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A new class of antisense RNAs that regulate gene expression

Cellular senescence is characterized by a stable cell proliferation arrest in response to different stresses such as oncogene activation. It is thus considered as a major anti-cancer barrier. However, the accumulation of senescent cells can lead to diseases related to normal and pathological aging. Cellular senescence is accompanied by the setting up of a specific gene expression program and important changes in chromatin structure. Long non-coding RNAs (ncRNAs) participate in the regulation of gene expression through the regulation of chromatin structure.

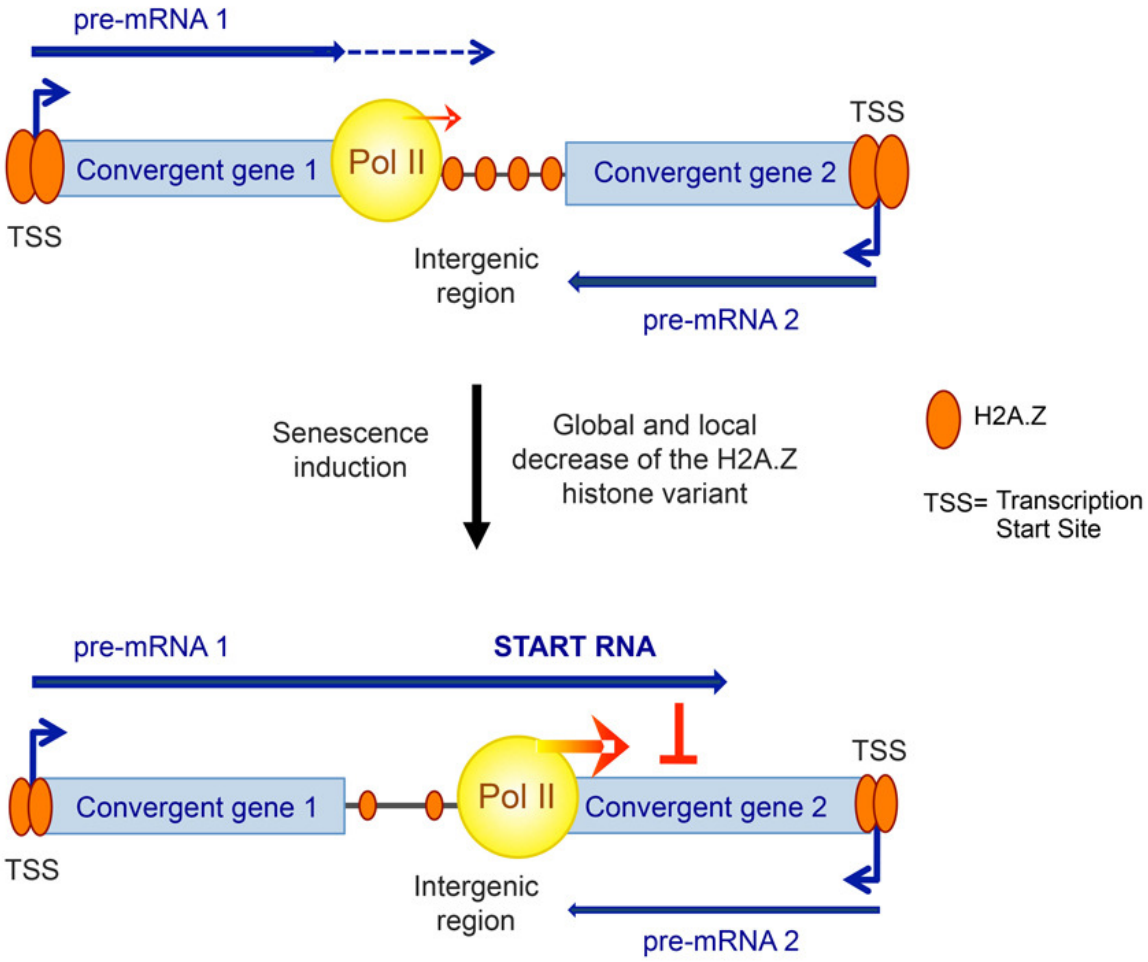

Fig. 1. Model of START RNA regulation and function during senescence induced by the activation of the RAF1 oncogene, modified from Muniz et al., Cell Reports, 2017.

In an attempt to identify new long ncRNAs playing a role in the control of cell senescence, Muniz, Deb et al. performed bioinformatics analyzes of RNA-seq datasets in proliferation and in oncogene-induced senescence of human cells. They discovered a new class of ncRNAs produced from converging protein-coding genes (two

adjacent genes in opposite orientation in the genome). The production of these ncRNAs is due to a defect of transcription termination at one of the two converging genes (Fig. 1).

These RNAs, called START RNAs (Senescence-Triggered Antisense Read-Through RNAs), are antisense to the other gene in the converging gene pair and repress its expression during oncogene-induced senescence. The production of these regulatory RNAs is increased in senescence by mechanisms involving the regulation of the localization of the histone variant H2A.Z as well as an increase in the elongation rate of RNA polymerase II (pol II) downstream of the termination site.

This work highlights a new mechanism allowing the rapid regulation of gene expression without new transcription initiation events, based on the epigenetic control of the RNA pol II elongation rate downstream of genes. This suggests the importance of gene positioning and orientation in the genome as well as epigenetic control of intergenic regions for the correct expression of the genome. In addition, START RNAs, as new actors in the senescence gene expression program, could play important roles in normal and pathological cell aging and tumor suppressor mechanisms.

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Publication

Control of Gene Expression in Senescence through Transcriptional Read-Through of Convergent Protein-Coding Genes.
Muniz L, Deb MK, Aguirrebengoa M, Lazorthes S, Trouche D, Nicolas E
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