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Review

Senotherapy for attenuation of cellular senescence in aging and organ implantation

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ABSTRACT

Cellular senescence in transplant is induced by aging and therapy-induced stress, which is caused by generation of senescent cells in transplant during engraftment. These senescent cells induce transplant failure due to secretion of senescence-associated secretory phenotype (SASP). So, elimination of senescent cells in transplant is important for successful comes. Recently, numerous studies have focused on the development of various senolytic agents such as dasatinib, quercetin, and navitoclax according to cellular type of transplant. Therefore, this study reviews the influence of cellular senescence in transplantation and capacity of senolytic agents as a new therapeutic strategy for successful outcomes of transplant.

Contents

Introduction

Primary cells undergo a finite number of divisions before experiencing irreversible cell cycle arrest. However, when cells are exposed to oncogenic insults, the cell cycle is arrested by cellular senescence, demonstrating an anti-cancer effect to inhibit cancer cell division [1,2]. On the other hand, it is known that cellular

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senescence cause general tissue dysfunction and aging [3–5], which is important in organ/cell transplantation. In practice, older donors are an unavoidable choice due to organ or cell shortage because the age can affect long-term survival of the transplant by increasing acute organ injury and reducing tissue regenerative capacity [6]. In addition, the transplants experience several stresses, including proteotoxic stress, oxidative stress, and DNA damage, which can also induce cellular senescence in the transplant. When senescent cells are occurred in the aged organ or transplanted cells, they secrete the senescence-associated secretory phenotype (SASP) molecules such as proinflammatory cytokines and growth factors, thereby affecting regenerative capacity, chronic inflammation and over-activity of metabolism. A recent study of senescence indicated that clearance of senescent cells could delay aging-associated disorders [7]. In this review literature, therefore, we focus on the influence of cellular senescence in transplantation and a therapeutic opportunity to increase graft survival by using senolytic agent in a process called 'senotherapy'.

Cellular senescence

The cellular senescence process consists of two pathways, i.e., the DNA-damaged response (DDR) pathway and the DDR-independent pathway (Fig. 1). The DDR pathway initiates exposure of uncapped free double-stranded chromosome ends by telomere erosion. In sequence, ataxia telangiectasia mutated (ATM), a damage sensor, induces the stabilization of tumor

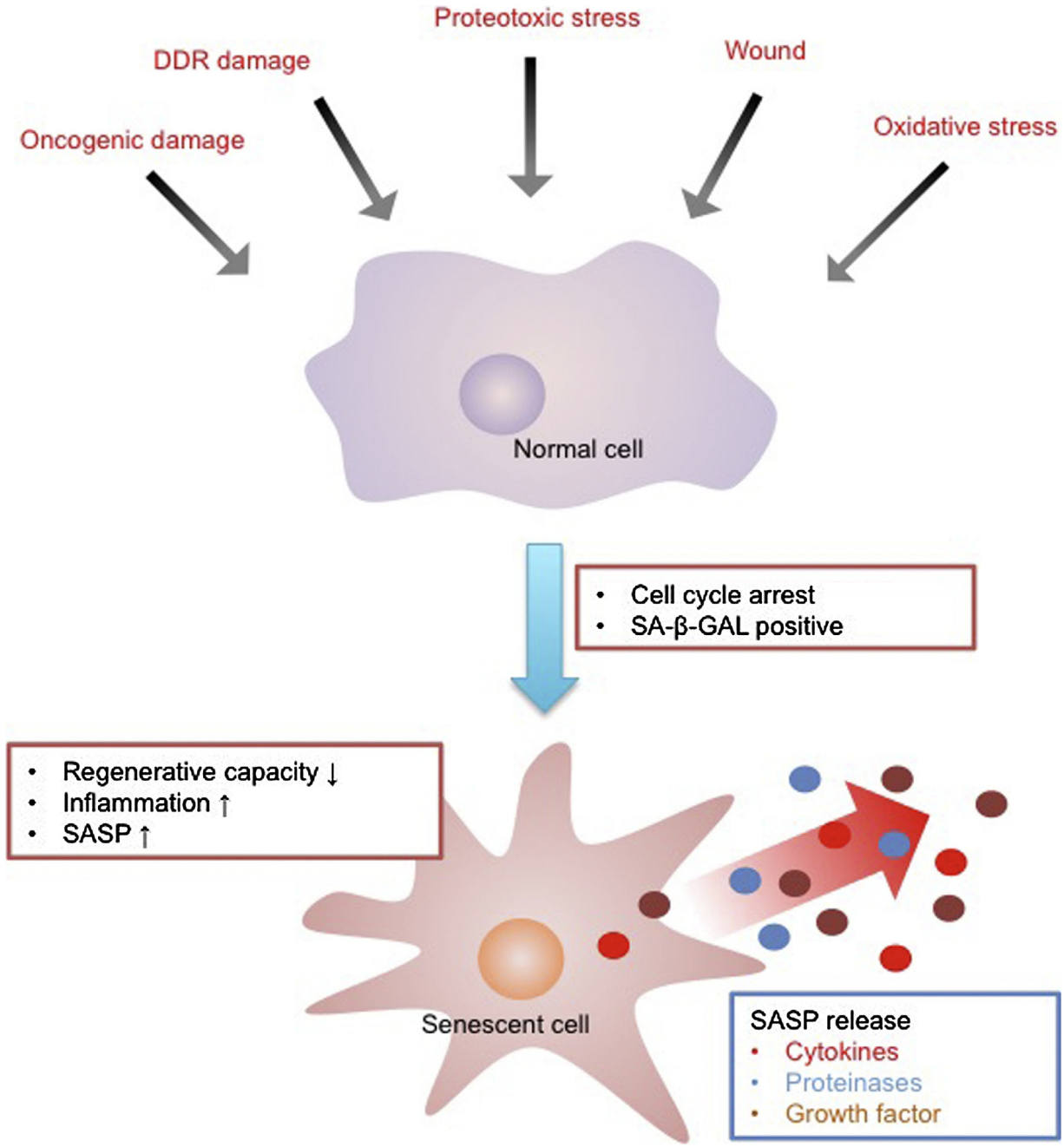

Fig. 1. Effector pathways of senescence. A variety of stresses can activate the cellular senescence process. These stressors generate various cellular signaling cascades. DDR dependent or DDR-independent pathways activate $p16^{Ink4a}$ or p53/p21 pathways, accelerating senescence process. Senescent cells can loss of regenerative capacity and induce inflammation through secretion of SASP, such as proinflammatory cytokine, proteinases, and growth factor.

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