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Senescence-associated tissue microenvironment promotes colon cancer formation through the secretory factor GDF15

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Abstract

The risk of colorectal cancer (CRC) varies between people, and the cellular mechanisms mediating the differences in risk are largely unknown. Senescence has been implicated as a causative cellular mechanism for many diseases, including cancer, and may affect the risk for CRC. Senescent fibroblasts that accumulate in tissues secondary to aging and oxidative stress have been shown to promote cancer formation via a senescence-associated secretory phenotype (SASP). In this study, we assessed the role of senescence and the SASP in CRC formation. Using primary human colon tissue, we found an accumulation of senescent fibroblasts in normal tissues from individuals with advanced adenomas or carcinomas in comparison with individuals with no polyps or CRC. In in vitro and ex vivo model systems, we induced senescence using oxidative stress in colon fibroblasts and demonstrated that the senescent fibroblasts secrete GDF15 as an essential SASP factor that promotes cell proliferation, migration, and invasion in colon adenoma and CRC cell lines as well as primary colon organoids via the MAPK and PI3K signaling pathways. In addition, we observed increased mRNA expression of GDF15 in primary normal colon tissue from people at increased risk for CRC in comparison with average risk individuals. These findings implicate the importance of a senescence-associated tissue microenvironment and the secretory factor GDF15 in promoting CRC formation.

KEYWORDS
colon organoids, colorectal cancer, GDF15, microenvironment, senescence

Guo and Ayers share first authorship.