Ageing Research Reviews 43 (2018) 64–80

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Role of Sirtuin1-p53 regulatory axis in aging, cancer and cellular reprogramming

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ARTICLE INFO

Keywords:
Sirtuins
Localisation of sirtuins
Senescence
Cellular energy metabolism
Inflammation
Tumour suppressor
Tumour promoter
Pluripotency

ABSTRACT

Regulatory role of Sirtuin 1 (SIRT1), one of the most extensively studied members of its kind in histone deacetylase family in governing multiple cellular fates, is predominantly linked to p53 activity. SIRT1 deacetylates p53 in a NAD+-dependent manner to inhibit transcription activity of p53, in turn modulate pathways that are implicated in regulation of tissue homoeostasis and many disease states. In this review, we discuss the role of SIRT1-p53 pathway and its regulatory axis in the cellular events which are implicated in cellular aging, cancer and reprogramming. It is noteworthy that these cellular events share few common regulatory pathways, including SIRT1-p53-LDHA-Myc, miR-34a,-Let7 regulatory network, which forms a positive feedback loop that controls cell cycle, metabolism, proliferation, differentiation, epigenetics and many others. In the context of aging, SIRT1 expression is reduced as a protective mechanism against oncogenesis and for maintenance of tissue homeostasis. Interestingly, its activation in aged cells is evidenced in response to DNA damage to protect the cells from p53-dependent apoptosis or senescence, predispose these cells to neoplastic transformation. Importantly, the dual roles of SIRT1-p53 axis in aging and tumourigenesis, either as tumour suppressor or tumour promoter are determined by SIRT1 localisation and type of cells. Conceptualising the distinct similarity between tumorigenesis and cellular reprogramming, this review provides a perspective discussion on involvement of SIRT1 in improving efficiency in the induction and maintenance of pluripotent state. Further research in understanding the role of SIRT1-p53 pathway and their associated regulators and strategies to manipulate this regulatory axis very likely foster the development of therapeutics and strategies for treating cancer and aging-associated degenerative diseases.

1. Introduction

Vicious cycle of cellular stress and acute inflammation induced by both external and internal stimuli activates multiple regulatory pathways and mechanisms in order to regulate homeostasis, degeneration, regeneration and functional activities of tissues. It is noteworthy that cells have the inherent capability to self-regulate the cellular events associated stress and acute inflammatory through cell cycle regulation, DNA repair mechanism, gene expression, energy metabolism, autophagy, apoptosis and stress resistance mechanism. Ideally, stress-induced DNA damages activate the guardian of genome, p53 which eventually leads to activation of cell cycle arrest to facilitate actions of DNA repair mechanism, as depicted in Fig. 1. In this mechanism, p53 facilitates transcription and activation of its downstream targets which are involved in repair of DNA damages and genome integrity (Albrechtsen et al., 1999; el-Deiry, 1998). Once the damages are repaired, cells re-enter cell cycle progression or resume their normal cellular functions. However, in the event whereby DNA damages are of higher threshold, the cells will not be able to execute a complete repair to restore genome integrity. This eventually led to the sustained activation of p53 to activate senescence-like event and/or lead to programmed cell death. Intriguingly, these cellular fates to either undergo repair or senescent/apoptosis, are govern through the presence of acetylated p53 (activated form of p53) in an intermittent or persistent manner respectively (Luo et al., 2017). In the event when those cells are unable to undergo efficient DNA repair to restore the genetic integrity, the unrepaired DNA mutations will eventually lead to accumulation of further mutations/DNA damages, which confer neoplastic characteristics in the cells to undergo uncontrolled proliferation. Interestingly, these fundamental cellular processes are also implicated in the reprogramming of somatic cells into pluripotent or multipotent state (stem cell-like fates), whereby cellular events such as halting cellular proliferation, metabolic programming, mesenchymal-epithelial transition and acquisition of stemness, expression of oncogenic and self-renewal markers (common

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https://doi.org/10.1016/j.arr.2018.02.004
Received 30 October 2017; Received in revised form 23 January 2018; Accepted 16 February 2018
Available online 21 February 2018
1568-1637/

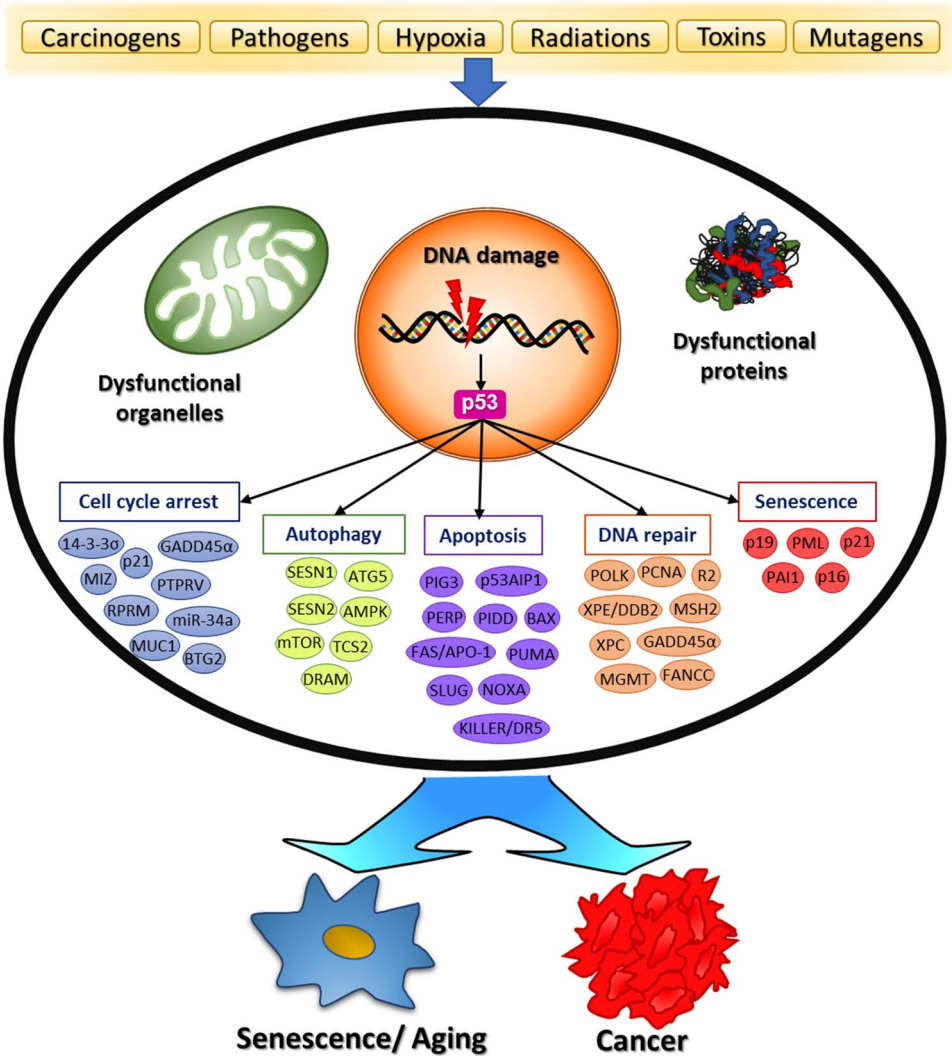

Fig. 1. p53-mediated cellular responses toward external stimuli.
Cells exposed to external stimuli (carcinogens, pathogens, hypoxia, radiations, toxins and mutagens) become susceptible to DNA damage, dysfunctional organelles and molecules. DNA damage activates p53 which leads to expression of its downstream targets and regulates cell cycle arrest, autophagy, apoptosis, DNA repair and senescence. If the damages persist without repair, the cells eventually become aged cells or cancer cells.

markers shared by stem cells and cancer cells) are evident through many studies (Gupta et al., 2015; Li and Simon, 2013; Li et al., 2010; Menendez et al., 2016; Nagata et al., 2012; Spike and Wahl, 2011; Xu et al., 2013). Profoundly, there are many conserved regulatory pathways that are involved in regulating these cellular fates; aging, cancer and/or cellular reprogramming, which converged through events such as inflammation, metabolic reprogramming, bioenergetics, epigenetic and gene expression and many others.

Despite having many literature and research breakthrough in understanding role of p53, not until two decades ago when the partnership tale between SIRT1 and p53 was established, the important regulatory role of sirtuins family was begun to be explored in the context of aging and cancer. SIRT1 is a protein deacetylase, one of the key epigenetic regulators and tumour suppressors, which regulates transcriptions of multiple target substrates including p53. Many of the key cellular events are regulated through SIRT1-p53 interaction, that this regulatory partnership is discussed in details under Section 1.1. Profoundly, SIRT1 seems to be having a significant impact many cellular processes primarily through its roles as epigenetic modulatory and master regulator of p53. Hence, this review provides critical insights into the biology of SIRT and p53 that are relevant to many cellular events which are fundamentally associated with the onset and progression of aging and aging-associated chronic diseases (cardiovascular disease, diabetes and cancer). The knowledge is of paramount importance for exploiting critical pathways and nodes (or molecules) as legitimate target for the development of novel therapeutics that will allow rejuvenation, elimination or regeneration of target population which are of interest in the above-mentioned diseases in order to restore the impaired function of organ systems.

1.1. *The tale of SIRT1-p53 partnership*

Silent information regulator 2 alpha protein (Sir2p) was first discovered in yeast, *Saccharomyces cerevisiae*. The mammalian homolog of this protein is known as sirtuins (SIRTs). These regulators belong to the nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylases (HDACs) family, and are primarily involved in deacetylation of lysine residues. They catalyse the reaction whereby cleavage of NAD forms a deacetylated substrate, nicotinamide (NAM) and 2′-O-acetyl-ADP-ribose (2OAADPR) (Tanner et al., 2000). The generated products could be facilitating Sir2p complex assembly and binding on histone for deacetylation (Tong and Denu, 2010). Of seven SIRTs found in mammals, SIRT1, is the most studied regulator, plays important role in many cellular events especially aging, cancer and cellular reprogramming,