Key protein implicated in negative side effects of senescence
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Cellular senescence is a state in which normal healthy cells do not have the ability to divide. Senescence can occur when cancer-causing genes are activated in normal cells or when chemotherapy is used on cancer cells. Thus, senescence induces a mechanism that halts the growth of rapidly dividing cells. Once thought to only be beneficial to halt cancer progression, work from the The Wistar Institute has shown that during senescence there is an increase in secreted factors called cytokines and chemokines (small proteins important in immune responses) that may have detrimental, pro-tumorigenic side effects.

Researchers at The Wistar Institute have identified a protein that plays a critical role in the expression of cytokines and chemokines, and that decreasing this protein suppresses the expression of these secreted factors. This suggests that there may be ways of promoting the positive effects of senescence while suppressing its negative effects. The findings were published online by the Journal of Cell Biology.

Rugang Zhang, Ph.D., professor and co-program leader of the Gene Expression and Regulation program at Wistar, and colleagues focused on chromatin, a cellular structure responsible for holding the DNA in our cells together. During senescence, some of the chromatin is reorganized into senescence-associated heterochromatin foci (SAHF). When this happens, genes that are responsible for promoting proliferation are silenced. However, the expression of cytokine and chemokine genes—known collectively as the senescence-associated secretory phenotype (SASP)—is increased.

"When senescence happens, you have two closely linked phenomena occurring, yet one of these helps to halt tumor progression while the other causes an increase in potentially harmful inflammatory cytokines and chemokines," said Zhang, who is lead author of the study. "We pinpointed the architecture of chromatin and the proteins that influence chromatin organization as the proper place to start to try and solve this paradox."

The scientists looked at a set of proteins known as high mobility group proteins, which are responsible for altering chromatin architecture in order to regulate gene transcription. One such protein called high mobility group box 2 (HMGB2) binds to DNA to increase chromatin's accessibility to transcription factors. They showed that HMGB2 promotes SASP gene expression by preventing the spreading of heterochromatin and therefore preventing SAHF from silencing SASP genes. When the researchers silenced HMGB2, SASP genes were successfully silenced by SAHF, suggesting that the detrimental effects of senescence might be negated by inhibiting HMGB2.

"Understanding senescence is critical for understanding how tumor growth can be successfully suppressed," said Katherine Aird, Ph.D., a staff scientist in the Zhang lab and first author of the study. "With the information from this study, we may be able to increase the effectiveness of chemotherapeutic agents that are able to induce senescence by silencing HMGB2 and decreasing the expression of unwanted secreted factors."

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