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Too much or too little

Harnessing senescence to control oncogene-driven cancer

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The global effort to understand the molecular drivers of cancer onset and progression is now coming to fruition with the identification of specific genomic and epigenomic events that influence signaling through key oncogenic pathways. Genetic studies using inducible expression of the critical growth controlling oncogenes MYC, RAS, PI3K and AKT have shown unequivocally that, in conjunction with secondary genetic mutations, they can drive transformation and induce oncogene addiction.[1,2] Since the majority of human tumors exhibit dysregulated signaling via one or more of these pathways,[1,2] this provides an unprecedented opportunity to improve patient outcome by therapeutically targeting this addiction.

These key drivers of malignant transformation do so by controlling many of the processes regarded as hallmarks of cancer, including proliferative cell growth and resistance to apoptosis, reprogramming of energy metabolism, angiogenesis and metastasis.[3] Paradoxically, however, the MYC, RAS and PI3K/AKT oncogenic pathways can also induce cellular senescence in non-transformed cells. Pandolfi and colleagues proposed that RAS oncogene-induced senescence (OIS) differs from loss of the tumor suppressor PTEN-induced cellular senescence (PICS) by the absence of a DNA damage response,[4] and our publication demonstrated oncogenic AKT-induced senescence similar to PICS.[5] In all three cases, senescence relies on modulating p53 levels and activity and/or INK4A mediated inhibition of cyclin-dependent kinases (CDKs) and, thus, inactivation of the retinoblastoma protein, RB.[4] However, while elevated p53 activity alone typically promotes cell cycle arrest or quiescence, it is the presence of a chronically stimulated, growth-promoting signaling pathway that mediates cellular senescence, which is coined geroconversion.[6] This paradox has led to the hypothesis that genomic hyperactivation of oncogenic pathways in non-transformed or pre-neoplastic cells (PNC) and perhaps in cancer-initiating cells (CIC), induces cellular senescence that acts as a "brake" for tumorgenesis[5] (**Fig. 1**).

Adding to this paradigm, in oncogene-addicted tumor cells, where this "senescence brake" has been disengaged, the targeting of these oncogenic pathways to induce cellular senescence has shown promise for cancer treatment. Major advances in treating patients have already been observed by targeting RAS/RAF signaling in melanoma[7] and PI3K/AKT/mTORC1 in renal cell carcinoma and neuroendocrine tumors.[8] While the response to these targeted therapies varies between the induction of apoptosis or senescence depending on cellular context, there is now considerable interest in the use of pro-senescence therapy to treat established disease, targeting quiescent CICs in pre-neoplastic lesions or tumors and preventing the development of acquired resistance or secondary tumors[4] (**Fig. 1**).

A range of pro-senescence therapies have been proposed to enhance targeted and traditional therapies for oncogene-addicted tumors (**Fig. 1**), including telomerase inhibition, cell cycle control (cell cycle inhibitors induce senescence and synthetic lethality in RAS and PI3K driven tumors) and p53 re-activation (e.g., by the MDM2 inhibitor, nutlin).[2,4,9] While targeting MYC-driven tumors has proven extremely difficult, inhibition of bromodomain and extraterminal (BET) proteins such as BRD4 by small molecules, including JQ1, has been shown to indirectly inhibit MYC and induces a senescence response in hematological malignancy.[9]

There remain some key issues to be considered when utilizing such an approach. The cellular response observed with these therapies can vary markedly depending on tissue and tumor type, or as a result of relatively subtle differences in the strength of signaling downstream of the oncogenes. For example, modest changes in PTEN activity or RAS signaling can result in a switch from promoting senescence to proliferation.[9] Importantly, our recent observations[5] have provided an added twist to the senescence paradox—inhibitors of PI3K/AKT/mTOR signaling can reduce the p53 response through negative effects on its stability and translation. Furthermore, mTOR inhibition can prevent senescence by inhibiting geroconversion.[6] Thus, while providing an antitumor response, they may actually dampen the tumor suppressive activity of senescence in non-transformed cells subject to "oncogenic assault"—potential CICs in pre-neoplastic lesions or existing tumors (**Fig. 1**). Thus, combinations of oncogene-targeted therapies with pro-senescence agents, rationally chosen based on the molecular characteristics of individual tumors (e.g., oncogene signaling, p53 and INK4A status), may markedly improve

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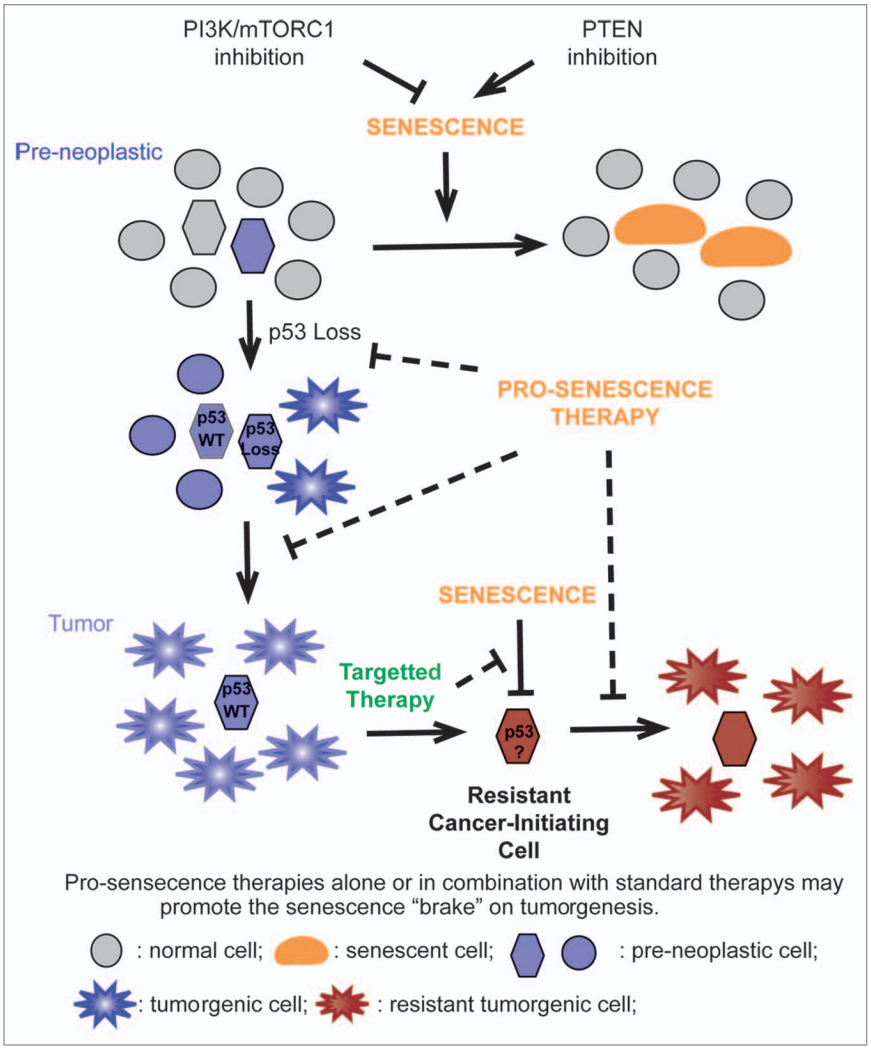

Figure 1. Pro-sensecence therapies alone, or in combination with standard therapies, may promote the sensecense "brake" on tumorgenesis.

patient outcome by harnessing both arms of the paradox—inducing senescence by reducing oncogene-driven signaling while maintaining OIS control of pre-malignant cells including CICs.

Pandolfi proposed the concept of improving tumor response by stimulating oncogene activity in the CICs and hence promoting OIS/PICS, for example, by using PTEN inhibitors, before initiating targeted therapies.[4] Alternatively, it may be possible to use combination therapies to enhance both modes of senescence inhibition of cancer. We proposed that combining PI3K/AKT/mTORC1 inhibitors and MDM2 inhibitors, such as nutlin-3a, that preserves p53 expression may maintain the senescence brake in CICs while the pathway inhibitors target the active tumor cells.[5]

An alternative approach lies in further targeting of critical oncogene-driven processes. MYC, RAS and/or PI3K pathways are the key modulators of ribosome biogenesis, and elevated ribosome synthesis is critical for their role in promoting cancer.[10] We have shown this may be a potent target for PI3K/AKT pathway inhibitors in hematologic malignancy resulting in either apoptosis[10] or senescence and tumor clearance (Wall et al., unpublished). More strikingly, a direct inhibitor of ribosome biogenesis acting on RNA polymerase I, CX-5461, promotes senescence in normal and solid tumor cells. Importantly, we have also demonstrated CX-5461 induces selective killing of MYC-driven lymphomas[11] and, thus, in combination with PI3K/AKT pathway inhibition, may show cooperative inhibition of lymphoma viability.

Together, combinations of targeting oncogene-dependent signaling and ribosome biogenesis may promote potent inhibition of tumor cell growth, without releasing the "senescence brake" in potential CICs, providing a new paradigm for treatment of oncogene-addicted tumors.

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