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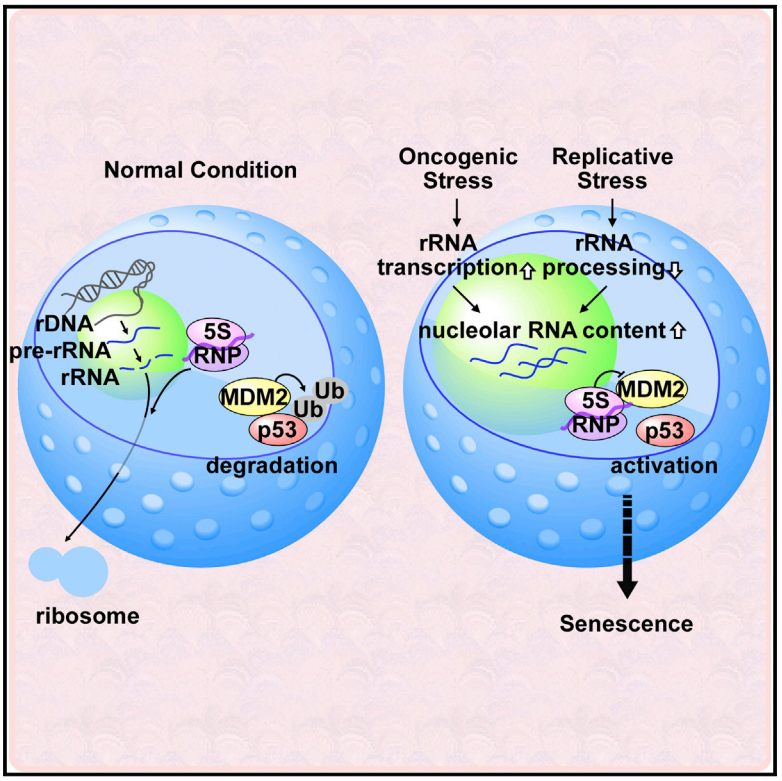
Perturbation of Ribosome Biogenesis Drives Cells into Senescence through 5S RNP-Mediated p53 Activation

Graphical Abstract



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In Brief

Somatic cells stop growing after repeated passage in a culture or oncogene activation, a state termed senescence. Nishimura et al. reveal that the nucleolus acts as a key regulator of senescence. Senescence was delayed by controlling ribosome biogenesis, providing a link between nucleolar function and the induction of senescence.

Highlights

- Oncogenic stress enhances rRNA transcription, inducing p53 activation and senescence
- Replicative stress delays rRNA processing, inducing p53 activation and senescence
- 5S RNP is required for p53 activation and senescence under these stresses
- Exogenous expression of rRNA-processing factors extends the replicative lifespan

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Perturbation of Ribosome Biogenesis Drives Cells into Senescence through 5S RNP-Mediated p53 Activation

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SUMMARY

The 5S ribonucleoprotein particle (RNP) complex, consisting of RPL11, RPL5, and 5S rRNA, is implicated in p53 regulation under ribotoxic stress. Here, we show that the 5S RNP contributes to p53 activation and promotes cellular senescence in response to oncogenic or replicative stress. Oncogenic stress accelerates rRNA transcription and replicative stress delays rRNA processing, resulting in RPL11 and RPL5 accumulation in the ribosome-free fraction, where they bind MDM2. Experimental upregulation of rRNA transcription or downregulation of rRNA processing, mimicking the nucleolus under oncogenic or replicative stress, respectively, also induces RPL11-mediated p53 activation and cellular senescence. We demonstrate that exogenous expression of certain rRNA-processing factors rescues the processing defect, attenuates p53 accumulation, and increases replicative lifespan. To summarize, the nucleolar-5S RNP-p53 pathway functions as a senescence inducer in response to oncogenic and replicative stresses.

INTRODUCTION

Most mammalian somatic cells lose proliferative capacity as a consequence of a finite number of population doublings, activation of oncogenes, inactivation of tumor suppressor genes, or treatment with DNA damage-inducing drugs, a state termed cellular senescence (Campisi and d'Adda di Fagagna, 2007; Kuilman et al., 2010; Pérez-Mancera et al., 2014). Although cellular senescence acts as a barrier to tumor formation by preventing proliferation or by inducing immune clearance of pre-malignant cells, recent studies have revealed that senescent cells are associated with age-related dysfunction through the inflammatory response (Baker et al., 2011; Campisi and d'Adda di Fagagna, 2007; Kang et al., 2011; Xue et al., 2007).

Several cellular events, including telomere dysfunction, DNA damage response (DDR), and oxidative stress response, activate p53-p14/p19^{Arf} and p16^{INK4A}-RB pathways during senescence (Campisi and d'Adda di Fagagna, 2007; Cichowski and Hahn, 2008; de Lange, 2009; Kuilman et al., 2010; Parrinello et al., 2003; Schramek et al., 2011). The tumor suppressor p53 acts as a vital regulator of stress response by inducing distinct classes of target genes for cell-cycle arrest, apoptosis, DNA repair, or cellular senescence (Levine and Oren, 2009; Prives and Hall, 1999; Vousden and Lane, 2007). Under normal physiological conditions, p53 is maintained at low levels by its interaction with E3 ubiquitin ligases such as MDM2 (Kruse and Gu, 2009; Lee and Gu, 2010). MDM2 is inhibited in response to cell stress, followed by upregulation of p53 transcriptional activity and the production of a number of downstream effects (Kruse and Gu, 2009; Lee and Gu, 2010; Levine and Oren, 2009; Prives and Hall, 1999; Vousden and Lane, 2007). For example, Arf binds and inhibits MDM2, thus preventing the degradation of p53 during replicative senescence and oncogene-induced senescence (Kamijo et al., 1998; Pomerantz et al., 1998; Randle et al., 2001; Zhang and Xiong, 1999).

Recent studies have revealed that the nucleolus senses various stressors and plays a coordinating role in p53 activation (Boulon et al., 2010; Rubbi and Milner, 2003). The most well-known function of the nucleolus is ribosome biogenesis, which involves transcription of precursor ribosomal RNA (pre-rRNA), pre-rRNA processing, and assembly of mature rRNA with ribosomal proteins. The nucleolus comprises RNA and a large number of proteins, some of which are released during stress (Andersen et al., 2005). For example, nucleophosmin, nucleolin, nucleostemin, and the ribosomal protein L11 (RPL11), RPL5, RPL23, and RPS7 directly bind to MDM2 and prevent ubiquitin-mediated p53 degradation, which delays proliferation under nucleolar stress (Dai and Lu, 2004; Manfredi, 2010; Marechal et al., 1994). RPL11 is a well-studied participant in the p53-nucleolar stress response pathway (Bhat et al., 2004; Lohrum et al., 2003; Macias et al., 2010; Zhang et al., 2003). Translational upregulation of RPL11 is observed during impaired 40S ribosome biogenesis, resulting in p53 activation (Fumagalli et al., 2009, 2012). Several studies have revealed that RPL11 regulates