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CELL SIGNALLING

Limiting the side effects of senescence

> by enhancing the translation of the cell surface-bound cytokine interleukin-1α (IL-1α), mTOR promotes the senescence-associated secretory phenotype

mTOR is a Ser/Thr kinase that senses nutrient and growth signals and regulates many processes including cell proliferation, cell survival and autophagy. mTOR can also limit longevity in mice, but the mechanisms underlying this effect remain unclear. Campisi and colleagues now show that by enhancing the translation of the cell surface-bound cytokine interleukin-1α (IL-1α), mTOR promotes the senescence-associated secretory phenotype (SASP) that can contribute to age-related pathologies, including cancer.

The SASP is a major feature of senescent cells and involves the secretion of cytokines, growth factors and proteases. Cellular senescence, which is a state of permanent cell cycle arrest, usually inhibits tumorigenesis, as it prevents the proliferation of potential cancer cells. However, as senescent cells accumulate with age, persistent inflammation associated with the SASP can be damaging for tissues and can also contribute to cancer progression.

To explore the role of mTOR in cellular senescence and the link between mTOR activity and the SASP, the authors exposed senescent human cells to rapamycin, which selectively inhibits mTOR complex 1 (mTORC1). Rapamycin reduced the secretion of ~35% of the different SASP factors; importantly, it substantially decreased the secretion of the major SASP component IL-6.

Rapamycin suppresses mTORC1-mediated translation, but most SASP proteins are upregulated at the level of mRNA synthesis. The authors tested whether rapamycin could decrease nuclear factor-κB (NF-κB) activity in senescent cells, as NF-κB promotes the transcription of many SASP genes. Indeed, NF-κB activity was reduced by ~80%, suggesting that rapamycin suppresses NF-κB activity and SASP gene transcription by an indirect mechanism.

The pro-inflammatory cytokine IL-1α is not secreted by senescent cells, but it is abundant at their surfaces and has a key function in establishing and maintaining the SASP. NF-κB and IL-1α form a positive feedback loop that promotes the transcription of several genes encoding inflammatory cytokines. The authors observed that IL-1α mRNA levels were almost unaffected by rapamycin, but that protein levels on the surface of senescent cells were substantially lower. Moreover, depletion of IL-1α suppressed IL-6 secretion. These observations suggest that inhibition of mTORC1 by rapamycin interferes with the IL-1α–NF-κB feedback loop, which in turn suppresses the SASP. Consistent with this idea, rapamycin reduced IL-1α signalling, which prevented NF-κB nuclear translocation and transcriptional activation of target genes, including IL-6. Importantly, rapamycin specifically suppressed the translation of IL-1α.

Lastly, when prostate tumour cells were grafted into mice together with senescent cells, tumour growth was enhanced, but the tumour-promoting effects of senescent cells were reduced if they were pretreated with rapamycin. This suggests that mTOR signalling promotes tumour growth *in vivo*.

This work reveals a role for mTOR in driving the SASP by promoting the translation of IL-1α. As chemotherapy and radiotherapy induce cellular senescence, and such senescent cells might contribute to cancer relapse, the mTOR inhibitor rapamycin could potentially be used as adjuvant therapy for cancer.

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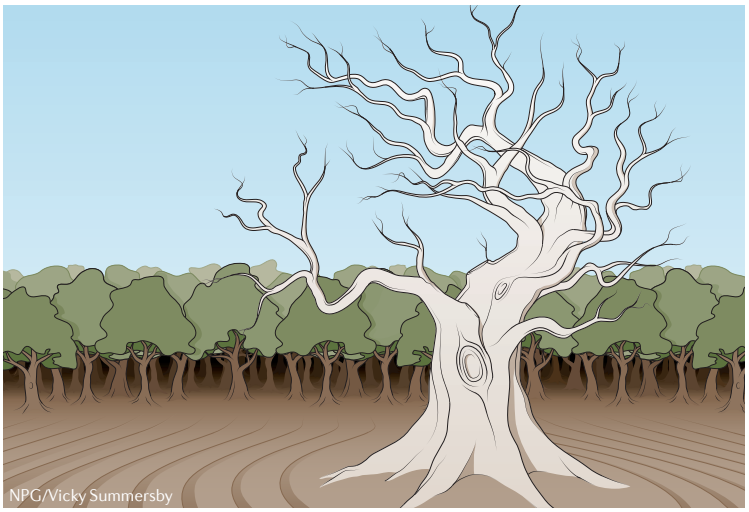

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ORIGINAL RESEARCH PAPER Laberge, R.-M. *et al.* MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. *Nat. Cell Biol.* http://dx.doi.org/10.1038/ncb3195 (2015)

FURTHER READING Muñoz-Espín, D. & Serrano, M. Cellular senescence: from physiology to pathology. *Nat. Rev. Mol. Cell Biol.* **15**, 482–496 (2014) | Zoncu, R., Efeyan, A. & Sabatini, D. M. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev. Mol. Cell Biol.* **12**, 21–35 (2010)