Biology of cancer and ageing

Diana van Heemst

Department of Gerontology and Geriatrics, Leiden University Medical Center, RC Leiden, The Netherlands

The ageing process is characterised by an increasing risk of death with advancing age. Ageing is thought to be caused by molecular damage that accumulates over the lifetime of an individual. Numerous agents can lead to persistent damage, including reactive oxygen species (ROS), which are produced as byproducts of cellular metabolism. Persistent damage will interfere with the functionality of different macromolecules and disrupt the integrity of cells, tissues and the organism. To deal with the many different types of macromolecular damage, several dedicated systems for maintenance and repair have evolved. The biological significance of these many DNA repair mechanisms is highlighted by their evolutionarily conservation and by the phenotypes of patients with inherited defects in DNA repair genes. Strikingly, defects in DNA repair mechanisms can be associated with very different clinical phenotypes, including cancer and (premature) ageing [1].

Xeroderma pigmentosum (XP) is an example of a human cancer prone syndrome that is associated with inborn defects in global genome nucleotide excision repair (GG-NER) [2]. Due to the defects in GG-NER, XP patients and corresponding mouse models show an accumulation of mutagenic lesions [3]. Mutagenic lesions may cause small point mutations if not properly repaired and their persistence will put cells at a higher risk of neoplastic transformation [4], which may explain the over 1000-fold increased risk of developing UV induced skin cancer observed in XP patients. Cockayne syndrome (CS) and Trichothiodystrophy (TTD) are two examples of human accelerated ageing syndromes that are associated with inborn defects in transcription coupled repair (TCR). Due to the defects in TCR, CS and TTD patients and corresponding mouse models show an accumulation of cytotoxic lesions in actively transcribed genes [3]. The persistence of cytotoxic lesions will lead to the induction of apoptosis and/or senescence. An excessive induction of apoptosis and/or senescence may explain for the absence of cancer as well as the presence of the segmented accelerated ageing phenotypes observed in CS and TTD patients and corresponding mouse models [5,6].

Is it likely that these same mechanisms also play a role in the pathologies and degenerative diseases commonly observed in humans at advanced ages? DNA damage does accumulate with age and will include, besides mutagenic lesions, cytotoxic lesions that will interfere with primary DNA metabolism, making cells more prone to trigger apoptosis and/or senescence [4]. Moreover, emerging data raise the possibility that cells from elderly individuals may respond differently to damage than cells from younger subjects. In mouse cells derived from tissues from young and old mice exposed to high doses of ionising irradiation (IR), an age-related decline was observed in the apoptotic response [7]. A similar reduction in mean apoptotic response with age has also been observed for human cells [8]. It has also been found that the number of senescent cells accumulates with age and that senescent cells are present at sites of age-related pathologies [9–11]. The accumulation of senescent cells in aged tissues may involve different mechanisms, including enhanced induction through the accumulation of damage, an alteration in damage response mechanisms, as well as functional changes induced by the senescence programme itself, such as resistance to apoptosis [12,13].

Upon induction of cellular senescence, a cell undergoes many morphological changes as well as several functional changes, such as the accumulation of senescence associated beta-galactosidase activity [14]. Although most of the changes induced upon senescence are beneficial, in the long run, some of these changes can also have a negative impact on tissue function and integrity, especially if senescent cells accumulate to sufficiently high numbers. Senescent cells adopt a secretory phenotype, with enhanced expression of pro-inflammatory cytokines and receptors that enhance immune surveillance by potentiating natural killer (NK) cell function. Moreover, senescence can be induced by hypermitogenic signalling, which blocks cell cycle progression, but not cell growth [15] and which may cause senescent cells to become growth

factor resistant and secrete growth factors in a futile attempt to overcome the cell cycle blockage [16]. The growth factors secreted by senescent cells may stimulate premalignant cells to form tumours [17]. Thus, while clearly beneficial for tumour suppression in the short run, induction of cellular senescence may have negative late life consequences on the development of age-related diseases, which are likely related to the hypermitogenic and secretory phenotype of senescent cells, and which may include, paradoxically, the development of late life cancer.

Earlier, we observed a relationship between the *Pro/Pro* carriership of a common codon 72 polymorphism in the human *TP53* gene and a proportionally increased late life cancer mortality [18]. Recently, compared to fibroblasts derived from 90-year-old *Arg/Arg* subjects, fibroblasts derived from 90-year-old *Pro/Pro* subjects were found to give rise to a higher ionising irradiation (IR) dose dependent increase in the percentages of cells positive for senescence associated beta-galactosidase activity as well as higher percentages of cells displaying signs of genomic instability [19]. These results also raise the possibility that in humans a relationship might exist between a higher propensity of cellular senescence induction and/or a higher accumulation of persistent senescent cells and late life cancer risk.

Conflict of interest statement

None declared.

References

1 Hoeijmakers JH. DNA repair mechanisms. *Maturitas* 2001; **38**(1):17–22.
2 de Boer J, Hoeijmakers JH. Nucleotide excision repair and human syndromes. *Carcinogenesis* 2000;**21**(3):453–60.
3 Dolle ME, Busuttil RA, Garcia AM, et al. Increased genomic instability is not a prerequisite for shortened lifespan in DNA repair deficient mice. *Mutat Res* 2006;**596**(1–2):22–35.
4 Hoeijmakers JH. Genome maintenance mechanisms are critical for preventing cancer as well as other aging-associated diseases. *Mech Ageing Dev* 2007;**128**(7–8):460–2.
5 de Boer J, Andressoo JO, de Wit J, et al. Premature aging in mice deficient in DNA repair and transcription. *Science* 2002 Apr 11.
6 van der Pluijm I, Garinis GA, Brandt RM, et al. Impaired genome maintenance suppresses the growth hormone–insulin-like growth factor 1 axis in mice with Cockayne syndrome. *PLoS Biol* 2007; **5**(1):e2.
7 Feng Z, Hu W, Teresky AK, Hernando E, Cordon-Cardo C, Levine AJ. Declining p53 function in the aging process: a possible mechanism for the increased tumor incidence in older populations. *Proc Natl Acad Sci USA* 2007;**104**(42):16633–8.
8 Camplejohn RS, Gilchrist R, Easton D, et al. Apoptosis, ageing and cancer susceptibility. *Br J Cancer* 2003;**88**(4),487–90.
9 Krishnamurthy J, Torrice C, Ramsey MR, et al. Ink4a/Arf expression is a biomarker of aging. *J Clin Invest* 2004;**114**(9): 1299–307.
10 Paradis V, Youssef N, Dargere D, et al. Replicative senescence in normal liver, chronic hepatitis C, and hepatocellular carcinomas. *Hum Pathol* 2001;**32**(3):327–32.
11 Vasile E, Tomita Y, Brown LF, Kocher O, Dvorak HF. Differential expression of thymosin beta-10 by early passage and senescent vascular endothelium is modulated by VPF/VEGF: evidence for senescent endothelial cells in vivo at sites of atherosclerosis. *FASEB J* 2001;**15**(2):458–66.
12 Marcotte R, Lacelle C, Wang E. Senescent fibroblasts resist apoptosis by downregulating caspase-3. *Mech Ageing Dev* 2004; **125**(10–11):777–83.
13 Seluanov A, Gorbunova V, Falcovitz A, et al. Change of the death pathway in senescent human fibroblasts in response to DNA damage is caused by an inability to stabilize p53. *Mol Cell Biol* 2001;**21**(5):1552–64.
14 Campisi J, d'Adda di Fagagna. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol* 2007;**8**(9): 729–40.
15 Chen Z, Trotman LC, Shaffer D, et al. Crucial role of p53-dependent cellular senescence in suppression of Pten-deficient tumorigenesis. *Nature* 2005;**436**(7051):725–30.
16 Blagosklonny MV. Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. *Cell Cycle* 2006; **5**(18):2087–102.
17 Krtolica A, Campisi J. Cancer and aging: a model for the cancer promoting effects of the aging stroma. *Int J Biochem Cell Biol* 2002;**34**(11):1401–14.
18 van Heemst D, Mooijaart SP, Beekman M, et al. Variation in the human TP53 gene affects old age survival and cancer mortality. *Exp Gerontol* 2005;**40**(1–2),11–5.
19 den Reijer PM, Maier AB, Westendorp RG, van HD. Influence of the TP53 codon 72 polymorphism on the cellular responses to X-irradiation in fibroblasts from nonagenarians. *Mech Ageing Dev* 2008;**129**(4),175–82.