Senescent cells spread the word: non-cell autonomous propagation of cellular senescence

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Senescence has long been considered a cell autonomous arrest programme restricting the propagation of damaged cells in tissues. Now there is accumulating evidence that senescent cells can communicate with their environment. In a recent report by Gil and colleagues (Acosta *et al*, 2013), it now seems senescence can be transmitted in a paracrine fashion in several *in vitro* and *in vivo* contexts. In addition to broadening our understanding of the biology of senescence, these new findings may have interesting implications for tissue homeostasis and future cancer therapies.

Senescence is a form of stress-induced cell cycle arrest that restricts the proliferative capacity of damaged and/or potentially harmful cells (Rodier and Campisi, 2011), thereby promoting tissue homeostasis and tumour suppression. While the senescence-associated cell cycle arrest involves the well-studied Rb and p53 pathways, senescent cells also possess the less understood ability to secrete growth factors, cytokines and chemokines into their environment. This process, collectively known as the senescence-associated secretory phenotype (SASP; Rodier and Campisi, 2011), was originally used to mark senescent cells, but is now known to

Figure 1 Cell autonomous and non-cell autonomous effects of cellular senescence. Stress stimuli such as activation of oncogenes and DNA damage can trigger normal mitotic cells to go into senescence. This involves inflammasome-mediated activation of IL-1 signalling, which initiates the SASP response. The SASP acts cell autonomously (autocrine) to reinforce the senescent phenotype via cytokines such as IL-6. The SASP also acts non-cell autonomously (paracrine) to influence the cells in the surrounding environment. For example, SASP components such as VEGF, TGFβ and CCL2 can trigger bystander senescence on neighbouring cells. Paradoxically, the SASP can also exert pro-mitogenic stimulation of neighbouring cells via cytokines like IL-6, which appear to play dual roles depending on the context. Furthermore, the SASP can act on the immune system via pro-inflammatory cytokines, leading to immune cell recruitment and subsequent targeting and clearance of senescent cells. Alternatively, the SASP can trigger upregulation of p16 and p21 levels on neighbouring immune cells, the functional consequences of which are not yet so clear.

enforce cell cycle arrest, modify the microenvironment and trigger immune surveillance of senescent cells (Xue *et al*, 2007; Krizhanovsky *et al*, 2008; Rodier and Campisi, 2011).

Adding to our understanding of this process, a recent report by Gil and colleagues showed that the SASP can also mediate paracrine transmission of cellular senescence (Acosta *et al*, 2013). By co-culturing cells undergoing oncogene-induced senescence (OIS) with normal cells, the authors showed that the senescence phenotype could be transmitted to surrounding cells via the soluble SASP proteins. Coupling quantitative proteomics with small-molecule inhibitor screens, they identified key players mediating the paracrine transmission of senescence, including TGF β , VEGF and CCL2 pathways. A search for upstream regulators of SASP pointed at IL-1 signalling and the inflammasome, molecules that operate cell autonomously to control SASP production and non-cell autonomously to spread the senescent phenotype via the SASP (Figure 1). Complementing the *in vitro* senescence findings, experiments using mouse and human models of OIS demonstrated evidence for paracrine senescence transmission *in vivo*.

The ability of senescent cells to propagate their phenotype is consistent with previous studies identifying IGFBP7 as a paracrine senescence regulator (Wajapeyee *et al*, 2008) and provides important insights into senescence biology. It is conceivable to think that the induction of paracrine cell cycle arrest could expand the senescence footprint of the pre-neoplastic lesion to the surrounding epithelium. This could potentially serve to amplify the tissue damage signal, recruit more immune cells and ensure more efficient clearance of damaged cells. In parallel, the induction of paracrine senescence in other cell types within the tissue, for example tumour-associated fibroblasts, could repress their reported paracrine tumour-promoting effects (Krtolica *et al*, 2001).

Despite the biological implications, a number of questions remain. Why, for instance, is paracrine senescence triggered in some cells surrounding pre-neoplastic lesions but not in others? Similarly, what is the functional significance of paracrine senescence induction in the surrounding immune cells? Intriguingly, recent evidence implies that p16 can also be induced in tumour-infiltrating immune cells

(Burd *et al*, 2013). It will be important to determine whether the paracrine p16 induction in immune cells leads to the same consequences as in non-immune cells and whether the induction of a potential arrest programme compromises the ability of the immune cell to clear senescent cells.

Beyond the biological implications, the key regulators of paracrine senescence have potential to be manipulated therapeutically. It is commonly believed, for instance, that senescent cells accumulate in aging tissues and disrupt tissue architecture and function (Rodier and Campisi, 2011). In this context, antagonists of paracrine senescence might limit the spread of senescence and prove beneficial for some age-associated disorders. In the context of cancer, both chemotherapeutic drugs and radiation are known to induce senescence in tumour cells (Schmitt, 2007; Prise and O'Sullivan, 2009). The use of agents agonizing paracrine senescence as adjunctive therapy could potentially increase the effectiveness of chemo- and radiotherapy by triggering a bystander response.

Nonetheless, it is critical to keep in mind that the SASP may not always relay an arrest-inducing message onto the surrounding cells. Indeed, the SASP component IL-6 has been shown to elicit a pro-mitogenic response in a paracrine fashion (Kuilman *et al*, 2008). Similarly, the SASP has been shown to be pro- and anti-tumorigenic depending on the microenvironment (Krtolica *et al*, 2001; Xue *et al*, 2007; Lujambio *et al*, 2013; Figure 1). Collectively, these findings suggest that the ultimate outcome of senescence within a tissue is highly dependent on the context. But what then determines this context? One decisive factor could be whether or not the senescence signal engages in sufficient modulation of the immune system to provoke clearance. In cases where the senescent cells in a tissue are not cleared, the pro-mitogenic arm of the SASP signal could persist long enough to have an overall pro-tumorigenic effect. It will thus be important to understand all the flavours of SASP to modulate it safely for therapeutic purposes.

Conflict of interest

The authors declare that they have no conflict of interest.

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