Chromosomes reconfigure as cell division ends

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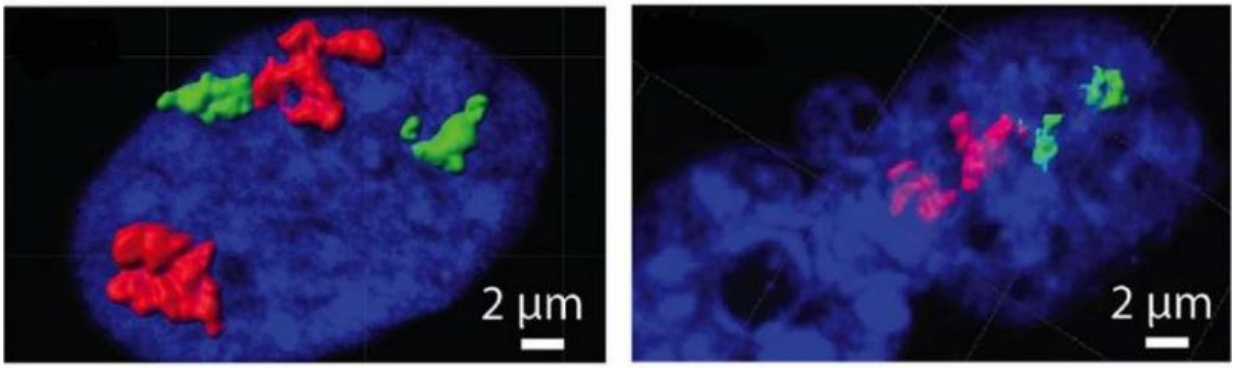

Chromosomes 4 (red) and 18 (green) are noticeably smaller in the nucleus of a senescent cell (right) than in a nonsenescent cell (left). Credit: Nicola Neretti/Brown University

Cellular senescence—when a cell can no longer divide—is a programmed stage in a cell's life cycle. Sometimes, as in aging, we wish it didn't happen so much and sometimes, as in cancer, we wish it would happen more. Given its important impacts on health, biologists wish they could explain more about what's happening in cells when senescence takes hold. A new study helps by showing that chromosomes become somewhat transformed, altering their patterns of gene expression.

"There is a reconfiguration of their three-dimensional structure, which was kind of unexpected in my opinion," said Nicola Neretti, assistant

professor of biology at Brown University and senior author of the study in *Science Advances*.

Overall, Neretti's team found, chromosomes become much more compact, though some parts of them expand in volume. An analysis of their spatial organization finds that most genes move into areas called "B" compartments that are locked down by tightly wound chromatin that prevents their expression. Many, however, move into "A" compartments that are looser and therefore more open for gene expression.

The kinds of genes affected by these changes are often ones of relevance to senescence. In their analysis, for example, the scientists found that about one in eight genes associated with cell proliferation and other relevant cell functions switch from relatively loose A compartments to more restrictive B compartments.

The study combined two techniques. "Hi-C" chromosome conformation capture, first published in 2009, allowed them to discover the changes in genes' positioning in A or B chromatin compartments. Meanwhile, with the imaging technique "FISH" (fluorescence in situ hybridization) they fluorescently labeled different points on the chromosome to directly measure the physical distance between them. That revealed overall physical changes such as the size and compactness of the chromosomes before and after senescence. Researchers further imaged chromosomes using many FISH probes, a technique called "chromosome paint," allowing them to highlight whole individual chromosomes and their constituent parts within the nucleus.

"The Hi-C gives you a lot of information about what's happening locally in the genome, but doesn't give you information about the physical distances, so that's why we moved to FISH," Neretti said. "We 'fished' out the distances."

FISH and chromosome paint, for example, showed which parts of the chromosome got more compact and which expanded. In their research, the scientists saw that while the chromosomes' arms and the "telomeres" at their tips scrunched up, the relatively tiny middle—the centromere—expanded. Within the centromere certain areas of repetitive DNA called alpha satellites expanded dramatically and become expressed.

All of this information allowed them to create the first 3-D models of how chromosomes change in senescent cells, Neretti said.

Graduate student Steven Criscione of Neretti's lab and postdoctoral fellow Marco De Cecco of John Sedivy's lab co-led the work. Neretti also praised the contributions of two undergraduate co-authors Benjamin Siranosian and Yue Zhang.

The results follow a study two years ago by many of the same authors, also including Jill Kreiling, assistant professor (research) of biology. They showed that a molecular corollary of aging is that senescent cells lose their tight chromatin grip on often-harmful sequences of DNA called transposons, leading to greater replication of those "rogue" elements.

Now the team is delving deeper into the compartment switches (between A and B) that change the regulation of genes in senescent vs. nonsenescent cells, Neretti said. They hope to understand and model those transitions and their consequences in greater detail.

The new research helps to answer a fundamental question about what genetic changes come along with senescence, Neretti said. That answer might eventually take on clinical significance. Now that they know something about the physical changes afoot in chromosomes, scientists could look for the proteins that likely mediate these changes, he said.

Down the road, perhaps, targeting these proteins could provide a way to slow down senescence or to speed it up.

More information: Reorganization of chromosome architecture in replicative cellular senescence, *Science Advances*, advances.sciencemag.org/content/2/2/e1500882

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