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An open or closed case for HMGA

Senescence turns a chromatin-activating protein towards the dark side. Upon senescence induction, high mobility group A (HMGA) protein helps to make silent heterochromatin, report Masashi Narita, Scott Lowe, and colleagues (Cold Spring Harbor Laboratory, NY).

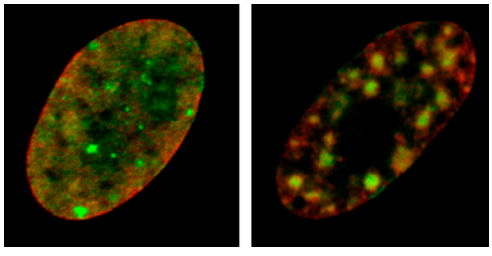
HMGA proteins promote open and active chromatin, are highly expressed in the early embryo, and can promote tumorigenesis. But the new results now show that HMGA is also found in senescent cells, which—in stark contrast to embryonic or tumor cells—no longer respond to mitogenic stimuli.

Senescent cells often form dense nuclear chromatin blobs called senescence-associated heterochromatic foci (SAHF), which the Lowe lab first described three years ago. While working to determine the chromatin components and epigenetic modifications that characterize SAHFs, they found that HMGA was upregulated in senescent cells. Its previously diffuse nuclear distribution in normal cells became a punctate pattern, as HMGA colocalized at SAHFs with the HP1 heterochromatin protein.

HMGA does not just passively associate with SAHFs; knock down of HMGA revealed that it is needed both to establish and maintain SAHFs. The transcriptional repression of multiple genes, including cell cycle factors, also depended on HMGA.

How can HMGA switch between such opposite roles? Evidence suggests that HMGA can be phosphorylated, acetylated, and methylated at specific amino acids. Acetylation, at least, has been shown to alter HMGA's transcriptional activity. It is therefore possible that, just as the chromosomal histones are modified to either condense or open chromatin, so too is HMGA. JCB

Reference: Narita, M., et al. 2006. *Cell.* 126:503–514.



LOWE/ELSEVIER

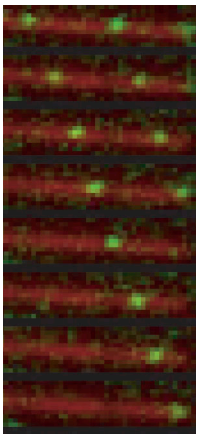
HMGA (red) colocalizes with HP1 (green) at SAHFs in senescent cells (right).

Microtubule munching

A yeast kinesin rapidly munches long microtubules, but its munching speed slows as the microtubules get shorter, report Vladimir Varga, Jonathon Howard, and colleagues (Max Planck Institute, Dresden, Germany). Along with Mohan Gupta, David Pellman, and colleagues (Harvard, Boston, MA), the team also shows that this kinesin-8, called Kip3p, paradoxically eats away at the growing ends of microtubules.

Microtubule length must be tightly controlled for cell functions as diverse as transport, motility, and division. In vitro studies by both groups showed that Kip3p binds all along the length of microtubules, but then motors along to accumulate at their plus ends, where it functions as a depolymerase.

Varga et al. found that Kip3p had a bigger appetite for longer microtubules, as these were devoured more rapidly than short microtubules. The authors suggest that longer microtubules bind more Kip3p and thus accumulate more depolymerase at their plus ends. The ends probably lose some Kip3p as they shorten, and shorter microtubules have less room to pick up more of the motor.



HOWARD/MACMILLAN

Kip3p (green) binds to microtubules (red) and motors along to their plus ends (right).

Plus-end accumulation of Kip3p was seen both in vitro and in cells. In the cell, however, the plus end is where growth and shrinkage occur. "The plus end is the place where the action is happening," says Varga. At this end, he says, there is probably, "a fight between polymerization and destabilizing proteins." He suggests that microtubules might grow from their plus ends until enough Kip3p accumulates to swing the battle in favor of shortening. JCB

References: Varga, V., et al. 2006. *Nat. Cell Biol.* doi:10.1038/ncb1462.
Gupta, M.L., et al. 2006. *Nat. Cell Biol.* doi:10.1038/ncb1457.

Live long and cancer-free

Mutations that prolong the life span of worms also suppress tumor formation, report Julie Pinkston, Cynthia Kenyon, and colleagues (University of California, San Francisco).

Mutations in the *gld-1* gene of *Caenorhabditis elegans* cause germ cells to proliferate uncontrollably, giving rise to lethal tumors. In most organisms, tumor susceptability increases with age, so Pinkston et al. were interested in how mutations that increase the life span of *C. elegans* might affect *gld-1* mutant worms.

Four different mutations that each promote longevity also suppressed tumorigenesis. When *gld-1* worms carried mutations in *daf-2, eat-2, isp-1,* or *clk-1* genes, the proliferation rate of germ line tumor cells was dramatically reduced. Remarkably, however, none of these mutations affected the proliferation rate of germ cells in worms without the *gld-1* mutation.

Mutations in *daf-2* interfere with insulin signaling, *eat-2* mutations restrict calorie intake, and *isp-1* and *clk-1* mutations impair mitochondrial activity. These apparently diverse routes may lead to both longevity and protection against cancer by limiting energy or nutrient availability to cells, says Kenyon.

In normal worms, the mutations do not cause nutrients to fall below levels necessary for cell division. In rapidly growing tumor cells, however, the demand for nutrients is higher. The mutations may then be sufficient to starve the tumor cells, inducing a stress response that ultimately shuts down the cell cycle machinery. JCB

Reference: Pinkston, J.M., et al. 2006. *Science.* 313:971–975.