 33 hybrid tomato lines, Zamir and colleagues identify the gene *SINGLE FLOWER TRUSS* (*SFT*) as a determinant for increased yield in hybrids. The combination of a defective and a functional allele in a hybrid plant leads to a reduced dose of the gene product of *SFT*, which together with a related gene *SELF PRUNING* (*SP*) regulates the balance between vegetative growth and the development of flowers. These results should spur the search for other single genes that control heterosis for desirable traits and suggest that tuning the balance between *SFT* and *SP* may be a general strategy applicable to other crops. (*Nat. Genet.*, published online 28 March 2010; doi:10.1038/ng.550) *ME & CM*

Notch receptors dissected

Notch signaling plays important roles in both development and tumorigenesis. However, attempts to modulate Notch signaling for therapeutic benefit through inhibition of the gamma secretase have been problematic due to redundancy of the pathways (four Notch receptors exist), and lack of knowledge of the function of individual Notch receptors. Using phage display technology, Wu and colleagues report in *Nature* the isolation of antibodies specific for either Notch-1 or Notch-2 (anti-NRR1 and anti-NRR2). Testing each antibody separately, they found that the antibodies affected particular and different T-cell populations. In T-cell acute lymphoblastic leukemia (T-ALL) cells, where mutations in Notch receptors are common, anti-NRR1 inhibited signaling in cell lines bearing the three most common mutations. In xenograft models, anti-NRR1 induced tumor regression in even well-established tumors. In a related study in *PLoS ONE*, Aste-Amézaga *et al.* isolated Notch1-specific antibodies that bind two regions of the Notch1 receptor, the ligand binding region and negative regulatory region. Both inhibit Notch signaling in T-ALL cells carrying particular mutations. Whereas clinical application will require careful testing because of the potential side effects, these reagents should be immediately useful for further study of Notch pathways. (*Nature* **464**, 1052–1057, 2010; *PLoS One* **5**, e9094, 2010) *LD*

Calming the storm

Cytokine storm is a destructive overreaction of the innate immune system to infections or other conditions. When produced in excess, inflammatory cytokines can lead to vascular leakage, tissue edema, organ failure, shock and death. Therapeutic approaches are often based on damping various parts of the immune system, but these have had limited success owing to the complexity of the immune response in cytokine storm. A recent paper by London *et al.* proposes a new treatment strategy focused on strengthening the vascular barrier. Vascular hyperpermeability mediated by vascular endothelial growth factor was known to be antagonized by signaling of Slit family proteins through the endothelial-specific receptor Robo4. The authors tested the therapeutic utility of the active fragment of Slit in several disease models, including bacterial endotoxin exposure, polymicrobial sepsis and H5N1 influenza. The Slit fragment reduced vascular permeability, multiorgan edema and death in all of these models, suggesting that stabilization of the endothelial barrier could be beneficial in a wide variety of infectious diseases. (*Science Transl. Med.*, published online 6 April 2010; doi:10.1126/scitranslmed.3000678) *KA*

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