Cellular Signalling 23 (2011) 6–13

Contents lists available at ScienceDirect

Cellular Signalling

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

Review

Jailbreak: Oncogene-induced senescence and its evasion

Fiona K.E. M^c^Duff, Suzanne D. Turner *

Division of Molecular Histopathology, Department of Pathology, University of Cambridge, Lab Block Level 3, Box 231, Addenbrooke's Hospital, Cambridge CB20QQ, UK

ARTICLE INFO

Article history:
Received 24 May 2010
Accepted 6 July 2010
Available online 13 July 2010

Keywords:
Oncogene-induced senescence
Tumourigenesis
p53
Rb

ABSTRACT

Aberrant oncogenic signals are typically counteracted by anti-proliferative mechanisms governed principally by the p53 and Rb tumour-suppressor proteins. Apoptosis is firmly established as a potent anti-proliferative mechanism to prevent tumour growth but it is only in recent years that oncogene-induced senescence has achieved similar recognition. Senescence is defined as an irreversible cell-cycle arrest suggesting that entry of oncogene-expressing cells into this static yet viable state is permanent. However, tumours do develop and express the very same oncogenes that landed them in jail. We ask whether this is because rogue incipient cancer cells find ways to escape this imposed imprisonment or otherwise entirely avoid capture by senescence gate-keepers.

© 2010 Elsevier Inc. All rights reserved.

Contents

1. Introduction . . . 6
2. Mechanisms of OIS . . . 7
   2.1. The role of p53 and the DDR in OIS . . . 7
      2.1.1. Activation of p53 in murine cells via ARF . . . 7
      2.1.2. Activation of p53 in human fibroblasts via the DDR . . . 7
      2.1.3. Common mechanisms of p53 activation in mouse and human cells via the p38 MAPK cascade . . . 7
   2.2. The p16/Rb pathway and SAHF in OIS . . . 8
   2.3. Senescence-associated secretory factors and OIS . . . 9
   2.4. Autophagy and OIS. . . . 9
   2.5. Negative-feedback signalling in OIS . . . 9
3. Jailbreak: escape or evasion of OIS? . . . 9
   3.1. Tumour formation: reversing the irreversible? . . . 9
      3.1.1. Evidence in favour of a model of senescence reversion . . . 9
      3.1.2. Caveats and considerations for a model of senescence reversion . . . 10
   3.2. Tumour formation: avoiding the entrapment . . . 11
4. Conclusions and perspectives . . . 12
Acknowledgements . . . 12
References . . . 12

1. Introduction

Hayflick and Moorhead formally described senescence in 1961 following their observations of human diploid fibroblast (HDF) cultures that initially exhibited robust proliferation (used here synonymously with cell growth) yet, after many population doublings (PDs), underwent a gradual decline in proliferative rate before the whole population eventually ceased growth (after 50–80 PDs). This occurred despite the abundance of growth factors and nutrients, and ample room for expansion [1]. Further studies revealed that the cells ceased proliferation due to the gradual erosion of telomeres with each cell division. Telomeres are stretches of repetitive DNA sequence (5′-TTAGGG-3′ in vertebrates) that protect the chromatin from damage or fusion by DNA-repair processes [2]. Due to the nature of DNA synthesis in eukaryotic cells the ends of the chromosomes cannot be completely replicated by DNA polymerases (a phenomenon known as the end-replication problem [3]) and thus there is a progressive

---

* Corresponding author. Tel.: +44 1223 762655; fax: +44 1223 586670.
E-mail addresses: fkem3@cam.ac.uk (F.K.E. M^c^Duff), sdt36@cam.ac.uk (S.D. Turner).

0898-6568/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.cellsig.2010.07.004

shortening (by approximately 50–200 base pairs) of the chromosomes with each cell division [4]. Therefore, telomeres prevent the loss of vital genetic information with each round of replication. Critical telomere shortening and eventual dysfunction triggers a classical DNA damage response (DDR) involving a host of cellular proteins, including kinases (for example Ataxia Telangiectasia Mutated (ATM) and CHecKpoint-2 (CHK2)), mediator proteins (for example, 53 Binding Protein-1 (53BP1), Nijmegan Breakage Syndrome-1 (NBS1) and p53) and chromatin regulators (for example, phosphorylated histone H2A.X (γ-H2A.X)). These cellular factors co-operate to initiate senescence, thereby preventing cellular proliferation in the presence of damaged chromosomes and hence limiting the acquisition of potential pathogenic mutations [5–8]. Cellular senescence following continuous culture *in vitro* is now more specifically termed as replicative senescence or cellular ageing to distinguish it from premature senescence, which occurs prior to critical telomere shortening. A number of different stressors trigger this latter form of senescence, including DNA-damaging agents, chromatin perturbations, expression of oncogenes and inactivation of tumour-suppressor genes [9,10].

The failure of senescent cells to proliferate in adequate growth conditions distinguishes senescence from quiescence; a form of cell-cycle arrest that is reversible following the receipt of appropriate cellular signals. Other characteristic features of senescent cells include morphological, biochemical, genetic and epigenetic changes. Thus many senescent cells become flat and enlarged [11]; activate acidic senescence-associated β-galactosidase (SA-β-Gal) [12]; undergo dramatic changes in gene expression including genes involved in regulation of the cell cycle, extra-cellular matrix (ECM) remodelling, cytokine signalling and inflammation [13]; and acquire striking changes in chromatin structure to form senescence-associated heterochromatic foci (SAHF) [14].

The realisation that aberrant expression of some oncogenes induces premature senescence yet cancer is a disease of unscheduled and unabated cellular proliferation led to the proposal that senescence may act to limit tumour growth [11]. Indeed, a number of studies have now paved the way in establishing oncogene induced senescence as a *bone fide* tumour-preventative mechanism [15–21]. It therefore follows that if senescence poses a barrier to tumourigenesis, how then do tumours arise? Two possibilities exist that are not necessarily mutually exclusive: i) senescent cells re-enter the cell cycle following the acquisition of additional genetic mutations that disable senescence pathways; or ii) tumours arise from a small population of cells that are resistant to senescence. This review summarises our current knowledge of the many cellular pathways implicated in OIS and in addition presents the existing experimental evidence supporting either escape from or evasion of OIS for tumour development.

2. Mechanisms of OIS

Premature senescence is triggered in both mouse and human cells independently of telomere length following expression of active oncogenes, and therefore constitutes a potent barrier to cellular transformation [11]. Multiple mechanisms are proposed to mediate OIS and these may act in concert to initiate or reinforce the growth arrest (Fig. 1). It is likely that the pathway(s) to OIS is determined by several biological parameters, including the nature and intensity of the oncogenic stimulus, the cell type and/or the microenvironment.

2.1. The role of p53 and the DDR in OIS

2.1.1. Activation of p53 in murine cells via ARF

The stability of p53 is regulated primarily by the opposing functions of two proteins: the E3 ubiquitin ligase MDM2 (HDM2 in humans), which negatively regulates p53 by facilitating its degradation [22]; and ARF, an inhibitor of MDM2 [23]. In unstressed cells, MDM2 binds p53 and directs its ubiquitination and degradation via the proteosome [22]. In response to cellular stress, ARF is up-regulated and binds MDM2, sequestering it in the nucleoli [24]. In this manner, p53 degradation is prevented and the protein accumulates [23]. The result of this co-ordinated activity is the transcription of p53-dependent gene targets, which mediate either an apoptotic or cell-cycle arrest programme [25]. In primary murine embryonic fibroblasts (MEFs), ARF is a designated “sensor” of inappropriate proliferative signals emanating from oncogenes. Several oncogenes induce high levels of ARF expression, ultimately leading to p53 stabilisation and the transcription of anti-proliferative genes, such as p21 [11,26]. Both p53 and ARF are essential for OIS of MEFs, since the respective null-MEFs do not senesce but are instead transformed following ectopic expression of oncogenes [11,26].

Conversely, ARF appears to be less prominently involved in OIS of HDFs suggesting some species-specific differences and the existence of multiple mechanisms of p53 activation and subsequent OIS [27,28]. Indeed, p53 is induced as part of the DDR in oncogene-expressing HDFs independently of ARF.

2.1.2. Activation of p53 in human fibroblasts via the DDR

Aberrant expression of several oncogenes including Ras, Myc and Cdc6, induces excessive cellular proliferation of HDFs, concomitant with DNA hyper-replication, replication-fork collapse, accumulation of DNA double-strand breaks (DSBs) and subsequent activation of the canonical p53-dependent DDR [29,30]. This response is sufficient to drive cells into a premature senescent state which is inhibited and/or reversed following the inactivation of one of several DDR genes including *ATM*, *CHK2* or *p53* [29,30]. These data demonstrate that the DDR plays a critical role in both the initiation and maintenance of senescence induced in response to the activation of at least a subset of oncogenes.

Activation of the DDR pathway via oncogene-induced hyper-replication does not preclude DDR/p53 activation by other means. It has been suggested that OIS may arise from an oxidative stress-mediated DDR since expression of oncogenic-Ras results in the accumulation of ROS [31,32], molecules well-known for their DNA-damaging effects [33]. Indeed, oncogenic-Ras-induced senescence of HDFs is bypassed when cells are grown in 1% oxygen (a concentration at which ROS production is inhibited), or following treatment with a ROS scavenger (specifically H_2O_2) under normoxic (20% oxygen) conditions [34]. Thus, ROS and DNA hyper-replication have been implicated in the OIS-associated DDR response that leads to p53 activation. However, p53 may also be activated via alternative kinase cascades involving PRAK as detailed below.

2.1.3. Common mechanisms of p53 activation in mouse and human cells via the p38 MAPK cascade

Whilst the DNA-damaging effects of ROS are well documented, there remains some debate as to the actual mechanism of ROS-induced senescence following oncogene expression. ROS production by oncogenic-Ras activates the p38 MAPK pathway, a tumour-suppressive pathway that coordinates the cellular response to various forms of stress [35,36]. Several independent studies had previously demonstrated a requirement for p38 activation in oncogenic-Ras-induced senescence but the precise mechanism, in particular the signal transducers acting downstream of p38, remained elusive [37–39]. Recently, Sun et al. demonstrated that PRAK, a kinase downstream of Ras and p38, is essential for oncogenic-Ras-induced senescence of both MEFs and HDFs *in vitro*, as well as in the suppression of tumour formation in a mouse model of oncogenic-Ras-driven skin cancer [40]. The authors showed that PRAK mediates senescence in response to oncogene expression by directly phosphorylating and activating p53 in both cell types. Thus, in addition to or instead of their effects on DNA oxidation and damage, ROS may trigger p53-dependent senescence through activation of p38 MAPK signalling via PRAK.

Download English Version:

https://daneshyari.com/en/article/1963811

Download Persian Version:

https://daneshyari.com/article/1963811

Daneshyari.com