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AUTHOR'S VIEWS

The senescence-associated secretory phenotype as a driver of tumor growth: does G3BP1 hold the key?

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ABSTRACT

Cellular senescence is a double-edged sword that, depending on the context, acts as either a potent tumor protective mechanism or an age-related driver of diseases such as cancer. Our recent findings show that the rasGAP SH3-binding protein 1 (G3BP1) activates the senescent-associated secretory phenotype (SASP) that, in turn, mediates cancer growth/progression.

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Although mortality rates have decreased over time, aging has become a leading risk factor for various age-related diseases such as cancer and neurological disorders. In an effort to find novel ways to prevent the impact of aging on the onset of age-related diseases, our recent work has shown that the rasGAP SH3-binding protein 1 (G3BP1) controls the pro-tumorigenic function of a subtype of cells known to promote age-related diseases, called senescent cells.[1] Specifically, we demonstrate that the expression of secreted factors from senescent cells, called the senescence-associated secretory phenotype (SASP), is controlled by G3BP1. Consequently, the G3BP1-mediated expression and secretion of these factors are a primary promoter of tumor growth controlled by G3BP1.[1]

Previous work has demonstrated that cellular senescence is one of the leading promoters of age-related diseases.[2] The most explicit demonstration of a link between senescence and age-related diseases is that the removal of senescent cells from mice decreases mortality, cancer occurrence, neuropathy, and frailty in several mouse models.[2,3] Consequently, the elimination of senescent cells has emerged as a promising anti-aging therapy. However, recent findings indicated that senescent cells' explicit removal may prove counterproductive as senescent cells do play critical roles in physiological functions such as glucose homeostasis and wound healing.[4,5]

Cellular senescence is a state of cell cycle arrest elicited in response to sustained stress.[3] Several external and internal signals, such as replicative stress, DNA damage, genomic instability, oncogenic stress, and many others, can lead to the induction of senescence in order to prevent the expansion of damaged or potentially harmful cells.[3] These cells undergo many notable phenotypic changes such as decreased genomic stability and chromatin organization, increased expression of key cell cycle inhibitors, resistance to cell death due to increased expression of anti-apoptotic genes, and, most notably, the SASP.[3] This unique group of secreted factors is comprised of a variety of cytokines, chemokines, angiogenic factors, extracellular matrix-remodeling proteases, and growth factors, such as Interleukin-6 (IL-6), Chemokine Ligand 8 (IL-8), Vascular Endothelial Growth Factor (VEGF), Matrix Metalloproteinase-3 (MMP-3), and Plasminogen Activator Inhibitor-1 (PAI-1).[3] These SASPs trigger local inflammation leading to the removal of these senescent cells by the immune system. However, with aging, the immune system's decreased efficiency leads to the accumulation of senescent cells that causes chronic systemic inflammation due to the secretion of the SASP.[3] This SASP-induced inflammatory state is thought to promote age-related pathology.[3]

Due to the harmful consequences associated with the accumulation with the age of senescent cells, significant efforts have been made to eliminate these cells as a means to combat age-related diseases. Various drugs and therapies have recently been developed to impair senescence or remove senescent cells. The most prevalent form of senescent cell elimination is senolytics.[6] These are a class of drugs believed to specifically inhibit pro-survival factors known to be upregulated in senescent cells, thereby promoting their death.[6] While senolytics have yielded promising outcomes, the potential for adverse effects, as previously mentioned, is worth recognition. Therefore, our group has focused on finding ways to decouple the deleterious and beneficial effects of senescent cells in order to prevent their global elimination to harness their advantageous impact while impairing their detrimental behavior.

Previous studies had shown that G3BP1 knockout mice exhibited premature aging phenotypes,[7] suggesting a potentially anti-aging role for G3BP1. Therefore, we sought to investigate whether loss of G3BP1 could drive

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age-related phenotypes by potentiating the deleterious behavior of senescent cells. Therefore, as a first step, we sought to deplete G3BP1 from these cells. However, in human primary fibroblasts, we demonstrated that depletion of G3BP1 had no biologically significant impact on cellular senescence, suggesting that the phenotypes observed in G3BP1 knockout mice may be independent of senescence. Therefore, to understand the consequence of G3BP1 loss on the function of senescent cells, we employed RNA sequencing analysis to assess genome-wide differences in mRNA expression in cells depleted or not of G3BP1. Surprisingly, we found that various pro-inflammatory pathways were downregulated, including those known to regulate the SASP (i.e., Signal Transducer and Activator of Transcription 3, STAT3, Nuclear Factor Kappa-light-chain-enhancer of activated B cells, NF-κB, and Interferon Regulatory Factor 3, IRF3, signaling). We corroborated these findings and showed that while these cells retain all characteristics of the senescence phenotype, they do not express or secrete inflammatory SASP factors, such as IL-6, IL-8, and Tumor Necrosis Factor-alpha (TNFα), due to downregulation of the type I interferon response. As such, these G3BP1-depleted senescent cells were termed "SASPless" (Figure 1).

Using epigallocatechin gallate (EGCG), a known pharmacological inhibitor of G3BP1 previously shown to inhibit the type I interferon response,[8] we could also induce the SASPless phenotype in senescent cells. Notably, we show that EGCG effects on the SASP were G3BP1-dependent. Other drugs such as rapamycin (a mammalian Target of Rapamycin, mTOR, inhibitor) or Menin-MLL Interaction Inhibitor (MI-2-2, a myeloid/lymphoid or mixed-lineage leukemia 1, MLL1, inhibitor) are known to elicit a similar inhibition of the SASP;[9,10] however, their use as therapeutics to treat age-related disease has remained limited. Taken together, our recent findings expand on the opportunity to develop drugs that neither inhibit senescence induction nor eliminate senescent cells but instead influence senescent cell behavior by targeting the SASP as seen with G3BP1 inhibition using EGCG. Therefore, expanding the therapeutic catalog of drugs that promote the SASPless phenotype in senescent cells through the development of more specific inhibitors against targets such as G3BP1 will likely maximize the beneficial role that senescence plays while eliminating their deleterious consequences due to the SASP.

While the previously mentioned findings demonstrated that G3BP1 is a promising target for SASP inhibition, we sought to investigate whether G3BP1-depleted SASPless cells impairs age-related disease progression, specifically when looking to the promotion of cancer. Using both *in vitro* and *in vivo* models, we clearly show that senescent cells depleted of G3BP1 cannot promote tumor growth and migration (Figure 1). Importantly, we unequivocally demonstrate that the SASP drive cancer cell proliferation and migration. However, further investigation is still required to understand how G3BP1 depletion or inhibition impacts senescent cells' targeting by immune cells. Indeed, the SASP has been demonstrated to be necessary for senescent cell clearance by the immune system;[3] however, whether their removal is required at all if the SASP is not expressed or secreted remains unclear. While considering these observations, future research should not understate

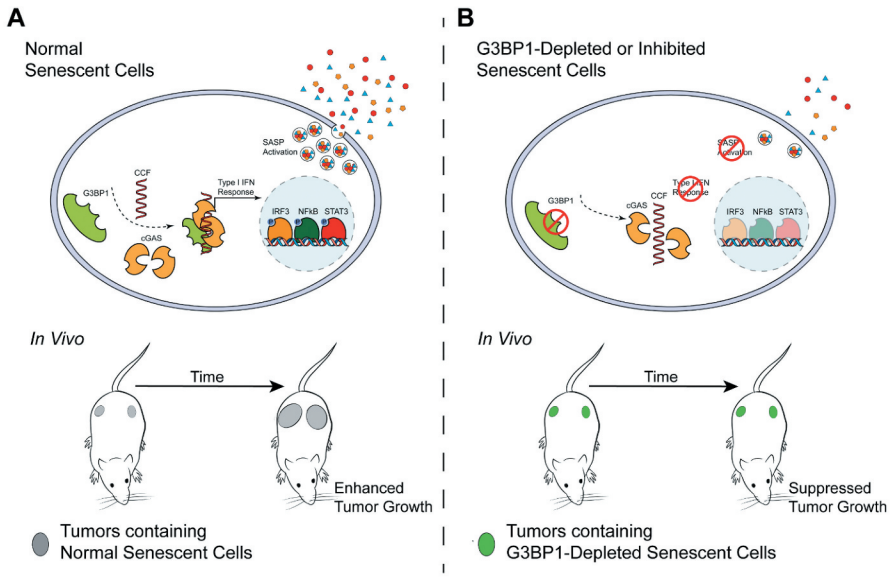

Figure 1. Impact of G3BP1 depletion in senescent cells on senescence-associated tumor growth. (a) rasGAP SH3-binding protein 1 (G3BP1) is required for normal senescent cells promote cyclic GMP-AMP synthase (cGAS) binding to cytosolic chromatic fragments (CCF) in order to induce the Type I Interferon (IFN) response during senescence thereby promoting senescence-associated secretory phenotype (SASP) secretion through activation of Signal Transducer and Activator of Transcription 3 (STAT3), Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB), and Interferon Regulatory Factor 3 (IRF3). Co-injection of normal senescent cells with tumor cells promotes tumor growth in vivo. (b) G3BP1 depletion or inhibition impairs SASP secretion in senescent cells. Co-injection of SASPless G3BP1-depleted cells with tumor cells suppresses tumor growth in vivo, thereby demonstrating that the SASP are promoters of tumor growth and that G3BP1 plays a central role in the harmful effects of senescent cells.

cellular the impact of senescence on other age-related pathologies. Understanding how senescent cells potentiate pathologies such as neurodegenerative disease, atherosclerosis, sarcopenia, and others[2] will be essential to the development of therapeutics. Taking our findings into account, we establish that the SASP is a clear and targetable component of the senescence phenotype that may be at the center of all age-related pathology. Pursuing inhibition of the SASP through essential factors such as G3BP1 and investigating how the SASP potentiates age-related disease systemically will expand the current landscape of senotherapies providing safe and reliable therapy.

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Disclosure of interest

The authors declare no competing interests.

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