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Review

Genome instability of ageing stem cells—Induction and defence mechanisms

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ABSTRACT

The mammalian organism is comprised of tissue types with varying degrees of self-renewal and regenerative capacity. In most organs self-renewing tissue-specific stem and progenitor cells contribute to organ maintenance, and it is vital to maintain a functional stem cell pool to preserve organ homeostasis. Various conditions like tissue injury, stress responses, and regeneration challenge the stem cell pool to re-establish homeostasis (Fig. 1). However, with increasing age the functionality of adult stem cells declines and genomic mutations accumulate. These defects affect different cellular response pathways and lead to impairments in regeneration, stress tolerance, and organ function as well as to an increased risk for the development of ageing associated diseases and cancer. Maintenance of the genome appears to be of utmost importance to preserve stem cell function and to reduce the risk of ageing associated dysfunctions and pathologies. In this review, we discuss the causal link between stem cell dysfunction and DNA damage accrual, different strategies how stem cells maintain genome integrity, and how these processes are affected during ageing.

Contents

1. DNA lesions and mutations accumulate with progressive ageing

There is substantial evidence for an ageing associated accumulation of DNA damage in various tissues despite the presence of different types of repair systems (Figs. 1 and 2; Dimri et al., 1995; Jackson and Bartek, 2009; Jiang et al., 2007). Markers of DNA damage accumulate in skin of ageing baboons (Herbig et al., 2006), in stem and progenitor cells of ageing murine intestine (Hewitt et al., 2012) as well as in ageing haematopoietic stem (HSC) and progenitor cells from mice and humans (Rossi et al., 2007a; Rübe et al., 2011). Although γH2AX foci in quiescent aged HSCs have recently been disputed to label sites of DNA damage (Flach et al., 2014), other studies demonstrate an accumulation of DNA breaks and mutations in ageing murine and human HSCs (Beerman et al., 2014; Busque et al., 2012; Corces-Zimmerman et al., 2014; Welch et al., 2012; Xie et al., 2014).

Accumulating mutations at stem and progenitor cell level appear to contribute to ageing associated defects in organ maintenance and an increase in cancer development (Visvader, 2011). Recently, whole genome sequencing approaches in the haematopoietic system revealed an age-associated increase of mutations in human HSCs and provided insight into the clonal

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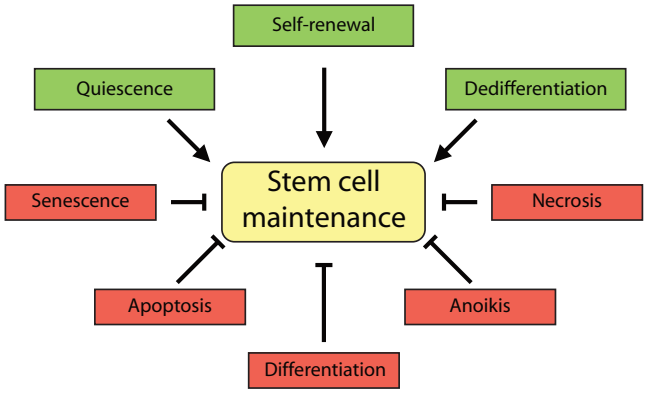

Fig. 1. Stem cell maintenance is affected by cell response pathways. A given stem cell pool is able to react to external cues with a repertoire of cellular reactions. Quiescence and self-renewal of stem cells, as well as dedifferentiation of committed progenitor cells back to more primitive stem cells positively influence stem cell maintenance. Senescence, apoptosis, anoikis (detachment induced cell death), differentiation, and possibly necrosis (so far not shown at stem level) influence stem cell numbers negatively. A balanced dynamic interplay guarantees for proper stem cell maintenance. For example, an external insult causing stem cell apoptosis can be compensated for by a wave of self-renewal divisions, which is followed by re-establishment of quiescence; lack of quiescence induction and continuous self-renewal would otherwise lead to stem cell depletion. The balanced interplay seems to be affected with advancing ageing making it more difficult for the body to react properly.

evolution of mutations and development of leukaemia (Busque et al., 2012; Corces-Zimmerman et al., 2014; Welch et al., 2012; Xie et al., 2014). The data suggest that mutations are acquired in a lifelong random manner, and that most mutations behave as neutral 'passengers' at HSC level until an additional 'driver' mutation supports clonal amplification of a subset of passenger mutations (Welch et al., 2012). The initial driver mutation may only support increased self-renewal (Busque et al., 2012), but may still depend on additional 'driver' hits to transform the HSC into a leukaemic stem cell (Fig. 3; Welch et al., 2012). Similarly, it could be demonstrated that individual driver mutations in male germline stem cells contribute a selective advantage to the affected cells allowing the clonal amplification and inheritance of the mutations (Goriely et al., 2009; Goriely et al., 2003). It remains to be determined whether mutations in stem cells accumulate in a simple stochastic manner or whether ageing associated exponential dynamics of mutation accumulation occur. Given some evidence that checkpoint function may decline with age (Feng et al., 2007) and that older HSC reveal slower *in vitro* DNA damage repair (Rübe et al., 2011) it is possible to assume a progressive increase of mutation accumulation during ageing. The mechanisms that drive ageing associated increases in mutation accumulation in stem cells represents an emerging research field that could include cell intrinsic and extrinsic factors (DeGregori, 2013).

2. A reduced capacity to repair DNA leads to stem cell depletion

It is conceivable that the accumulation of lesions and mutations observed during ageing of HSCs may in part be caused by acquired defects in DNA repair pathways (Fig. 2). Germline mutations affecting DNA repair factors cause an increasing accumulation of DNA lesions and have the potential to cause progeria syndromes thus linking DNA damage accrual to progressive ageing. Classic examples are Werner syndrome, Hutchinson-Guilford disease or Cockayne syndrome (Burtner and Kennedy, 2010; Hoeijmakers, 2009; Chu and Hickson, 2009), while additional progeria susceptibility factors, such as SPRTN are being discovered (Lessel et al., 2014). Defective DNA repair can furthermore be directly linked to a premature exhaustion of the stem cell pool of certain tissues. A dysfunctional Fanconi anemia (FA) pathway, which repairs interstrand crosslinks (ICL) causes a premature failure of bone marrow haematopoiesis in humans. This is due to an accumulation of DNA lesions resulting in an overstimulation of DNA damage checkpoint responses in HSCs and their progenitors (Ceccaldi et al., 2012). Interestingly, lack of ICL repair recently was shown to sensitize murine HSCs to damage caused by endogenous aldehydes (Garaycoechea et al., 2012). In addition to the data on the requirement of ICL repair for stem cell maintenance, studies on mice deficient for nucleotide excision repair demonstrate a critical role also for this pathway in HSC maintenance and prevention of premature ageing (Fig. 2; Rossi et al., 2007a).

HSC maintenance is furthermore affected by experimental manipulation targeting nonhomologous endjoining (NHEJ), which leads to defects in the haematopoietic reserve (demonstrated by mutation of Ligase 4, DNA dependent protein kinase catalytic subunit (DNA-PKcs), or loss of XRCC4-like factor (XLF)/Cernunnos; Avagyan et al., 2014; Nijnik et al., 2007; Zhang et al., 2011; Rossi et al., 2007a). However, also other organ compartments seem to rely on NHEJ, since reduced expression of Ku80 caused accelerated ageing of the skeletal muscle and muscle stem cells also known as satellite cells (Didier et al., 2012). NHEJ repairs double strand breaks (DSBs) by mediating the ligation of broken DNA ends after only minimal processing (Waters et al., 2014). In contrast to homologous recombination (HR), which also repairs DSBs and helps to restart stalled replication forks, NHEJ does not require a template and is thus considered error-prone. However, this independence of a template uncouples NHEJ from the cell cycle allowing execution of repair also during G0/G1. Since HSCs usually are quiescent and divide only rarely, they predominantly use NHEJ to repair DSBs (Mohrin et al., 2010). Although preferential use of the error-prone NHEJ allows quick repair of DSBs, this bears the risk of an elevated mutation rate. Recent evidence showed that DNA damage can remain unrepaired in quiescent HSCs possibly explaining an ageing associated DNA damage accrual. Furthermore, upon entry

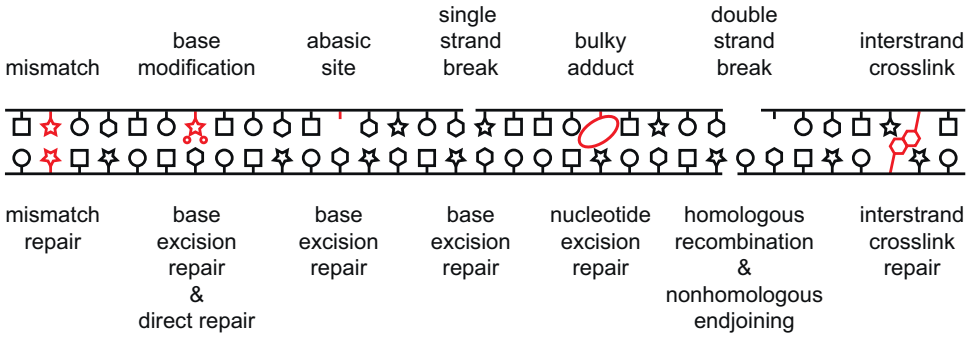

Fig. 2. Repair pathways revert distinct types of DNA lesions. On top different types of DNA lesions are highlighted, which are schematically represented in red. Indicated below is the pathway that repairs the specific subset of lesions.

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