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"Deciphering the Gene Regulatory Mechanisms Leading to Escape from Oncogene-Induced Senescence in Human Cells"

by
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Thursday, January 19th, 2023
11:00 AM
Cancer Center, G-1196, Zoom

Join Zoom Presentation:
https://rutgers.zoom.us/j/99540567570?pwd=aXJrNnpUbHZBQnlCMGVCRUVaeDFtUT09

Meeting ID: 995 4056 7570
Password: 677792

ABSTRACT

Oncogene-induced senescence (OIS) is a potent tumor-suppressive mechanism that causes cell cycle arrest in order to stop aberrant proliferation due to oncogenic stress. Features of OIS are observed in cells of human benign nevi and other human cancer precursor lesions in which H-Ras and B-Raf are aberrantly expressed, supporting the model that OIS arrests cells early during cancer development. OIS was thought to be a permanent state of arrest; however, recent studies from our laboratory, among others, demonstrated that normal human cells expressing the constitutively active H-Ras or B-Raf oncogenes could escape from OIS after a prolonged period in senescence. Senescence escape, therefore, could be a mechanism that contributes to malignant cancer progression. Although several possible causes for OIS escape have been identified in cell culture models, the gene-regulatory mechanisms driving escape from OIS are poorly understood. To address this, we performed extensive time-series experiments on human cells overexpressing H-Ras^{G12V} oncogene and determined global gene expression profiles using microarrays, mapped accessible chromatin sites and transcription factor dynamics using the Assay for Transposase-Accessible Chromatin followed by high throughput sequencing (ATAC-seq) and studied gene regulatory elements throughout the time course using chromatin immunoprecipitation followed by sequencing (ChIP-seq). Our study revealed an extensive enhancer remodeling as cells enter into and escape from OIS. We found that escape was facilitated by organized waves of transcription factor activity at enhancers and identified POU2F2 as a critical transcription factor in promoting escape from OIS. More specifically, senescence escapers resume proliferation after upregulating POU2F2 transcription factor, whose expression levels and activity peaked just before the cells escape. Additionally, downregulation of POU2F2 by shRNAs showed a stable arrest of these cells in senescence or a delay in the escape and a reduction in EdU incorporation compared to control cells. Analysis of human colorectal tissues by immunohistochemistry showed increased levels of POU2F2 expression in colorectal cancers (CRC) relative to normal colon. Lastly, high expression of POU2F2 in primary CRC tumors was associated with reduced overall survival. Collectively, our data demonstrate that cells arrested in OIS retain the potential to escape senescence by mechanisms that involve a temporally increase in POU2F2 activity and highlight POU2F2 as a potential therapeutic target in CRC.