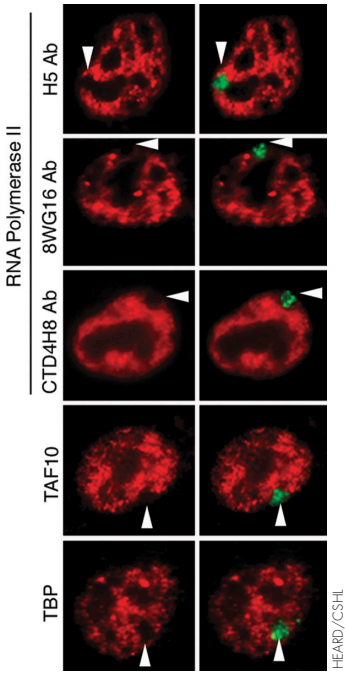
Research Roundup



RNA polymerase subunits and transcription factors (red) are excluded from regions where the Xist transcript (green) coats an X chromosome.

A transcriptional black hole

Silencing of the X chromosome creates a transcription-free nuclear compartment, based on findings from Julie Chaumeil, Edith Heard (Curie Institute, Paris, France), and colleagues.

For cellular gender equality, female cells silence one of their two X chromosomes. This silencing is initiated by the Xist RNA, which coats the chromosome from which it is expressed. In differentiating embryonic stem cells, the authors now show, this coating is rapidly followed by the exclusion of the transcription machinery.

The exclusion of RNA Pol II and transcription factors creates a transcription-free zone and is now the earliest event known to occur after *Xist* transcription. In fact, it happened even before several normally silenced X-linked genes were turned off. While still expressed, these genes were found on the periphery of the Xist zone, where they might reach polymerases.

When these loci were soon silenced, they repositioned to within the Xist domain. The timing of their movements suggests that transcription begins to shut down before a locus enters the domain. Local DNA reorganization appears to be necessary for their entry, as the Xist domain itself did not expand. Perhaps tethering to transcription factories prevents active loci from being internalized into the polymerase-free Xist environment.

The silencing of X-linked genes requires a conserved stretch of A-rich repeats in the Xist RNA. But the formation of the silent compartment was independent of these repeats, as was the silencing of repetitive X-chromosome sequences such as SINEs and LINEs within the Xist domain.

One model proposes that Xist RNA might create a zone that filters out transcription components and thereby silences the DNA that lies within, but Heard is not yet sure. "Is it that a nuclear compartment is created, and thus silencing happens," she says, "or is it that silencing happens, and thus you've created a compartment?" Either way, she wonders whether autosomes take advantage of the Xist compartment to silence their own genes. JCB

Reference: Chaumeil, J., et al. 2006. *Genes Dev.* 20:2223–2237.

Malignancy from cooperation

Cooperation among tumor cells may improve their odds of survival and eventual malignancy, as proposed by Robert Axelrod, Kenneth Pienta (University of Michigan, Ann Arbor, MI), and David Axelrod (Rutgers University, Piscataway, NJ). By applying the theoretical analysis of cooperation known as game theory, the authors offer a new way to view cancer progression.

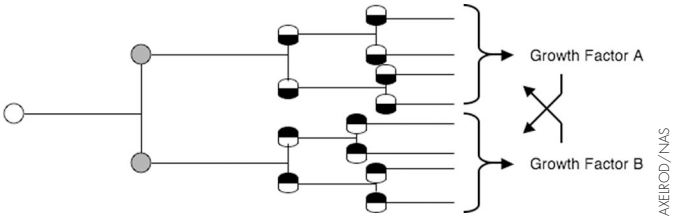
Originally an economic analysis, game theory is now widely used. "In terms of societies, businesses, even political parties," says David Axelrod, "competition, where one wins and one loses, is not necessarily the best strategy. But cooperate, and both can win." He and his colleagues argue that the same can be said for tumor cells.

Tumors are a mixed bag of cells that have acquired different mutations, creating unique lineages. Malignancy is thought to result only when a subclone gains all of the necessary mutations, while many others die out due to genetic instability or host defenses. Game theory, say the authors, adds to this thinking by suggesting that different tumor subclones share resources and thereby help each other survive and multiply.

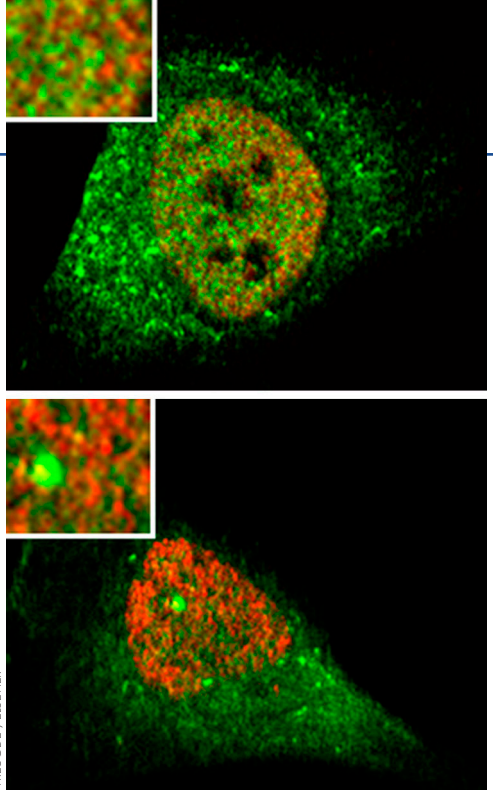
In a theoretical analysis, the authors discussed a few examples in which a hallmark of cancer is also a sharable resource. For example, one hallmark is the ability to produce growth factors. A lineage that secretes a necessary soluble growth factor may help nearby tumor cells that lack this factor but express its receptor. It may, in turn, get another growth factor from a second lineage. Another hallmark is angiogenesis. Tumor cells may produce diffusable angiogenic factors that induce blood vessels, which support neighboring cells that lack these factors.

According to the authors, the theory is consistent with what is known about tumor biology and makes predictions that can be tested, such as the presence of different growth factors expressed by nearby cells. But even before the theory's validity is tested, they hope that biologists and publishers will be open to theoretical reports that stimulate new experiments. "New ways of thinking can be as powerful as obtaining new data," says Axelrod. "As biologists, we've been in the business of collecting data. Now we have to start thinking about how this data can be put together." JCB

Reference: Axelrod, R., et al. 2006. *Proc. Natl. Acad. Sci. USA.* 103:13474–13479.



Partially transformed tumor cells that require two growth factors can cooperate. Those that make only factor A share with those that make only factor B, and vice versa.



VREUGDE /ELSEVIER

The association (top) of myosin VI (green) and RNA polymerase II (red) is lost when transcription is disrupted (bottom).

A myosin for RNA Pol II

Transcription gets a boost from myosin VI, according to findings from Sarah Vreugde (DIBIT Scientific Institute, Milano, Italy) and colleagues. The motor might drag genes into transcription neighborhoods.

While trying to understand the function of myosin VI, Vreugde noticed that its localization pattern looked much like that of RNA polymerase II. The authors then showed an association between the motor and polymerase that depends on ongoing transcription.

By cross-linking myosin VI to chromatin, the group identified several genes at which the motor is found. The mRNA levels of these genes decreased when myosin VI levels were reduced. Vreugde next hopes to inhibit just the nuclear pool of myosin VI and then do genome-wide analyses to identify more affected genes.

Assuming its influence is widespread, the motor might spool the DNA past aggregates of RNA polymerases or recruit stretches of DNA to transcription factories. "DNA recruitment to transcription factories would be heavy work," says Vreugde. "But myosin is well-suited to accomplish that."

Whether its unusual preference to move toward actin minus ends helps myosin VI at all is unclear, as the polarity of the nuclear actin network is not known and probably dynamic. The only other known nuclear myosin, myosin I, is plus-end directed but still enhances transcription by all the RNA polymerases. JCB

Reference: Vreugde, S., et al. 2006. *Mol. Cell.* 23:749–755.

Text by Nicole LeBrasseur
lebrasn@rockefeller.edu

T cells told to keep rolling

A T cell coreceptor keeps T cells moving so that they are not overactivated, according to Helga Schneider, Christopher Rudd (University of Cambridge, UK), and colleagues. By not lingering too long, killer T cells might be at their most efficient.

Rudd's group recently found that this coreceptor, called CTLA-4, was needed for integrin activation. Integrins go hand-in-hand with cell migration, which the authors now show is increased by CTLA-4 engagement.

When T cells meet the right antigen-presenting cell (APC), they normally stop and interact with the APC to get activated. This stopping phase, the authors show, is limited by CTLA-4, which is found on all activated T cells and binds to ligands on the APC.

By restricting the interaction time, CTLA-4 may prevent responses to low-affinity self-antigens that cause autoimmunity. This idea is supported by the severe autoimmunity found in mice lacking CTLA-4. Rudd suspects that their T cells "park next to an APC for so long that they start accumulating signals against self-antigens."

The anti–stop signal might have been designed to make cytotoxic T cells more efficient in killing infected or cancerous cells. It might also explain why anti–CTLA-4 antibodies succeed as cancer therapies, if they act as ligand mimics. "The release of [cytotoxic] granzymes is relatively quick," says Rudd. "The T cell can kill the tumor target cell and not stick around any longer than it needs to, take off again and encounter another target." JCB

Reference: Schneider, H., et al. 2006. *Science.* doi:10.1126/science.1131078.

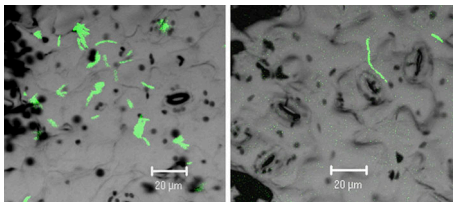
Stomata fight infection

Plants close up shop to prevent pathogen entry. Maeli Melotto, Sheng Yang He, and colleagues (Michigan State University, East Lansing, MI) show that stomata shut when bacteria are near.

Stomata are the plant's version of a window—an opening in the leaf epidermis where photosynthetic gas exchange occurs. This pore is a perfect way in for bacteria, which cannot themselves penetrate the epidermis. But the new findings show that, upon sensing bacterial proteins, the two guard cells that form the pore close the window.

Closure depends on signaling pathways activated by plant hormones, including salicylic acid and abscisic acid. A bacterial strain that successfully invades *Arabidopsis* overrides the closure and reopens stomata. This bypass requires a bacterial compound called coronatine, which antagonizes salicylic acid and abscisic acid, possibly by mimicking another hormone, called jasmonic acid.

Other successful bacteria lack coronatine. They might use other tricks to reopen stomata or wait around on the surface for heavy rain, which opens the pores for them.



HE/ELSEVIER

An epidermal peel shows that bacteria (green) that make coronatine (left) make it through stomata.

Defensive stomatal shutting has been overlooked because most plant pathogen researchers deliver bacteria directly below the epidermis—a "quick and easy" laboratory technique, according to He. But he believes that surface inoculations, a more natural state, will become more common now that this plant line of defense has been identified. JCB

Reference: Melotto, M., et al. 2006. *Cell.* 126:969–980.