Study shows GATA4 plays a key role in cell senescence

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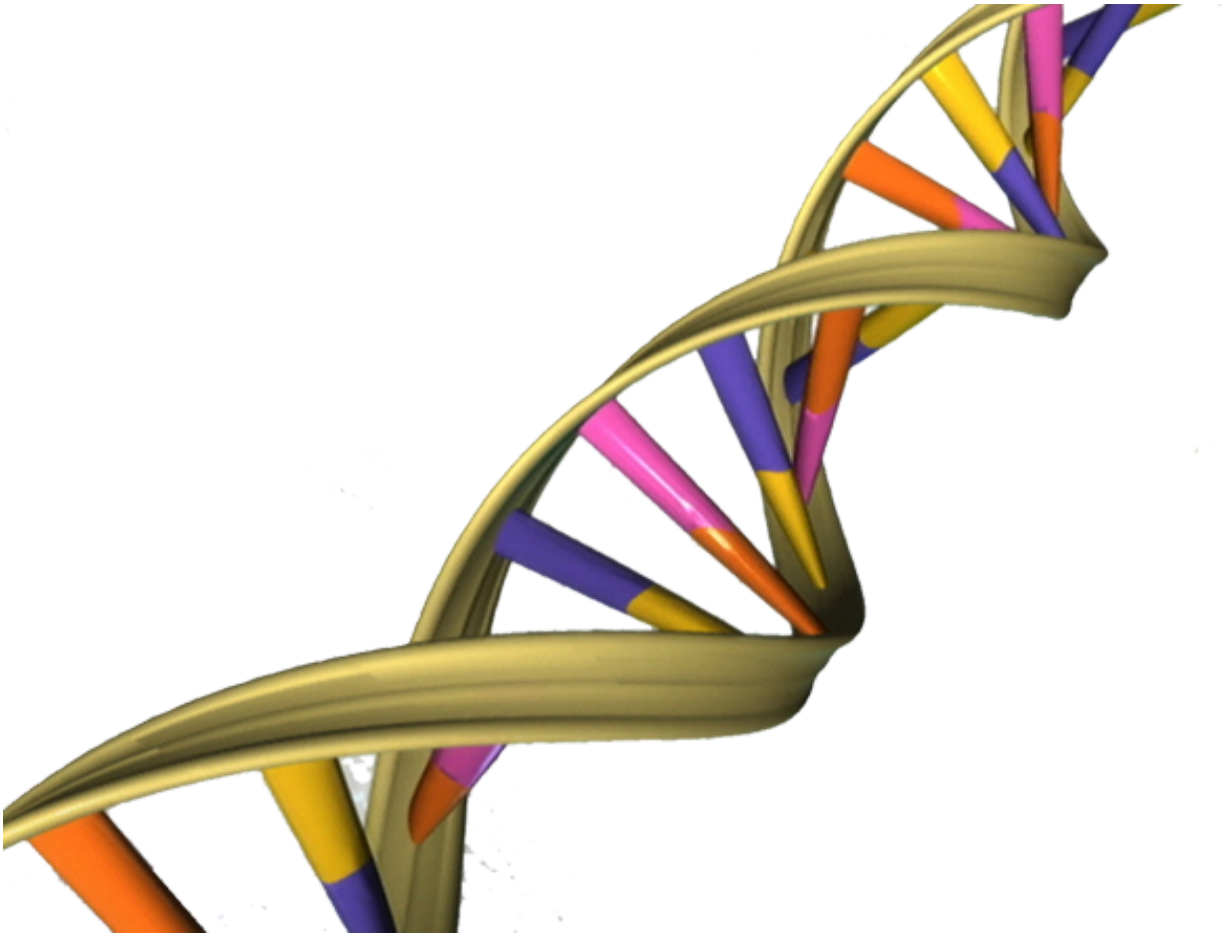

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

(Medical Xpress)—A team of researchers from Harvard Medical School and Buck Institute for Research on Aging has conducted a study that has revealed that GATA4 (a transcription factor) plays a significant role in cell senescence. In their paper published in the journal *Science*, the team describes their work and what they learned about cell aging. Liam Cassidy and Masashi Narita of the University of Cambridge offer a Perspectives piece on the work done by the team.

Cell senescence is a state that cells enter as they age or react to damage or other problems—once in this state they no longer progress through the cell cycle. Under normal conditions, senescence is a way for the body to maintain a healthy state. Sometimes however, the process does not work quite right and cells in a senescence state can accumulate, and that is a problem because it can lead to inflammation, neurodegenerative diseases or cancer. In order to understand and prevent such buildups, scientists need to better understand senescence-associated secretory phenotype (SASP) which is where a rise in pro-inflammatory growth factors, cytokines and chemokines and proteases occurs. In this new effort, the researchers looked at GATA4, a transcription factor (a protein that controls the transcription of genetic information from DNA to RNA) that has been associated with senescence in the past, but whose role was not clear.

To learn more the team caused senescence to come about in a sample of human connective tissue cells then scanned them closely to spot genetic elements that were expressed in large amounts by senescent cells but not in nonsenescent cells. They found that in normal cells, GATA4 was held back by autophagy—in cells that entered senescence, on the other hand, GATA4 was not held back as much. This suggested that GATA4 actually plays a key role in activating senescence. Furthermore, the team notes it helped to solve the problem of whether autophagy is a requirement for senescence to come about or whether it actually inhibits it from occurring. The new results suggest that it is a selective process;

non-targeted autophagy appears to be part of the initiation process whereas targeted autophagy of GATA4 actually stops it. They also saw that removing some autophagy components actually increased the number of GATA4 proteins. Additionally, they found that when GATA4 was expressed, genes linked with SASP were expressed, and when it was not, the same genes were not expressed.

More information: The DNA damage response induces inflammation and senescence by inhibiting autophagy of GATA4, *Science* 25 September 2015: Vol. 349 no. 6255 DOI: 10.1126/science.aaa5612

ABSTRACT
Cellular senescence is a terminal stress-activated program controlled by the p53 and p16INK4a tumor suppressor proteins. A striking feature of senescence is the senescence-associated secretory phenotype (SASP), a pro-inflammatory response linked to tumor promotion and aging. We have identified the transcription factor GATA4 as a senescence and SASP regulator. GATA4 is stabilized in cells undergoing senescence and is required for the SASP. Normally, GATA4 is degraded by p62-mediated selective autophagy, but this regulation is suppressed during senescence, thereby stabilizing GATA4. GATA4 in turn activates the transcription factor NF-κB to initiate the SASP and facilitate senescence. GATA4 activation depends on the DNA damage response regulators ATM and ATR, but not on p53 or p16INK4a. GATA4 accumulates in multiple tissues, including the aging brain, and could contribute to aging and its associated inflammation.