Senescence-Associated Secretory Phenotype

Subjects: Immunology

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The Senescence-Associated Secretory Phenotype (SASP), also known as Senescence-Messaging Secretome (SMS), is one of the fundamental characteristics of the senescent cell, consisting in the abundant secretion of generally proinflammatory compounds in the tissue microenvironment.

Keywords: senescence ; SASP

1. Introduction

The Senescence-Associated Secretory Phenotype (SASP), or Senescence-Messaging Secretome (SMS), can be defined as a highly variable, dynamic, and long-lasting program of senescent cells, consisting in the abundant secretion of generally proinflammatory compounds in the tissue microenvironment [1]. Investigators of SASP have demonstrated the presence and the biological relevance, among the secreted proteins, of numerous cytokines, growth factors, chemokines, and matrix-metalloproteinases. Moreover, the contribution of small molecules, such as ROS, miRNAs, and extracellular vesicles (EVs), which represent an intensively investigated area of research, may be considered an important target in the future [2][3].

The spectrum of secreted molecules seems to be so broad, diversified, and context-dependent that, unsurprisingly, contradictory interpretations have been proposed about the role of SASP in the pathophysiology of chronic diseases [4]. Albeit the general agreement on the detrimental aspects of the SASP in the context of cancer and age-related disorders, the evidence for a protective role of SASP-evoked immune response should not be neglected [5]. Indeed, the SASP has the potential to attract innate and adaptive immune cells in proximity of tumor cells and pre-malignant lesions [6][7][8] or enhance cytotoxicity against drug-induced senescent tumor cells [9][10][11][12].

The experimental models used to investigate senescence and SASP still confirm the intricacy of the subject. Certainly, the type and strength of the senescence-inducing stimulus, the identity of the cell undergoing senescence, the composition, and time-dependent variability of the secretome, are all crucial aspects to consider in the research on SASP. In addition, when evaluating the effects of SASP within tissues or tumors, the quality of the immune infiltrate and the persistence/accumulation of senescent cells over time represent additional layers of complexity. However, a certain degree of overlap has been demonstrated among various SASPs, with specific proteins being found almost invariably, namely IL-1, IL-6, IL-8, GROα/β, GM-CSF, MMP-1, MMP-3, MMP-10, ICAM-1, PAI-1, and IGFBPs [13].

2. Specifics

The emergence and maintenance of SASP are controlled by multiple stress response pathways; however, many of these seem to converge on two central transcription factors, NF-κB and GATA-4, which therefore are considered the main regulators of SASP transcriptional control [14][15].

The biological function of SASP is a highly debated subject. SASP is thought to contribute to age-related organ dysfunction; indeed, senescent cells accumulate in various tissues during aging and the inflammatory milieu created by them contributes to the so-called “inflammaging”, a low-grade, sterile and chronic state of inflammation that characterizes the aged organism [16]. Accordingly, the seminal work of Baker and colleagues (2011) demonstrated how the selective elimination of senescent cells (or at least of p16 Ink4a -expressing cells) in progeroid mice results in delayed onset of age-related conditions [17]. Abrogation of SASP in senescent preadipocytes using JAK inhibitors similarly reduces systemic inflammation and frailty in aged mice [18].

Being senescence often considered a tumor-suppressing mechanism [19], the pro-tumorigenic activity of SASP, demonstrated *in vivo* and *in vitro*, is difficult to explain [20]. For instance, SASP largely promotes the proliferation of malignant epithelial cells, presumably through the secretion of growth factors and matrix metalloproteinases [21][22]. The degradation of the extracellular matrix mediated by the secreted enzymes fosters tumor migration and metastatization [23].

In specific contexts, SASP shows to promote tumor angiogenesis through the production of VEGF and other angiogenic factors [24]. Consistently to this evidence, ablation of the proinflammatory secretome of premalignant senescent cells leads to a lesser number of neoplastic lesions in a mouse model of pancreatic cancer [25].

In contrast, in an experimental model of liver carcinoma, the SASP is required for the effective tumor clearance mediated by innate immune cells, especially by Natural Killer cells [26]. The immune surveillance of senescent cells evoked by the SASP may represent an important mechanism to control the development of pre-malignant lesions in the liver [27].

From the point of view of evolution, the apparent contradiction between the tumor-suppressive role of senescence and the pro-tumorigenic activity of SASP has been partially addressed with the concept of “antagonistic pleiotropy” [28].

According to this concept, senescence as a tumor-suppressive mechanism underwent positive selection because of the benefit it confers at young ages. On the other hand, the detrimental effects of SASP on tumor development and age-related conditions are manifested only in aged organisms, on which negative selection does not act. It is clear that the accumulation of senescent cells is typical of old age and might be due to the decline of immune surveillance and induction of paracrine senescence. Therefore, the negative impact of SASP could be prevalent only in tissues highly populated by senescent cells and not in young tissues.

An alternative explanation can be found in functions unrelated to aging and cancer, like the positive role of senescence on tissue regeneration and remodeling during embryonic development [29][30][31].

Strategies aimed at abrogating or modulating the SASP are currently being investigated for translational purposes, although this area of research is still in its infancy [32][33].

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