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# SIN3B, the SASP, and pancreatic cancer

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**Abbreviations:** PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; SASP, senescence-associated secretory phenotype

Cellular senescence is classically considered a tumor suppressive mechanism. In addition to having stably exited the cell cycle, senescent cells secrete inflammatory factors. We recently demonstrated that senescence correlates with accelerated cancer progression in a mouse model of pancreatic ductal adenocarcinoma. Here, we discuss the implications of this study.

## Author View

Pancreatic ductal adenocarcinoma (PDAC) is primarily an incurable disease with a median survival of only 6 months, due in large part to the late clinical presentation of the disease. The majority of PDACs arise from activating mutations within the GTPase Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene that drive the development and stepwise progression of preneoplastic lesions called pancreatic intraepithelial neoplasms (PanINs). As PanINs progress the cells acquire additional mutations within various tumor suppressor genes including cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and tumor protein p53 (*TP53*), and the lesions display increased dysplasia and proliferation.[1] It is believed that oncogene activation drives the cells that consitute early PanIN lesions into cellular senescence, thus halting their proliferation and preventing PanIN progression.[2] Cellular senescence corresponds to an irreversible exit from the cell cycle that is triggered by various stimuli and prevents the uncontrolled proliferation of damaged cells. Studies in both mouse and human tissues have demonstrated that senescent cells accumulate within preneoplastic lesions including PanIN, but are absent in frank carcinoma. Furthermore, in numerous mouse models of cancer, abrogating the molecular pathways required for entry into cellular senescence correlates with accelerated cancer progression. These observations helped establish the classically accepted role for senescence as a barrier to cancer progression.[3]

Recently, we demonstrated that mouse embryonic fibroblasts with inactivation of the chromatin-associated SWI-independent transcription regulator family member B (Sin3B) protein are refractory to oncogene-induced senescence. Unlike other proteins required for cellular senescence, including $p16^{INK4A}$ (encoded by *CDKN2A*) and p53 (encoded by *TP53*), deletion of Sin3B does not sensitize cells to transformation.[4] Therefore, modulating Sin3B levels, as opposed to other regulators of senescence, provides a context within which the effects of cellular senescence in cancer progression can be studied without the confounding effects of accelerated transformation. To better understand the role of cellular senescence in PDAC progression, we genetically engineered mice with pancreatic-specific expression of oncogenic $KRas^{G12D}$ concomitant with deletion of the *Sin3B* locus. Based on the requirement for Sin3B for entry into cellular senescence and the role of senescence as a barrier to cancer progression, we hypothesized that *Sin3B* deletion would accelerate $KRas^{G12D}$-driven PDAC progression in the mouse. Surprisingly, we observed the opposite phenomenon: *Sin3B*-deleted animals exhibited delayed PanIN and PDAC progression and displayed increased survival compared to their wild-type counterparts.[5]

We initially asked whether this unexpected observation was due to a requirement for Sin3B in acinar-to-ductal metaplasia (ADM), an initiating event in at least some PDAC models. Although ADM was delayed in *Sin3B*-deleted pancreata *in vivo*, ADM initiation did not require Sin3B *in vitro*. We hypothesized that this discrepancy reflected a non-cell autonomous effect of Sin3B on the pancreatic microenvironment. Emerging evidence suggests that cellular senescence has both cell autonomous and non-cell autonomous effects, and that senescent cells, although no longer cycling, actively communicate with neighboring cells and the surrounding tissue. Senescent cells produce and secrete numerous factors such as cytokines, chemokines, proteases, and growth factors, collectively referred to as the senescence-associated secretory phenotype (SASP). The SASP reinforces senescence in both an autocrine and a paracrine fashion, and recruits innate and adaptive immune


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cells.[3] Since PDAC relies on an inflammatory microenvironment, we postulated that the SASP, driven by Sin3B-dependent senescence, may paradoxically promote PDAC progression by recruiting immune cells that generate an inflammatory microenvironment. Accordingly, we observed lower expression levels of markers of senescence in *Sin3B* null pancreata, and the infrequent PanIN lesions within *Sin3B*-deleted pancreata were negative for established markers of senescence. Furthermore, we detected a drastic reduction in immune cell infiltration in *Sin3B*-deleted pancreata. We concluded that Sin3B was required for both KRas-induced senescence and inflammation *in vivo*, and that entry into senescence surprisingly correlated with pancreatic cancer progression.[5] While these observations remain correlative, we hypothesize that senescent cells stimulate the generation of an inflammatory microenvironment and promote PDAC progression, questioning the classical view of cellular senescence as merely a tumor suppressive mechanism *in vivo* (**Fig. 1**).

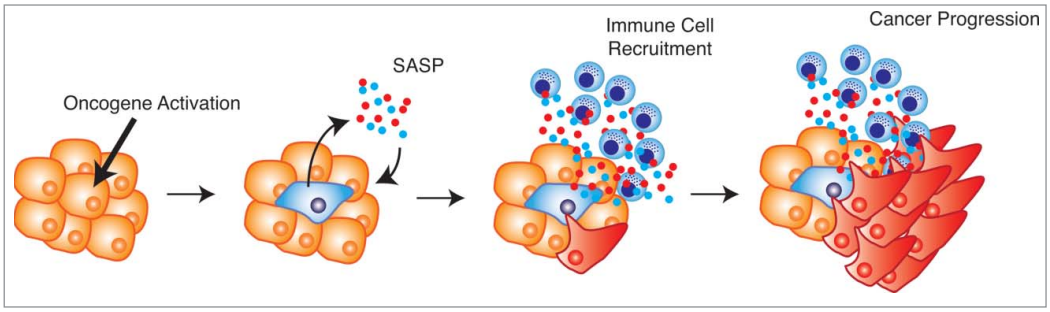


**Figure 1.** Senescence-associated cytokines establish an inflammatory microenvironment and promote cancer progression. Upon oncogene activation cells become senescent. The senescent cells produce and secrete the senescence-associated secretory phenotype (SASP), which reinforces senescence within the lesion and recruits immune cells to the surrounding tissue. The immune cells, along with the SASP, generate an inflammatory microenvironment, which in certain contexts fuels cancer progression.

Recent studies identified a role for the SASP in liver cancer development. However, although one study observed that the SASP inhibited tumor development,[6] the other reported that the SASP promoted tumor progression.[7] Although the reason for this difference is not immediately clear, it could be due to the different models used by the 2 groups, adding further complexity to the role of senescence and the SASP. To better define its role in cancer progression, factors that are required for the SASP but are not involved in cell cycle exit should be identified. In our model, interleukin-1 α (IL-1α) levels correlated with senescence and the inflammatory response in both mouse and human tissue. Several groups have previously identified IL-1α as an upstream regulator of the SASP both *in vitro* and *in vivo*.[8,9] Moreover, Chia and colleagues recently described that oncogenic KRas induces IL-1α expression in PDAC, which in turn stimulates NF-kβ activity, previously described to be required for the SASP.[10] These studies, in combination with our observations, point to a central role of IL-1α in stimulating an inflammatory microenvironment through the SASP. We believe that dissecting the contribution of IL-1α in various cancers, such as PDAC and hepatocellular carcinoma, will provide an avenue to directly investigate the role of the SASP in cancer progression. If the SASP promotes cancer progression in at least some contexts, IL-1α inhibition may represent a novel treatment option.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.


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