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COMMENTARY

Intronic Polyadenylation and Cellular Senescence: A Novel Perspective

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Cellular senescence, a state of irreversible cell cycle arrest, can be triggered by DNA damage, telomere shortening, oncogene activation, and mitochondrial dysfunction (Di Micco et al. 2021). This process is regulated by multiple signaling pathways. For instance, nuclear factor-κB (NF-κB) induces the senescence-associated secretory phenotype (SASP), promoting chronic inflammation (Muñoz-Espín and Serrano 2014). While initially recognized as a tumor-suppressive mechanism, cellular senescence also contributes to aging and age-related diseases through inflammation and tissue dysfunction (Krtolica et al. 2001). Its complexity in various biological processes has led to extensive research (Di Micco et al. 2021), yet its molecular regulation remains unclear, largely due to the complexity of gene regulatory mechanisms.

One potential mechanism is alternative polyadenylation (APA), which generates mRNA isoforms with altered 3′ untranslated region (3′UTR) length by selecting alternative polyadenylation signals (PASs) in pre-mRNA, a process mediated by the cleavage and polyadenylation (CPA) machinery (Mitschka and Mayr 2022). APA changes can influence critical biological functions such as immune responses and cancer susceptibility (Chen et al. 2024; Li et al. 2023).

In addition to the 3′UTR regions, APA events also occur within introns, known as intronic polyadenylation (IPA), where RNA polymerase II (Pol II) terminates transcription at an intronic PAS, generating alternative last exon isoforms with physiological functions and cell-type-specific expression (Ma et al. 2023). Moreover, dysregulated IPA can lead to disease by producing non-functional truncated transcripts. For example, in B-cell leukemia, IPA-induced truncation of tumor suppressor genes results in gene inactivation, promoting disease development (Lee et al. 2018).

Previous studies suggest that 3′UTR APA affects cellular senescence (Chen et al. 2018), but the role of IPA in this process remains unexplored. In this context, Li et al. first revealed IPA's regulatory role in cellular senescence (Fig. 1), focusing on IPA-mediated changes in *Glutaminase* (*GLS*) (Li et al. 2025). *GLS* encodes glutaminase, an enzyme which converts glutamine (Gln) to glutamate (Glu), playing a key role in glutamine metabolism and cellular function (Grinde et al. 2019). Its splicing variant *GAC* is highly expressed in cancer cells, accelerating the tricarboxylic acid (TCA) cycle to support the rapid proliferation of cancer cells (Cassago et al. 2012). Li et al. found that GAC, generated by *GLS* IPA events, is downregulated during cellular senescence, triggering cell cycle arrest and increased SA-β-Gal staining. The mechanism may be related to elevated reactive oxygen species (ROS) levels and reduced ATP synthesis. Further research identified CPSF6 as a key regulator of *GLS* IPA, where CPSF6 knockdown mimics GAC loss-induced cellular senescence, while GAC overexpression reverses this effect (Li et al. 2025).

However, the study still has some limitations. Firstly, the physiological relevance is limited due to differences between *in vitro* and *in vivo* environments. Therefore, further validation in animal models is essential. Secondly, although Li et al. (2025) proposed that reduced GAC expression induces cellular senescence due to increased ROS levels and decreased ATP, the specific molecular details remain unclear. Previous studies have shown that *GLS* supports the TCA cycle, thereby supplying ATP (Yoo et al. 2020), and promotes glutathione (GSH) synthesis to regulate ROS levels (Matés et al. 2020). Future research could focus on these mechanisms to better understand how reduced GAC expression induces cellular senescence. Additionally, this study links *GLS* IPA regulation to cellular senescence and cancer but lacks insight into tissue and cell-type specificity. Future research could use single-cell RNA sequencing (scRNA-seq) to analyze the expression of *GLS* and its isoforms across tissues and cell types, and validate *GLS* IPA as a potential biomarker in aging-related disease models or clinical samples. Finally, while the study suggests that *GLS*

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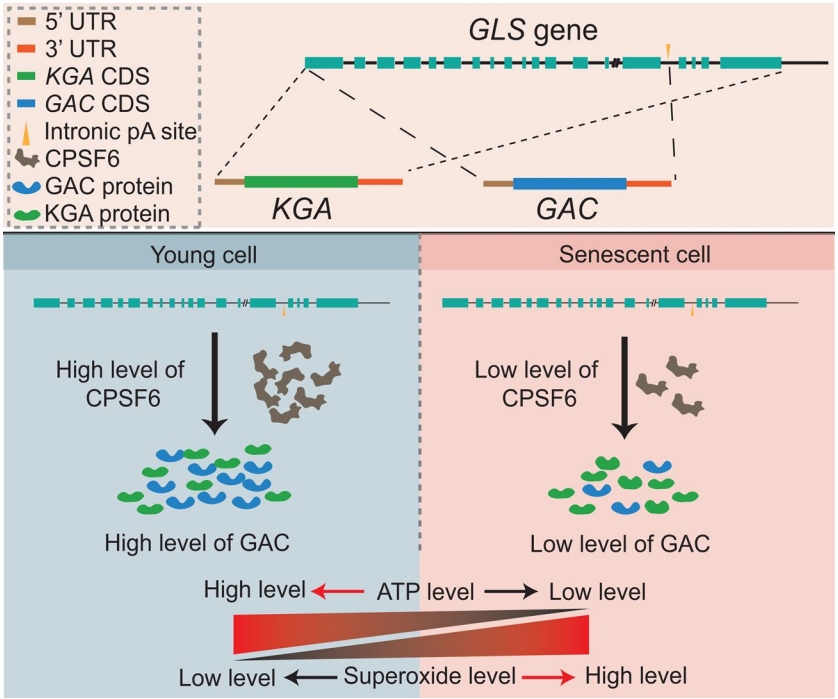

Fig. 1 Schematic depicts reduced *GLS* IPA usage promoting cellular senescence

IPA dysregulation could serve as a therapeutic target, potential therapeutic strategies remain unexplored. Future studies could investigate small molecules to enhance CPSF6 activity as a potential therapeutic strategy.

Taken together, the study by Li et al. (2025) reveals the regulatory role of IPA in cellular senescence and the underlying mechanisms. This provides a new perspective on the molecular regulation of cellular senescence and therapeutic strategies for aging and cancer.

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Declarations

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