Journal club

INSTRUCTIVE POWER OF SENESCENCE

Since its discovery more than 50 years ago and until recently, cellular senescence has been primarily associated with permanent withdrawal from the cell cycle, which was suggested to contribute to organismal ageing in a cell-autonomous manner, whereby senescent cells accumulate during ageing and prevent tissue self-renewal. Concomitantly, this stable cell cycle arrest was viewed as a barrier to aberrant cell proliferation during tumour initiation, raising the question of how the accumulation of senescent cells during ageing and the increased susceptibility to cancer with age could be reconciled.

In the past 10 years our understanding of the impact of cellular senescence on cancer development and ageing has largely evolved owing to the discovery of paracrine effects associated with senescence, known as the senescence-associated secretory phenotype (SASP). Numerous proteins covering a wide range of biological activities, such as inflammation, immunity, fibrosis, wound healing and reprogramming, have been shown to be secreted by senescent cells (Coppé et al., 2008). Recently, these senescent-associated secreted factors (SASFs) have been extended to lipids (Loo et al., 2017).

Even though the details of the SASF profiles of different cell types remain unknown, it is now apparent that SASP does not comprise a single response but rather that SASF expression and thus the SASP secretome can be flexibly regulated, resulting in different types of SASP (Herranz et al., 2015; Laberge et al., 2015; Hoare et al., 2016). Accordingly, depending on SASF composition and signal duration, local tissue environment and the type of the signal-receiving cell, senescent cells might communicate largely different, even opposing, instructions; for instance, tissue fibrosis versus wound healing or paracrine senescence and degeneration versus cell proliferation and reprogramming.

In summary, the discovery that senescent cells communicate with their environment to control different behaviours largely modifies the previous dogma of cell senescence as a dormant state and advocates for its multifunctionality, which now needs to be explored in more detail.

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The author declares no competing interests.

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RNA METABOLISM

TUT-TUTting retrotransposons

Retrotransposons are mobile genetic elements that, once transcribed, are capable of self-driven re-integration at various genomic sites through reverse transcription (retrotransposition), with consequences to genomic variation and stability. Retrotransposons constitute a considerable proportion of the human genome. Although most of these elements have lost the ability to retrotranspose, some, including 80–100 copies of long interspersed element-1 (LINE-1), remain active. How LINE-1 transposition is controlled, particularly at the post-transcriptional level, is incompletely understood. Warkocki et al. now show that 3′uridylation of LINE-1 mRNAs by terminal uridyltransferases (TUTases) inhibits LINE-1 retrotransposition.

3′Uridylation is a prevalent post-transcriptional mRNA modification that in most cases drives mRNA degradation. The authors found that in human cells and mouse testes, LINE-1 mRNAs prominently undergo 3′uridylation by two cytoplasmic TUTases, TUT4 and TUT7. Depletion of the TUTases caused an upsurge in LINE-1 retrotransposition. The opposite effect was observed with TUT4 or TUT7 overexpression and the presence of even a single 3′uridine considerably reduced the efficiency of retrotransposition. Furthermore, 3′uridylation was associated with decreased 3′adenylation, and uridylated LINE-1 mRNAs lacking poly(A) tails completely lost the capacity for retrotransposition.

TUT4 (but not TUT7) localized to distinct cytoplasmic foci, where 3′uridylation seemed to promote the destabilization of LINE-1 mRNAs. Both TUT4 and TUT7 interacted with a known but insufficiently understood regulator of LINE-1 retrotransposition, the helicase MOV10. In vitro studies revealed competition for LINE-1 mRNAs between MOV10 and the LINE-1-encoded nucleic acid chaperone. This chaperone was shown to inhibit 3′uridylaton in a dose-dependent manner, likely by protecting the LINE-1 mRNAs from the activity of TUTases.

Credit: Lara Crow/Springer Nature Limited

The authors propose a model in which, by displacing the protective chaperone from LINE-1 mRNAs, MOV10 promotes TUT4 and TUT7 recruitment and subsequently uridylation at the mRNA 3′end. In addition, the presence of 3′uridines likely interferes with the initiation of reverse transcription of LINE-1 in the nucleus, which is primed by oligo(dT)–poly(A) interactions.

Interestingly, another recent study indicates that TUT4 and TUT7 uridylate RNAs of animal RNA viruses, thereby restricting viral replication. This is perhaps not surprising, considering the extensive mechanistic similarity between retrotransposons and retroviruses — RNA viruses that use reverse transcription and integration into host DNA as a part of their lifecycle. Thus, studies of retrotransposon restriction could provide valuable insights into antiviral responses.

Paulina Strzyz

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