Article

mTOR regulates MAPKAPK2 translation to control the senescence-associated secretory phenotype

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ABSTRACT

Senescent cells secrete a combination of factors collectively known as the senescence-associated secretory phenotype (SASP). The SASP reinforces senescence and activates an immune surveillance response but it can also display pro-tumorigenic properties and contribute to age-related pathologies. In a drug screen to find novel SASP regulators, we uncovered the mTOR inhibitor rapamycin as a potent SASP suppressor. Here we report a mechanism by which mTOR controls the SASP by differentially regulating the translation of the MK2/MAPKAPK2 kinase through 4EBP1. In turn, MAPKAPK2 phosphorylates the RNA binding protein ZFP36L1 during senescence, inhibiting its ability to degrade the transcripts of numerous SASP components. Consequently, mTOR inhibition or constitutive activation of ZFP36L1 impairs the non-cell-autonomous effects of senescent cells both in tumour-suppressive and promoting-promoting contexts. Altogether, our results place regulation of the SASP as a key mechanism by which mTOR could influence cancer, age-related diseases and immune responses.