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Senescence and cancer: An evolving inflammatory paradox

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ABSTRACT

The senescent phenotype was first described in 1961 as a phenomenon characterized by the cessation of cellular division. After years of debate as to whether it represented a tissue culture artifact or an important biological process, it is now appreciated that senescence plays an important role in tumorigenesis. Further, senescence is integral to normal biological processes such as embryogenesis and the maintenance of tissue homeostasis. Now with defined roles in development, wound healing, tumor promotion and tumor suppression, it is not surprising that attention has turned to refining our understanding of the mechanisms behind, and consequences of, the induction of senescence. One emerging role for senescence lies in the ability of senescence to orchestrate an inflammatory response: factors secreted by senescent cells have been identified in multiple contexts to modulate various aspects of the immune response. As with many of the previously described roles for senescence, the type of inflammation established by the senescence phenotype is varied and dependent on context. In this review, we discuss the current state of the field with a focus on the paradoxical outcomes of the senescence-induced inflammatory responses in the context of cancer. A more complete understanding of senescence and an appreciation for its complexities will be important for eventual development of senescence-targeted therapies.

1. The senescence phenotype

Cellular senescence has documented roles in halting tumor development through its induction of an irreversible cell cycle arrest and ability to elicit potent immune-mediated clearance of incipient tumor cells [1–6]; however, like many cellular processes, the complexities that surround the senescence phenotype are still not fully understood. While there is convincing evidence that senescence can function in a cell-autonomous manner to halt tumor development in preneoplastic epithelial cells, the nuanced outcomes of cellular senescence both in the stromal compartment and the epithelial compartment have proven varied, and at times paradoxical [7–9]. Indeed, in xenograft settings stromal senescence can be potently tumor promoting. More recently, senescent cells have been found to modulate host immune responses, in addition to roles in regulating tumor cell intrinsic mechanisms fostering neoplastic progression [3,4,9–15]. Interestingly, there is now evidence that this interplay between senescent cells and immune cells is bidirectional given that tumor-infiltrating Gr-1$^+$ myeloid cells can antagonize senescence induction within tumor epithelium [16]. This review focuses on the impact senescent cells have on host immune responses, and how this relationship impacts overall tumorigenesis.

1.1. Hallmarks of the senescence phenotype

There are many inducers of the senescence phenotype: oncogene-induced senescence (OIS), telomere dysfunction (known as replicative senescence, (RS)), therapy-induced senescence (TIS), and chronic stress stimuli such as high levels of reactive oxygen species (ROS), among others [1,2,17–21]. All of these inducers converge upon activation of a chronic DNA-damage response (DDR), induction of the tumor suppressor p53, or independent activation of the cell cycle inhibitor p16^{INK4A} (p16). Activation of p16 drives irreversible exit from the cell cycle through inhibition of CDK4- and CDK8-mediated phosphorylation of the retinoblastoma protein (Rb) [11,22,23].

While no single marker is sufficient to identify senescent cells, a combination of biomarkers and cellular characteristics identify senescent cells both in vivo and in vitro. Importantly, these markers are sufficient to identify senescent cells regardless of the senescence inducer or cell type. Typically, senescent cells are immunoreactive for senescence-associated beta-galactosidase (SA-βgal), express p16, display a flattened and enlarged morphology in vitro, and express an altered gene expression profile, e.g., the senescence-associated secretory phenotype (SASP), activated in response to chronic DNA-damage

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response (DDR), and sustained by activation of the stress kinase p38MAPK (p38) [24–28]. Adding further complexity to understanding senescence is the fact that SASP itself varies depending on the cell type being examined [29–37]. Of note, a recent study reported that the SASP of oncogene-induced senescent cells propagates the senescence phenotype to neighboring cells via paracrine mechanisms highlighting a particular importance for interleukin (IL)-1α in this process [38]. In any case, it is the SASP that functionally dictates the striking diversity in cell-autonomous and cell-non-autonomous roles of senescence phenotypes [26,34,35].

1.2. Molecular mechanisms governing SASP expression

A significant body of literature exists concerning the molecular control of the SASP [26,28,32,39–41]. Though many questions still remain, it is known that robust SASP expression results from chronic activation of the DDR, in response to DNA damaging agents, expression of oncogenes or loss of tumor suppressors, increased ROS, telomere dysfunction, and other prolonged cellular stresses [26,31,32,34,39,42]. In most settings, this requires activation of ataxia-telangiectasia mutated (ATM) and subsequent activation of nuclear factor kappa B (NFκB) signaling [41,43]. Once established, sustained activation of p38 plays a pivotal role in maintaining expression of a significant number of SASP factors though not all SASP factors require activation of NFκB or p38 [26,41,43]. Interestingly, and often confusing to many, p53 plays a key role in suppressing the SASP; indeed, loss of p53 in the face of a chronic DDR leads to increased expression of a cadre of SASP factors [26,32].

2. Multifaceted roles for senescence

While many studies focus on roles for senescence in tumor promotion and progression, senescence was first discovered as a potent tumor suppressive mechanism [3,4,44]. Senescence within preneoplastic cells limits their expansion and consequently is important for maintenance of tissue integrity [7,8]; senescence, in this way, poses a barrier to incipient tumor development. Indeed, it is necessary for neoplastic cells to bypass the senescence phenotype, typically through loss of p53 and/or Rb, for preneoplasia to progress to frank neoplasia, and on to malignancy [44,45]. In addition to limiting replicative capacity, activation of senescence within certain neoplastic cell types, under specific contexts, leads to increased expression of inflammatory cytokines that elicit immune-mediated tumor clearance [5,6,46]. Senescence-induced, anti-tumorigenic, inflammatory phenotypes will be discussed in detail below.

2.1. Developmentally programmed senescence

There are several roles emerging for senescence outside the context of tumor development; a new role for senescence was recently discovered in embryonic development. Two seminal papers reported that developmentally programmed senescence occurs during embryogenesis at multiple sites and is important for patterning of mammalian embryos [47,48]. This senescence program is dependent on p21 but differs from oncogene-induced senescence (OIS) or replicative senescence (RS) in that it is independent of DDR signaling and p53. In development, these senescent cells express a SASP with many overlapping factors with OIS SASP. Storer and colleagues, in conjunction with the findings from Muñoz-Espín and colleagues, revealed that senescence induction during development elicits macrophage-mediated senescent cell clearance where clearance of senescent cells results in tissue remodeling necessary for normal morphogenesis [47,48]. These findings support the notion that senescence activation in post-embryonic tissues marks an evolutionarily co-opted mechanism of an otherwise necessary developmental process. It however remains unclear how SASP mechanistically results in recruitment of macrophages during embryogenesis. It is possible that studies focused on senescent cell clearance from tumors will provide insights into this developmental process.

2.2. Senescence promotes wound repair

In addition to development, senescence induction was recently discovered to play an integral part in the maintenance of tissue homeostasis where Demaria and colleagues [49] reported an essential role for senescence in optimal wound repair. Using a model of cutaneous injury, these investigators reported that following wounding, rapid induction of senescence was detected in both endothelial cells and fibroblasts. In this system, senescence induction accelerated the rate of healing by SASP factor, platelet-derived growth factor AA (PDGF-AA), mediated myofibroblast differentiation. Wounds depleted or devoid of senescent cells exhibited delayed kinetics in wound closure, thus identifying a unique and non-deleterious role for the SASP in adult tissues [49]. Whether wound-induced senescence modulates the host immune response remains an interesting and important question.

2.3. Dual roles for senescence in tumorigenesis

New evidence indicates beneficial outcomes for the senescence program in addition to its well-accepted, and first noted, role in cell-autonomous inhibition of neoplastic cell proliferation [3,4,44]. However, research from several groups over the past two decades has convincingly demonstrated a paradoxical role for senescence emanating from its distinct secretory profile [9,26,34,35]. A clear, cell-non-autonomous, role exists for senescence in neoplastic progression of solid tumors [26,50–52]. SASP factors such as osteopontin (OPN), amphiregulin (AREG) and GROα can drive proliferation of preneoplastic and neoplastic cells [33,42,53]. Extracellular matrix modifying enzymes, such as the canonical SASP factor matrix metalloproteinase (MMP)-3, disrupts normal tissue structure and drives invasive properties along with factors such as IL-6 and IL-8 [26,54,55]. Growth of tumors is further supported through increased angiogenesis derived from heightened expression of SASP factor vascular endothelial growth factor (VEGF) [56]. Evidence from in vitro studies indicates that IL-6 and IL-8 can also promote epithelial-to-mesenchymal transition (EMT) from premalignant cells and non-aggressive tumor epithelial cells [26]. In this way, senescent stromal cells were found to function analogously to cancer-associated fibroblasts (CAFs), which also express a plethora of tumor promoting factors [10,28,33,57,58].

While the tumor-promoting functions of the SASP are varied, the majority of the research elucidating these phenotypes relied on xenograft models and immune-compromised mice [42,50,51,53]; thus, in recent years, introduction of immune-competent murine models has revealed additional roles for senescence in the inflammatory response associated with cancer [5,6,30,47–49]. It had long been hypothesized that senescent cells could impact tumor-associated inflammation given that the SASP is enriched in many cytokines and chemokines. However, it was not until recently that the complexities of senescence-orchestrated inflammation have been brought to light. As is the story of senescence in nearly all contexts investigated, senescence-associated inflammation exerts its effects in a context-dependent manner resulting in paradoxical outcomes dependent on the cells and tissue of origin [5,6,30,47–49].

3. A role for senescence in inflammation: The SASP

Inflammation, like senescence, within the context of cancer is a double-edged sword (reviewed in [59,60]). Indeed there are clear roles for acute inflammation in the detection of early preneoplastic lesions where immune surveillance and lymphocyte-mediated tumor cell clearance are an indispensible part of anti-tumor immunity [61]. However, many studies have reported that chronic inflammation can be a key driver of tumor development and indeed a hallmark