Editorial

Senescence lncRNAs govern cell surface components: *lncRNA-OIS1* transcriptionally elevates DPP4

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With advancing age, senescent cells accumulate in tissues and organs, accelerating aging and age-related disease (e.g., diabetes, neurodegeneration, and cancers) (1). Cellular senescence is triggered by sublethal stresses including telomere shortening (replicative senescence), damage to DNA or other molecules (premature senescence), and oncogenic activation (oncogene-induced senescence, OIS) (2-5). Regardless of the trigger, all forms of senescence share common features like cell cycle arrest *via* p53 (TP53)/p21 (CDKN1A) and p16 (CDKN2A)/RB pathways, increased senescence-associated β-galactosidase (SA-β-Gal) activity, and the onset of a senescence-associated secretory phenotype (SASP) (6,7). OIS is tightly linked to tumor suppression, as it is elicited by unscheduled expression of oncogenic proteins such as HRAS, E2F1, RAF, BRAF, and MOS (8-11). The oncogenic protein $HRAS^{G12V}$ (bearing a mutation of G to V at amino acid position 12 in HRAS) triggers senescence and is commonly used as a model to trigger OIS (12).

Long noncoding RNAs (lncRNAs) are transcripts longer than 200 nucleotides that generally lack protein-coding potential. RNA sequencing (RNA-seq) analysis has identified a large number of lncRNAs expressed in various cells and developmental conditions (13-15). Although lncRNAs do not encode proteins, they are potent regulators of gene expression both at the transcriptional and post-transcriptional levels. They control transcription by modifying chromatin structure and recruiting transcriptional activators or repressors (16,17). For instance, the lncRNA *HOTAIR* (*HOX* transcript antisense RNA) is transcribed from the *HOXC* locus and mediates gene silencing of the *HOXD* locus by binding and recruiting the polycomb repressive complex 2 (PRC2) (18). Unlike *HOTAIR*, lncRNA *Evx1as* enhances EVX1 transcription by binding to Evx1as/EVX1 enhancer site and looping the chromatin between the promoter and enhancer. This conformation facilitates the assembly of machineries required for efficient EVX1 transcription (19). Post-transcriptionally, lncRNAs regulate gene expression in many different ways. They can form scaffolds enabling protein assembly of complexes and act as decoys to regulate the availability of microRNAs and RNA-binding proteins (RBPs) to mRNAs (20,21). They can also influence the formation of ribonucleoprotein complexes encompassing mRNAs and RBPs (22,23); for example, 7*SL* binds the 3' untranslated region (3'UTR) of *TP53* mRNA and suppresses expression of the tumor

suppressor TP53 by competing with the RBP HuR for interaction with *TP53* mRNA (24). LncRNAs can also form partial hybrids with mRNAs and thereby control mRNA turnover and translation. Together, these findings indicate that lncRNAs regulate gene expression by different mechanisms and are thus capable of regulating cellular processes like differentiation, proliferation, stress response, and senescence (25-27). Accordingly, they also influence pathologies including cardiovascular disease, cancer, diabetes, AIDS, and neurodegeneration (28).

There is growing interest in the function of lncRNAs in cellular senescence. An earlier survey of senescence-associated lncRNAs (SAL-RNAs) was conducted in replicatively senescent WI-38 fibroblasts. This study identified senescence-regulatory lncRNAs; for example, reduction of SAL-RNA1 enhanced the appearance of senescence traits (29). Other SAL-RNAs, including *TERC*, *HOTAIR*, *MALAT1*, *PINT*, *MEG3*, *ANRIL*, *Gadd*7, 7*SL*, *UCA1* and *PANDA*, have been functionally linked to senescence (24,26,30). However, little is known about the lncRNAs that might be implicated in regulating OIS. Using RNA-seq analysis, Li *et al.*, have recently reported altered expression of lncRNAs upon $HRAS^{G12V}$ induced-senescence in BJ fibroblasts. Among them, *lncRNA-OIS1* is upregulated during OIS and its silencing using shRNA selectively enhanced cell proliferation and reduced SA-β-gal activity (31).

To understand the mechanism through which *lncRNA-OIS1* regulates OIS, the authors analyzed gene expression profiles and found that cell cycle-related genes were highly enriched in *lncRNA-OIS1*-depleted cells. *In situ* hybridization (ISH) analysis indicated that *lncRNA-OIS1* is localized both in the nucleus and the cytosol, indicating that it may regulate gene expression in both compartments. As highlighted above, lncRNAs can regulate transcription in *cis* by influencing transcription in the vicinity of the locus from which they are transcribed or in *trans* by influencing transcription at a distant locus. Global run-on sequencing (GRO-seq) analysis revealed enhanced transcription of *lncRNA-OIS1* and the nearby gene *DPP4* (dipeptidyl peptidase 4, also known as CD26) upon OIS, while silencing *lncRNA-OIS1* lowered *DPP4* mRNA production. DPP4 is an integral transmembrane glycoprotein that is widely expressed in several tissues (32). DPP4 is linked to cardiovascular diseases, metabolic diseases and cancer (33-35). It is involved in Type II diabetes mellitus (T2D), as it functions in the degradation of incretins such as glucagon-like peptide-1 (GLP-1); accordingly, a DPP4 inhibitor was developed to treat T2D and maintain insulin by preventing the degradation of incretins (36). While the specific mechanisms whereby DPP4 influences senescence are unknown, DPP4 was found to be highly abundant on the cell surface of senescent WI-38 cells and was used to target senescent cells using the antibody-dependent cell-mediated cytotoxicity (ADCC) methodology (37). Despite the robust increase of *DPP4* mRNA levels in senescent cells (33), the molecular regulators of this rise were unknown until *lncRNA-OIS1* was reported by Li *et al.*, (31). The notion that DPP4 was a key effector of the *lncRNA-OIS1*-elicited senescence was supported by the fact that silencing DPP4 restored senescence even if *lncRNA-OIS1* was silenced (31). These findings indicate that *lncRNA-OIS1* rises during OIS and transcriptionally induces DPP4, which becomes a major effector of the ensuing senescent program.

While the full set of *DPP4* transcriptional regulators is unknown, the identification of *lncRNA-OIS1* is a major step forward, paving the way for the discovery of associated transcription factors. Since DPP4 expression was found elevated in other senescent models, including replicative and premature senescence, we hypothesize that *lncRNA-OIS1* may drive DPP4 induction under different senescent triggers (*Figure 1*). It will be interesting to investigate if *lncRNA-OIS1* also regulates the transcription of other RNAs upregulated in senescence, both coding and noncoding. The function of *lncRNA-OIS1* in senescence *in vivo* also warrants analysis. With rising interest in devising approaches to eliminate senescent cells due to their harmful impact in older age, targeting *lncRNA-OIS1* could have therapeutic benefits, possibly reducing damaging senescence-associated processes like inflammation. Finally, since DPP4 is further linked to diseases like T2D, there could be additional therapeutic value in targeting *lncRNA-OIS1* in diabetes.

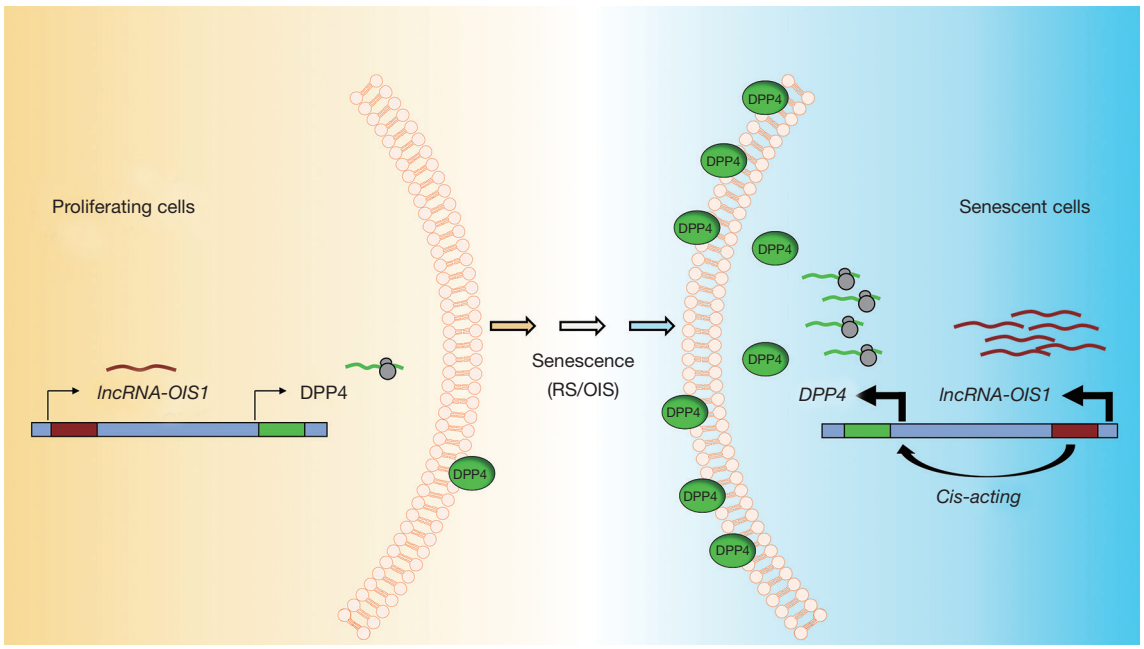

Figure 1 *LncRNA-OIS1* transcriptionally elevates DPP4 during senescence. In proliferating cells, *lncRNA-OIS1* and DPP4 are expressed at very low levels. Upon oncogene-induced senescence (OIS), *lncRNA-OIS1* is expressed to promote the transcription of *DPP4* mRNA. DPP4 in turn accumulates on the cell surface and accelerates the appearance of senescence traits.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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