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Chromosome organisation during ageing and senescence

Tamir Chandra[1,2] and Kristina Kirschner[3]

Acute cellular stress caused by oncogene activation or high levels of DNA damage can engage a tumour suppressive response, which can lead to cellular senescence. Chronic cellular stress evoked by low levels of DNA damage or telomere erosion is involved in the ageing process. In oncogene induced senescence in fibroblasts, a dramatic rearrangement of heterochromatin into foci and accumulation of constitutive heterochromatin is well documented. In contrast, a loss of heterochromatin has been described in replicative senescence and premature ageing syndromes. The distinct nuclear phenotypes that accompany the stress response highlight the differences between acute and chronic stress models, and this review will address the differences and similarities between these models with a focus on chromosome organisation and heterochromatin.

Addresses
[1] Epigenetics Programme, The Babraham Institute, Cambridge CB22 3AT, UK
[2] The Wellcome Trust Sanger Institute, Cambridge CB10 1SA, UK
[3] Cambridge Institute for Medical Research, Wellcome Trust/MRC Stem Cell Institute and Department of Haematology, University of Cambridge, Hills Road, Cambridge CB2 0XY, UK

Corresponding authors: Chandra, Tamir (tamir.chandra@babraham.ac.uk) and Kirschner, Kristina (kk429@cam.ac.uk)

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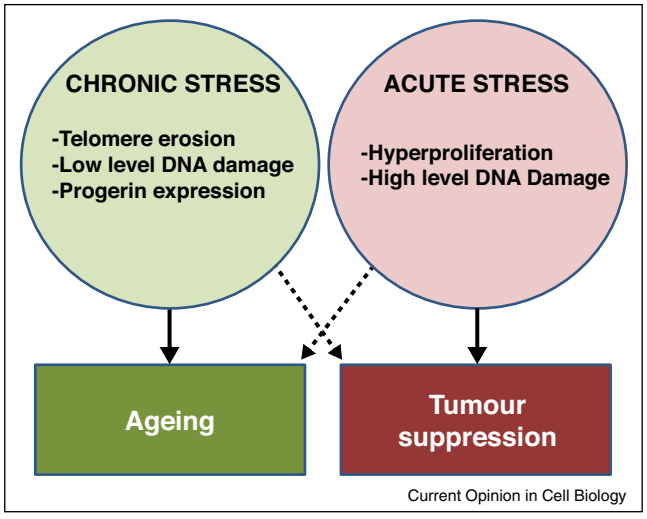
Introduction

Cellular senescence describes the response of a cell to cellular stress, which is mostly linked to genotoxic stress or DNA damage [1–5]. However, the senescence stress response can be very heterogeneous depending on the way the stress is induced. A useful working model of classifying stress responses has been by dividing them into models where damage accumulates slowly over months and years, such as in replicative senescence; and acute stress models that evoke a senescence response within hours, such as oncogene induced senescence (OIS) (Figure 1). The exact event downstream of oncogene activation triggering the senescence response is still debated. However, oncogene activation can lead to complete senescence of a fibroblast population in 48 hours in the presence of ectopic telomerase [6]. This distinction between chronic and acute stress models allows comparisons to stress situations that might not be considered senescence models per se, such as premature ageing (progeroid) syndromes, which can be considered chronic stress situations based on their slow kinetics. In addition there are many lines of evidence linking progeroid syndromes and cellular senescence [7,8,9••]. Werner syndrome is an adult onset premature ageing syndrome caused by mutations in the Wrn DNA helicase gene, leading to increased levels of DNA damage in patients [10••]. Mesenchymal stem cells (MSCs) derived from Wrn null (−/−) embryonic stem cells display a pronounced senescence phenotype upon serial passaging *in vitro* and in stem cell transplantation experiments [10••]. Hutchinson–Gilford progeria syndrome (HGPS or progeria) is caused by a mutation in the lamin A (LMNA) gene and manifests in early childhood [11,12]. Cells from HGPS patients show many hallmarks of senescence such as elevated DNA damage levels and telomere attrition [9••,13,14]. As such, chronic stress situations have mostly been studied in the context of cellular ageing, whereas acute models have served to understand the tumour suppressive role of senescence [15]. While the distinction between stress situations and phenotype seems useful, there have been interesting observations suggesting a crosstalk between the two (indicated by the dashed arrows in Figure 1). One example of such cross-talk is a recently discovered barrier to oncogenic transformation in progeroid cells [16•].

The way that senescence or chronic cellular stress contributes to organismal ageing is not fully understood. However, there is evidence for at least two independent scenarios in which senescence has been implicated in ageing. The p53 and INK4a/ARF loci have long been associated with senescence and there is emerging evidence that both loci are implicated in organismal ageing via deregulation of the stem cell pool [15]. Chronic hyperactivation of p53 was shown to result in reduced proliferation of haematopoietic stem cells (HSC) upon stress through transplantation experiments [17]. However, there is also evidence that the role of p53 activation in ageing might be more complex [18]. With age, increased DNA damage and p16Ink4a expression leads to a reduction in HSC cell cycle activity [19,20]. Environmental stress or cells reaching their replicative life span stimulate

Figure 1



Chronic (green) and acute stress (red) induced DNA damage leads to different cell fate choice. In the schematic the circles represent the two different types of stress with selected underlying causes. Chronic stress is characterised through slow kinetics and a gradual accumulation of damage, which has mostly been studied in the context of ageing on the cellular and organismal level (left hand side of diagram). In contrast, oncogene activation and subsequent hyperproliferation or high level DNA damage activate an acute stress response, leading to senescence as part of the organismal tumour suppressive response (right hand side of the diagram). However, crosstalk between the two models exist (dashed arrows), for example through progeria mediated resistance to transformation by inhibiting oncogenic dedifferentiation.

stem cells to replenish the pool of somatic cells. As an organism ages, or in chronic stress situations, the stem cell pool is functionally diminished and therefore unable to reconstitute tissue (Figure 1). Slow kinetics characterise this process, with the rate of senescence determining the rate of stem cell exhaustion.

Another way senescence has been implicated in ageing is through its senescence associated secretory phenotype (SASP), which is characterised by secretion of cytokines and matrix-metallo-proteases [21–23]. SASP functions in two ways: it reinforces the senescence response in neighbouring cells through its secretome and it recruits immune cells to clear senescent cells. However, senescent cells that are not cleared can contribute to age-related pathologies over time, most likely through chronic inflammation triggered by their SASP response (Figure 1) [15]. Indeed it seems that some age related pathologies can be alleviated by eliminating p16Ink4a senescent cells from tissue [24].

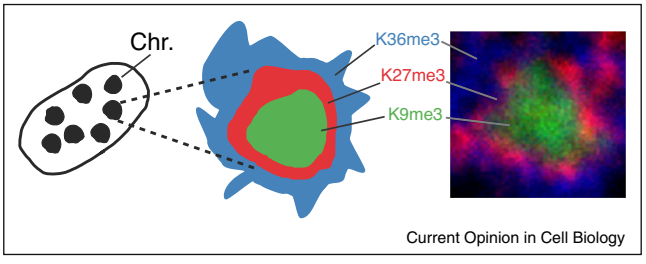
Nuclear organisation and constitutive heterochromatin (cHC)

The distinct nuclear phenotypes that accompany the stress response highlight the differences between acute and chronic stress models, and this review will address the differences and similarities between these models with a focus on chromosome organisation and heterochromatin. Although a role for cHC and the nuclear architecture in cellular ageing was first proposed nearly 20 years ago [25], the concept received spotlight attention in 2003 due to the discovery that HGPS is caused by mutations in the LMNA gene [11,12]. In the same year a new nuclear phenotype was described in cells undergoing oncogene-induced senescence and other forms of acute stress and was named for its spotty pattern of heterochromatic domains: senescence associated heterochromatic foci (SAHF) (Figure 2) [26]. Mapping heterochromatic markers revealed striking differences in the fate of cHC marks: a loss in chronic stress situations [27–29] and an accumulation during stress induced senescence [26].

Acute stress: SAHF positive cells

SAHF formation in senescent cells is a striking nuclear phenotype (see Figure 2), which leads to the formation of 4',6-diamidino-2-phenylindole (DAPI) intense foci. Studies using chromosome painting have revealed that each focus consists of exactly one chromosome [30,31,32•]. The core area of the SAHF is enriched with markers for constitutive heterochromatin such as Histone 3 lysine 9 trimethylation (H3K9me3), heterochromatin protein 1 (HP1) and macro Histone 2A (mH2A) [26,33], whereas the SAHF periphery is enriched with the facultative heterochromatin mark Histone 3 lysine 27 trimethyl (H3K27me3) [32•]. Euchromatic regions can be found outside the DAPI intense focus and the H3K27me3 ring. Figure 2 depicts the overall architecture of SAHF [32•,34]. The geometry of chromatin domains therefore

Figure 2



Senescent chromosomes form senescence associated heterochromatic foci (SAHF), which show a segregation and clustering of different chromatin types. On the left a schematic of a SAHF positive nucleus is drawn as it would appear after being stained by DAPI (black). Each of the foci represents a SAHF, which represents an individual chromosome (Chr). One of the foci is schematically enlarged to visualise the multilayer chromatin structure found in SAHF (center). To the right, an immuno-fluorescently stained SAHF is shown for comparison. The chromatin types are represented here through histone modifications. The core of the SAHF is enriched in H3K9me3 (green, constitutive heterochromatin). A ring at the periphery of the SAHF is enriched in H3K27me3 (red, facultative heterochromatin/polycomb silencing). Active euchromatin can be found outside the SAHF and is shown by H3K36me3 (blue).