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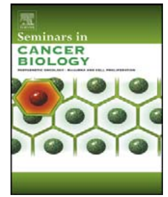

Review

Epigenetic alterations associated with cellular senescence: A barrier against tumorigenesis or a red carpet for cancer?

Anabelle Decottignies [a,*], Fabrizio d'Adda di Fagagna [b,*]

[a] Genetic and Epigenetic Alterations of Genomes, de Duve Institute, Catholic University of Louvain, Brussels, Belgium
[b] IFOM Foundation – FIRC Institute of Molecular Oncology Foundation, Milan, Italy

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ABSTRACT

Cellular senescence is eminently characterized by a permanent cell cycle arrest and the acquisition of morphological, physiological and epigenetic changes. The establishment of cellular senescence can occur in response to telomere attrition associated with cell turnover and ageing or following oncogene activation. Although seemingly two distinct phenomena, cellular senescence and cancer share similarly altered global epigenetic profiles comprising changes in DNA methylation, involving global hypomethylation of repetitive DNA sequences and regional hypermethylation of some gene promoters, and in histone post-translational modifications. As epigenetic and genetic alterations are likely to act synergistically in cancer, anomalous epigenetic marks acquired during ageing or in response to oncogene activation might play important roles in tumorigenesis and cancer progression. These potentially tumor-promoting epigenetic alterations include transcriptional repression of genes encoding tumor suppressors or developmentally regulated proteins, expression of non-coding repetitive RNAs and acquisition of distinct heterochromatin marks that may contribute to suppress cell death by reducing DNA damage response.

Cellular senescence may thus be viewed as a double-edged sword that, although acting as a potent anti-proliferative barrier, may pave the way to tumorigenesis in senescence-escaping cells by altering their epigenetic make up.

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1. Introduction

Under optimal *in vitro* growth conditions, replicative senescence is commonly triggered by telomeres shortening below a critical length [1] and ensuing direct activation of the DNA damage response (DDR) signaling pathways [2,3]. *In vivo*, progressive DDR activation at telomeres has also been observed in ageing primates [4]. In addition to telomere attrition, cells challenged with activated oncogenes may undergo a premature entry into senescence. Such oncogene-induced senescence (OIS) is currently believed to act as a potent tumor suppressor mechanism that can be overcome only if cell cycle checkpoint genes (such as p53 and Rb) are inactivated [5]. Most current models of tumor initiation and progression hypothesize that tumors derive from cells that either escaped from the senescence anti-proliferative barrier or avoided such a barrier altogether by acquiring cell cycle checkpoint mutations before oncogene activation. An addendum to this model is the potential contribution of stem cells and the possibility of mutations being acquired in this subpopulation. Presently, it is unclear whether stem cells behave differently in terms of checkpoint activation and in their ability to enter senescence following oncogenic stimuli or escape from it by checkpoint inactivation.

Therefore, cellular senescence can be the outcome both of physiological cell turnover with consequent telomere attrition during the process of ageing, and of the activation of oncogenes. Although ageing and oncogene activation represent two distinct processes, a growing body of evidence accumulated recently and discussed in this review, indicates that senescent and cancer cells share similar epigenetic profile alterations. This suggests that senescence, either induced by cell turnover in association with ageing or by oncogene activation, may be a common step in tumorigenesis. In line with the emerging idea that epigenetic alterations contribute to cancer together with DNA mutations, it is therefore possible that, although senescence constitutes an effective anti-proliferative barrier, anomalous epigenetic marks acquired during this stage might play important roles during tumorigenesis and cancer progression.

Abbreviations: HC, heterochromatin; SAHF, senescence-associated heterochromatin foci; OIS, oncogene-induced senescence; DDR, DNA damage response; HMT, histone methyltransferase; HDM, histone demethylase; HDAC, histone deacetylase; ROS, reactive oxygen species; DNMT, DNA methyltransferase; ncRNA, non-coding RNA.

* Corresponding authors.
E-mail addresses: anabelle.decottignies@uclouvain.be (A. Decottignies), fabrizio.dadda@ifom-ieo-campus.it (F. d'Adda di Fagagna).

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In this review, we discuss the epigenetic alterations of both senescent and cancer cells and the potential role of senescence-associated changes of the epigenetic landscape in the tumor progression process.

2. Similarities among epigenome alterations during *in vitro* cellular senescence, organismal ageing and tumorigenesis

2.1. Alterations of histone modification profiles, heterochromatin-associated factors and formation of senescence-associated heterochromatin foci (SAHF)

N-terminal tails of histones are subjected to a variety of post-translational covalent modifications, including acetylation, methylation, ubiquitylation, sumoylation and phosphorylation, that constitute the so-called "histone code" [6]. These modifications play important roles in DNA biology by regulating DNA transcription, replication and repair. Chromatin regulation by histone modifications has been recently extensively reviewed elsewhere [7]. Examples of histone modifications relevant to cellular senescence and cancer include trimethylation of histone 3 on either lysine 9 or lysine 27 (H3K9me3 or H3K27me3) and trimethylation of histone 4 on lysine 20 (H4K20me3). These modifications are catalyzed by, respectively, SUV39H1/2, EZH1/2 and SUV420H1/2 histone methyltransferases (HMTs) [7]. While histone acetylation is generally considered to be correlated with transcriptional activation, H3K9me3 and H3K27me3 are considered the two main silencing mechanisms in mammalian cells, with the H3K9me3 repressive mark often accompanied by DNA methylation. H3K9me3 and H4K20me3 marks are the major histone lysine methylation marks at pericentromeric heterochromatin (HC) and are also found at telomeres [8]. Histone modification patterns can be very dynamic and subjected to histone-modifying enzymes that include mark "erasers" like histone deacetylases (HDACs) and histone demethylases (HDMs). The complexity of histone modifications and the role these play on the accessibility of chromatin to a variety of other proteins has become evident during the past few years and was further increased by the discovery that both active (H3K4me3) and repressive (H3K27me3) marks can coexist on the promoter of a set of genes, namely developmentally regulated genes [9,10]. In embryonic stem cells, these genes are held in a repressed mode while, during differentiation, loss of H3K27me3 marks at these so-called bivalent promoters initiates a transcriptional response [11].

In addition to the repressive histone modifications mentioned above, another prominent mark of HC is its enrichment in heterochromatin protein 1 (HP1) [12]. HP1 is an evolutionary conserved protein with three isoforms in mammals: HP1α, HP1β and HP1γ – HP1α being specific for pericentromeric regions. Although HP1 molecules interact with chromatin by binding to H3K9me3 through their chromodomain, it has also been recently reported that HP1α molecules may be directly recruited to pericentromeric DNA through interactions with non-coding satellite RNAs [13] (see Section 2.2.1). HP1 proteins have been involved in various protein-protein interactions and are believed to function as structural adaptors for the assembly of HC. Given that SUV39H1 HMT is also able to bind to HP1, this has led to the proposal that there may be a self-feeding loop in which HP1 binds to H3K9me3 and this, in turn, recruits more SUV39H1 HMT to the locus [12]. In addition, HP1 molecules were shown to contribute to HC formation by recruiting DNA methyltransferase 1 (DNMT1) to chromatin [14], thus strengthening the repressive nature of these epigenetic marks at the locus.

Cellular senescence is associated with profound chromatin alterations. The most dramatic is the formation of senescence-associated heterochromatin foci [15]. While normal human cells tend to show a diffuse pattern of DAPI staining (a DNA staining dye), indicative of a homogeneous distribution of DNA within the nuclear space, cellular senescence is associated with the formation of discrete DAPI-dense regions named SAHF. These structures cannot be appreciated in mice where the centromeric regions (chromocenters) already stain intensely and the pathways involved in their formation seem not to be active in mouse cells [16]. SAHF represent highly compacted and heterochromatic forms of individual chromosomes [17] and stain positive both for several canonical HC repressive marks (H3K9me3, HP1 proteins, macroH2A) and others not commonly associated with HC and transcriptional repression such as the architectural proteins HMGA1 and HMGA2 [15,18]. To date, there has been no report on the presence of H4K20me3 marks in SAHF.

Although SAHF presence has been put in relation to p16 induction [15], it has also been reported that senescence can be established in the absence of p16 induction [19] and some of us have recently observed that when senescence is not associated with increased p16 levels, SAHF formation is not observed [20,21]. We have observed that, in the same human skin fibroblast strain, OIS is inevitably associated with robust p16 induction and SAHF formation, while senescence caused by telomere shortening, or by other exogenous DNA damaging treatments, is not [20]. This would point to SAHF as the outcome of oncogene activation rather than replicative ageing. However, as other groups have reported that replicative senescence in some cultured fetal lung fibroblasts strains can nevertheless associate with p16 accumulation and SAHF formation [15,17], this may occur with a contribution of the so-called "culture stress", a ill-defined mix of exogenous stresses associated with suboptimal *in vitro* growth conditions (e.g. too much oxygen and serum). Thus, it is possible that different cell types may respond differently to stressing stimuli in regard to p16 induction.

The above considerations should not be interpreted as an absence of p16 upregulation during physiological ageing. In fact, very robust *in vivo* evidence points to the opposite as p16 level increases have been observed in pancreas, blood and brain stem cells of ageing mice and this was shown to play a causative role in their proliferation exhaustion [22–24].

DDR-positive cells become progressively detectable in the skin of ageing primates [4]. These DDR-positive, and presumably senescent, cells are also almost invariably positive for HC and SAHF components (HP1β, HIRA, H3K9me2 and H3K9me3) [4]. This is consistent with a report proposing a genome-wide switch from euchromatin to HC during tissue ageing [25]. A more recent thorough analysis of HP1β and macroH2A (both HC and SAHF components) revealed that their levels increase during ageing, as determined by direct detection in tissues of ageing mice and primates [26]. However, the authors of this analysis conclude that actual SAHF do not accumulate *in vivo* during organismal ageing. Overall these conclusions are different from those reporting a reduction in H3K9me3 detection associated with a compensatory equal increase of H3K9me1 in human fibroblasts during replicative ageing [27], an altered distribution of HC marks in fibroblasts of aged individuals and a reported decrease of HP1γ and HDAC1 in skin fibroblasts form aged individuals [28].

SAHF have been proposed to enforce and maintain senescence by suppressing the transcription of proliferative E2F-target genes. Indeed the promoters of these genes are stably repressed in the senescence condition [15]. However, checkpoint inactivation allows oncogene-expressing cells to proliferate with seemingly undiminished levels of global heterochromatin and SAHF-like structures and, consistent with their robust proliferation, E2F promoters are not repressed in the same cells [20]. These observations revealed the possibility to uncouple transcriptional repression from SAHF formation. Importantly, HC markers such as H3K9me3

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