Mechanisms of telomere maintenance and attrition: linking cancer and ageing

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In 1961 Hayflick and Moorhead had already demonstrated that normal diploid fibroblasts obtained from human fetal explants can be grown in culture for several months (Hayflick and Moorhead, 1961). However, it soon became clear that it was impossible to subcultivate these cells for more than approximately 50 times and as they later lost the ability to divide, a phenomenon named replicative senescence, whose molecular mechanism was elucidated only decades later. However, the basic observation required for understanding the link between senescence and cancer was already made in the winter of 1951, when a 31-year-old patient, Henrietta Lacks, underwent a biopsy for a suspicious cervical mass (review Finkel et al. 2007). Routinely, the biopsy was sent to one particular pathology lab. Deviating from routine, a portion of the biopsy was instead diverted to two scientists, George and Martha Gey, who had spent almost 20 years unsuccessfully attempting to grow human cells indefinitely in culture. Unfortunately, the biopsy was confirmed to be cervical cancer and despite surgery and radiotherapy, Henrietta Lacks died 8 months later. On the day of her death Martha and George Gey announced that for the first time, it was possible to continuously grow human cells in culture. In memory of the unfortunate Henrietta Lacks, the new cell line was named “HeLa”.

A critical difference between the initially mentioned ‘normal’ fibroblasts and HeLa cells is their quantity of telomerase. Most normal cells express only limited amounts of

telomerase that are not sufficient to protect from telomere loss (Finkel et al. 2007). When telomere length falls below critical values, replicative senescence is induced. In contrast to fibroblasts, HeLa cells, similar to more than 95% of the numerous later established human cancer cell lines, aberrantly activate telomerase leading to immortality (Kim et al. 1994). The final proof that overexpressed telomerase is responsible for immortal growth came from experiments where telomerase was reintroduced into several primary human cell lines and shown to be sufficient to overcome replicative senescence (Bodnar et al. 1998).

Meanwhile, it has become clear that the well-known tumor suppressors retinoblastoma (RB), P53 and P21 are key players in the induction of senescence. In addition to telomere shortening, overexpression of oncogenes may cause senescence (Trost et al. 2005; Spangenberg et al. 2006). Oncogene-induced senescence may be interpreted as a fail-safe mechanism that must be bypassed before tumor progression can take place (Hengstler et al. 2006). However, environmental factors such as cigarette smoking and further DNA damaging substances can also accelerate telomere attrition and senescence (Acosta and Gil 2009; Finkel et al. 2007), thereby linking Toxicology to telomere and ageing research. On the other hand, genetic instability and DNA breakage may lead to amplification and increased expression of telomerase, although the involved mechanisms are not yet fully understood (Yatabe et al. 2004; Verdun and Karlseder 2007). Genetic instability (Florl and Schulz 2008; Hengstler and Bolt 2007, 2008; Stoiber et al. 2008; Beyersmann and Hartwig 2008) and DNA damage induction (Bolt 2008; Periyakaruppan et al. 2007; Borza et al. 2008; Bolt and Hengstler 2008; Zhang et al. 2008; Wong et al. 2008; Glahn et al. 2008; Krishnamurthi et al. 2008; Ullmann et al. 2008; Wozniak et al. 2007; Schmid et al. 2007; Nishimura et al. 2008; Schug et al. 2008) are

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examples of cutting-edge topics reported in our journal. Therefore, the editors are delighted by the contribution of Dr. Li Phing Liew and Dr. Chris J. Norbury from Oxford University to the current issue of Archives of Toxicology on telomere maintenance (Liew and Norbury 2009, this issue). In addition to providing a comprehensive review about the mechanisms and relevance of telomere maintenance, the authors also focus on the question how the double-stranded ends of chromosomes can be distinguished from the potentially catastrophic DNA double-strand breaks, although the chemical composition of broken DNA within the chromosomes does not obviously differ from normal DNA at the end of the chromosomes.

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