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Commentary
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Tumour Suppressors and Cellular Senescence

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Commentary

Cellular senescence is a stable growth arrest that normal human diploid fibroblasts undergo after a finite number of divisions, as a result of progressive shortening of telomeres and other genotoxic as well as non-genotoxic stresses. It is an example of antagonistic pleiotropy, as it plays an important role in tumour suppression during early life whereas later in life, it leads to deleterious traits, such as disrupted tissue function, thereby promoting organismal ageing and age-related diseases. Elucidating and understanding the signalling pathways involved in regulating the senescent state, is therefore of great biological importance.

Cellular senescence is a stable growth arrest, that normal human diploid fibroblasts undergo after a finite number of divisions [1], as a result of progressive shortening of telomeres [2]. However, further stressors such as oncogenic activation, DNA damage, oxidative stress and other non-genotoxic stresses were later found to also trigger this arrested state [3]. Senescence is an example of antagonistic pleiotropy, playing an important role in tumour suppression during early life, as it is a natural barrier to carcinogenesis. Later in life, it leads to deleterious traits, such as disrupted tissue function, consequently promoting organismal ageing and age-related diseases. Hence, elucidating the signalling pathways involved in regulating the senescent state is of great biological importance.

Multiple stimuli are known to activate the p53/p21 and p16/pRB tumour suppressor pathways, which have clearly been established to mediate senescence; however, the critical downstream targets have yet to be determined (Figure 1) [4]. Furthermore, it is unclear whether these pathways function in parallel or are linear, in establishing senescence [5]. p21WAF1, a downstream target of the p53 protein, is an inhibitor of cyclin-dependent kinases and can activate the pRB tumour suppressor pathway, by inhibiting cyclin D/CDK4,6 kinases [6]. p16INK4a inhibitor is also able to activate the pRB pathway, independently of the p53 pathway [5].

The specific cell type and whether the studies are conducted on human or mouse cells are important factors for determining which of the signalling pathways has a greater significance in inducing senescence. Fundamentally, the importance of these two pathways in establishing senescence has been demonstrated by reversing senescence by reducing p16INK4a levels and/or inactivating p53 [7-9].

To establish the downstream targets of p53 and pRB, previous studies have also focussed on the DREAM complex [15-17]. P53 and pRB are central in controlling cell cycle progression [18]. An integral component, regulating gene expression throughout the cell cycle, proposed by DeCaprio and colleagues, is the DREAM complex (Figure 2).

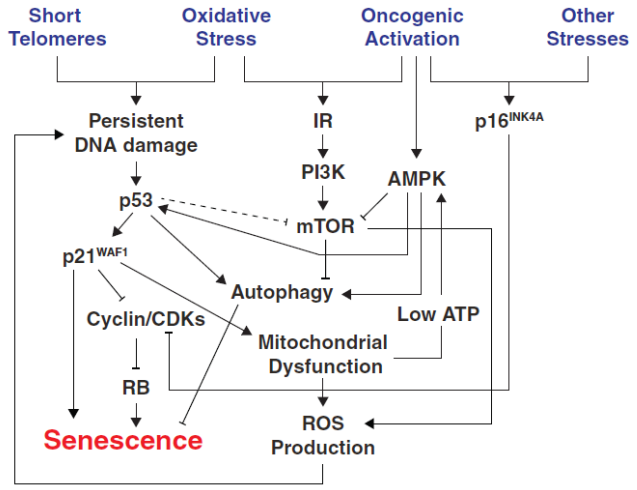

Figure 1: Schematic illustration of the signalling pathways involved in regulating cellular senescence.

The function of this complex has been characterised in quiescence [15], which suggests a potential role in senescence, but this remains to be verified. Although it is clear how p53 and pRB activation lead to quiescence, a greater understanding of downstream transcription factors and target genes involved in establishing senescence is essential, to distinguish between senescence and quiescence.

The DREAM complex is composed of the p130/p107 pocket proteins, homologous to pRB, E2F4 transcription factor, its dimerization partner 1 (DP1), and the multi-vulval class B (MuvB) proteins [LIN9, LIN37, LIN52, LIN54 and RBBP4]. In the active form, p130/p107 inhibit transcription required for cell cycle progression by binding to E2F4. Upon entry into the cell cycle, the MuvB core dissociates from the complex and sequentially recruits B-MYB and FOXM1 during S-phase and G2-phase, to promote late S-phase and mitotic gene expression, important for cell cycle progression (Figure 2). A link between the DREAM complex and senescence induction has been suggested by Litovchick et al. [16], using immortalised human BJ-hTERT skin fibroblasts. The DYRK1A protein kinase phosphorylates the Serine 28 residue of LIN52, enabling its interaction with p130/p107, to form an active DREAM complex. Mutating Ser28-LIN52 to Ala28-LIN52, thereby inhibiting its phosphorylation, suppresses oncogenic Ras-induced senescence [16]. However, the DREAM complex does not comprise the pRB tumour suppressor protein, so it is possible that during senescence p130/p107 and pRB play differing functions. Furthermore, Lowe and colleagues have shown that in another cell system, inhibiting only the pRB pocket protein bypasses Ras-induced senescence [19]. While these differences are likely to be

the result of using different cells, the different functions of the DREAM complex and RB require further investigation [20].

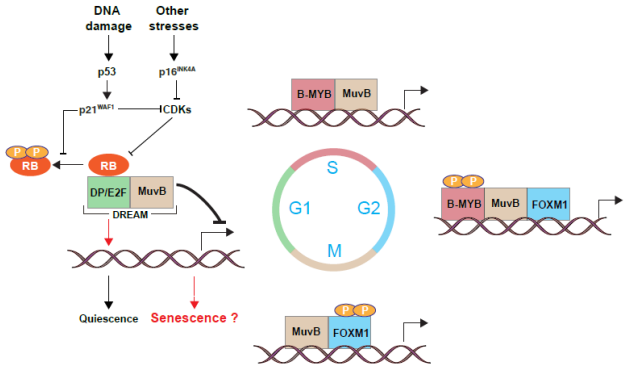

Figure 2: The DREAM complex : Assembly of this complex is mediated by MuvB, comprising LIN9, 37, 52, 54 and RBBP4, binding with the RB family members (p130/p107)-E2F4-DP, leading to quiescence. Upon stimulation of cell cycle re-entry, p130/p107 are phosphorylated, leading to their dissociation from the DREAM complex enabling MuvB to sequentially recruit B-MYB during S-phase and FOXM1 during G2/M phase, to promote cell cycle-dependent target gene expression. Expression of these target genes promotes transit through the cell cycle. During G2-phase, B-MYB undergoes phosphorylation-dependent degradation. Upon exposure to stimuli that repress cell cycle progression, LIN52 within MuvB is phosphorylated, promoting re-association of MuvB with p130/p107-E2F4-DP, to re-assemble the DREAM complex.

Emerging evidence indicates that the epigenetic machinery might also play a key role in the induction and regulation of cellular senescence in disease-associated cells. An interesting observation in cancer cells suggests that genetic depletion of histone methyltransferases SUV39H1and G9a, is able to prevent cell growth, and results in profound morphological changes with reduction of telomerase activity and shortened telomeres [21]. In fact, knocking down of SUV39H1 in cells led to a substantial increase within G2/M, whereas knocking down of G9a showed an increased DNA content and aberrant karyotype. As genetic depletion of SUV39H1/2 results in widespread genomic instability [22] and both G9a and SUV39H1 serve as the key H3K9 modifiers in mammals [23], it would be interesting to investigate the link between H3K9me, a key heterochromatin mark, and cell cycle regulation. Strikingly, since recent observations indicate that G9a also interacts with DNA methyltransferases (DNMTs) and protects DNA methylation [24], another heterochromatin mark in mammals, cell cycle arrest and senescence might be strongly associated with euchromatin/ heterochromatin turnover.

Identifying downstream targets of the p53 and pRB signalling pathways, as well as the role of epigenetics in regulating cellular senescence is integral to finding the causal factors and laying the foundation for a better understanding of the signalling circuits underlying cellular senescence. Multiple mechanisms could be involved in regulating senescence, as the responses vary between cell-types, tissues and species. Future research should additionally be targeted towards characterising these differences. The established signalling components could represent novel, important and direct targets for developing new therapies that promote healthier ageing and increase vitality of the older population through stimulating regeneration, repair and wound healing, while retaining the tumour suppressor properties of senescence, if possible. The key components will also be new therapeutic cancer targets, for developing small molecule inhibitors and activators aimed at inducing senescence in tumours. They may also be relevant for treatment of neurodegenerative disease, as it has been proposed that senescence in central nervous system cells may be a contributing factor towards neurodegeneration, due to secretion of pro-inflammatory senescence-associated secretory phenotype proteins [25-27].

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