Insights Into Stem Cell Aging

A. Herrera-Merchan, I. Hidalgo, L. Arranz and S. Gonzalez
Stem Cell Aging Group, Foundation Spanish National Cardiovascular Research Centre Carlos III. (CNIC), Madrid, Spain

1. Introduction

The increase in average life expectancy in many developed countries is generating an aging society and an associated increase in age-related health problems. Mammalian aging occurs in part because of a decline in the restorative capacity of tissue stem cells. The use of stem cells in regenerative medicine promises to revolutionize the treatment of acute and chronic degenerative conditions, and stem cell research holds the key to the development of such therapies. The hallmark of adult stem cells is their ability to both self-renew and differentiate into multiple lineages. This demands a complex and still poorly understood network of molecular interactions between diverse cell-intrinsic regulators of self-renewal, such as certain Polycomb proteins and the tumor suppressor p16^{INK4a}, both of which are absolutely required for the maintenance of certain stem cell population. Recent studies have begun to elucidate the molecular mechanisms underlying how stem cells decide between life and death, and highlight the importance of balance in their aging pathways.

2. Aging and stem cells

Recent advances in medicine research programs, and a better health care planning, have great influences in people living in many Western countries, increasing both quality of life and average lifespan. With the extension of lifetime, there is increasing interest in slowing or reversing the negative effects of aging. The fascinating discovery of tissue-resident adult stem and progenitor cells in recent years has led to an explosion of interest in the development of novel stem cell-based therapies to improve endogenous regenerative capacity or to repair damaged and diseased tissues.

A major function of stem cells and their differentiation hierarchies may be to preserve the DNA integrity of the whole organism. When mutations occur despite certain error-prevention capacities, potent tumor-suppressor mechanisms such as senescence and apoptosis eliminate the damaged stem cell, limiting its replicative expansion. However, when unrepaired genetic lesions in stem cells are passed on to their differentiated daughters, and accumulate with aging, it is required replacement of dead and non-functional cells with newly differentiated cells derived from stem- and progenitor-cells. To date, the best-studied adult tissue stem cell type is the hematopoietic stem cell (HSC), which gives rise to all of the mature blood cells, throughout the life of the organism. Hematopoiesis in mammals occurs in distinct temporal waves shifting from the

extraembryonic yolk sac and fetal liver in embryos to bone marrow in adults. Primitive HSCs are the "true" stem cells, also termed the long-term repopulating HSCs (LT-HSCs), because they replenish the pool of blood cells by both maintaining the stem cells and allowing daughter cells to differentiate into the lymphoid, myeloid, and erythroid lineages. The daily replenishment of blood cells is achieved in large part by divisions and subsequent stepwise differentiation of cells descendants of LT-HSC pool, namely short term repopulating HSC (ST-HSC), and slightly more committed hematopoietic progenitor cells (MPP-HSC). The relative quiescence of LT-HSCs pool protects their genomic integrity by reducing the rounds of DNA replication and thus the probability of acquiring DNA damage that might compromise multilineage differentiation potential and/or render them malignant over time, though they appear to age with the host (Orkin and Zon, 2008). The rapid turnover of the hematopoietic system and the availability of advanced methods to study HSCs by different markers have led to this system being widely used as a model of the effects of aging on stem cell functionality (Figure 1). It is worthy to mention that although some aspects of aging may be shared by all somatic stem cell fractions, the mechanisms of aging are likely to differ between stem cell populations located in specific tissues (for example, intestine, muscle and bone marrow).
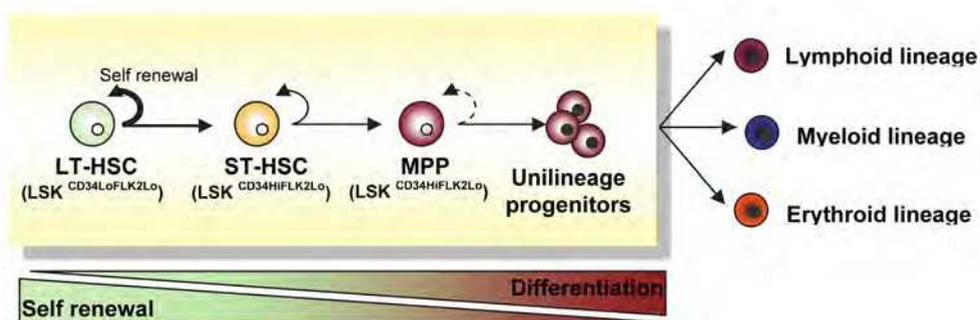

Fig. 1. The hierarchically primitive cells of the hematopoietic system. Long-Term hematopoietic stem cells (LT-HSC) maintain hematopoiesis by coordinating self-renewal, and production of short-term HSC (ST-HSC), and subsequently, the multipotent progenitors (MPP), which have an incredible capacity to divide and make other types of cells as they mature, although a limited ability to self-renew. Ultimately, this generates an array of mature blood cells with different functions: lymphoid blood cells (the B-cells; T-cells; natural killer or NK cells; plasma cells; dendritic cells and others), and erythroid and myeloid blood cells (the erythrocytes or red blood cells; megakaryocytes or platelet producing cells; granulocytes such as neutrophils, eosinophils, and basophils; and monocytes which make macrophages). The stem and progenitor cells can be purified to near-homogeneity by surface markers. For example, LT-HSCs express low levels of lineage markers, high levels of Sca1 and CD117/c-KIT receptor, and low levels of CD34 (LSK CD34 lo). With limited renewal potential, the ST-HSC pool has a similar surface immunophenotype to LT-HSC except that it has higher levels of CD34 (LSK CD34 hi). As ST-HSC in turn proliferates to form more differentiated MPP, they increase expression of another surface marker, FLK2 (LSK CD34 hi Flk2 hi).

3. The evidence for stem cell aging

A growing body of evidence shows that the capacity of stem cells to maintain tissue homeostasis declines with age, and suggests that this decline may account for many age-related phenotypes and diseases (Kirkwood and Austad, 2000). Significantly, engraftment of HSCs are capable of serial passages through a succession of mouse recipients, outliving the donor mouse (Ross et al., 1982; Siminovitch et al., 1964), though it is not possible to exceed up to five successful passages, and the recipients do not restore the hematopoietic system to the normal state (Gordon and Blackett, 1998). On the other hand, telomere length in blood cells of the transplanted recipient are 1-2 kb shorter than those in the donor, when evaluated several years following transplantation (Allsopp et al., 2003), which indicates that the level of telomerase is insufficient to prevent progressive telomere shortening in HSC. On the other hand, immunophenotypic characterization of hematopoietic stem- and progenitor-cell subsets diverges from function in old animals. The engraftment efficiency of immunophenotypically selected long-term HSCs from old mice approximately is threefold lower than that of the equivalent population from young mice (Morrison et al., 1997; Yilmaz et al., 2006). Also, age-related changes in stem-cell function include myeloid-biased differentiation and decreased homing ability (Liang et al., 2005). In conclusion, it has been extensively proved that the properties of HSCs change in several ways as they age, but still is poorly known which are the changes in the intrinsic and extrinsic factors involved that regulate the self-renewal and multilineage differentiation capacities of these regenerative cells (Huang et al., 2007).

Although the stem- and progenitor-cell proliferation guarantees tissue repair, and thereby regeneration, it can also develop hyperproliferative diseases, like cancer, risk that is moderated by tumor-suppressors mechanisms. For example, while the increased expression of tumor suppressors with age (p53, p16[INK4a]) inhibits the development of cancer (inducing apoptosis or/and senescence) (Krishnamurthy et al., 2004; Ressler et al., 2006), over time it may have a negative effect on stem cell functionality, reducing capacity for self-renewal or differentiation, and ultimately leading to aging phenotypes (Beausejour and Campisi, 2006; Rodier et al., 2007). Thus, it is thought that many of the same mechanisms that contribute to cellular aging also act as suppressors of neoplastic growth (Campisi, 2005) (Figure 2). We will therefore need a better understanding of age-related changes in stem cell function by altering genetically the expression of tumor suppressors, which may improve effective longevity-promoting therapies.

4. Self-renewal regulators in adult HSCs

Stem cells are crucial for the homeostatic maintenance of mature, functional cells in many tissues throughout the lifetime of the animal, and this pool of stem cells must itself be maintained (Muller-Sieburg and Sieburg, 2008). This is achieved by self-renewal, a specialized cell division in which one or both daughter cells remain undifferentiated and retain essentially the same replication potential of the parent. The self-renewal program must involve the activity of dedicated regulatory genes (Gazit et al., 2008); but although the phenotypic and functional properties of HSCs have been characterized extensively, we have only just begun to understand how self-renewal is regulated.
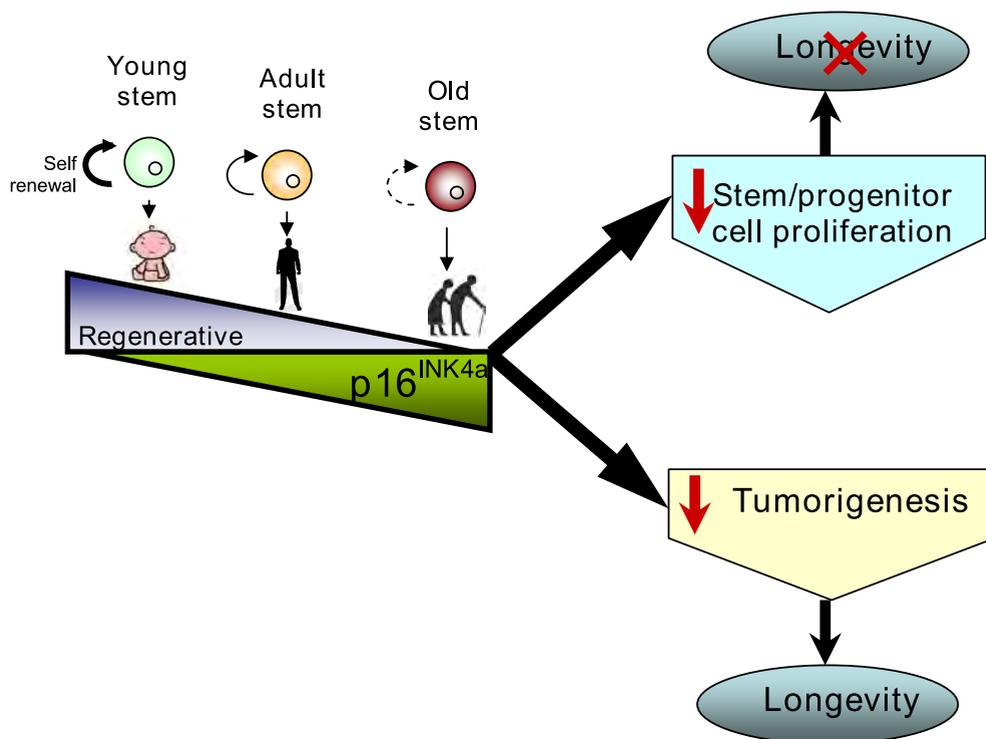
Fig. 2. Potential stem cell stage: interplay between aging and cancer. During normal aging, stem cells accumulate DNA damage as the consequence of endogenous (telomere dysfunction, oxidative stress) or exogenous (oxidative stress, g-irradiation, UV light, and others) attacks. This provokes subsequent stress-dependent changes (for example, accumulation of the products from the *INK4a/ARF* locus or telomere shortening), which activates checkpoint responses that result in apoptosis or cellular senescence. If these events occur in stem/progenitor cells, there is a decrease in the overall number and/or functionality of both stem and progenitor cells, leading an alteration of tissue homeostasis and regenerative capacity–a phenomenon that might contribute to aging and aged-related pathologies. If, instead, DNA mutations that inactivate these checkpoint pathways accumulate (for instance, loss of p16[INK4a] or reactivation of telomerase), then cancer can arise.

Polycomb complex in the maintenance of stemness. PcG proteins regulate self-renewal and lineage restriction in stem cells by inducing reversible chromatin modifications. PcG proteins have attracted increasing attention in stem cell and cancer stem cell research, given that it is now widely recognized that dynamic reprogramming of cells, for instance during differentiation, requires alterations to the epigenetic status of genes (Valk-Lingbeek et al., 2004). These features makes them interesting subjects for stem cell research, since it is conceivable that dynamic reprogramming of cells, for instance during differentiation, requires alterations in the epigenetic state of gene expression programs. The two major multiprotein PcG complexes identified to date, PRC1 and PRC2, function in a cooperative

manner to maintain gene silencing (Pietersen et al., 2008) (Table 1). PRC2 initiates silencing, whereas PRC1 maintains and stabilizes gene repression. PRC2 contains histone methyltransferases (HMTs) that methylate lysines 9 and 27 on histone H3 and lysine 26 on histone H1. Deletion of PRC2 genes in mice results in early embryonic death, underscoring their importance in development. PRC1 recognizes the H3 lysine 27 methyl group added by PRC2 (Valk-Lingbeek et al., 2004), and subsequently the monoubiquityl-ligase activity of the PRC1 proteins Bmi1 or Ring1A/B toward histone H2A generates uH2AK119, which prevents access of the transcription machinery and facilitates chromatin compaction (Wang et al., 2004). Mouse mutants of most PRC1 members, in spite of displaying homeotic transformations, survive until birth as a result of partial functional redundancy provided by homologues, an exception being Ring1B-deficient mice (Voncken et al., 2003).

PRC2 is recruited to target genes by the cofactor jARID2 (jumonji/ARID domain-containing 2). Paradoxically, jARID2 also seems to inhibit PRC2 methyltransferase activity and may therefore regulate both the targeting and fine-tuning of PRC2 activity in stem cells and during differentiation (Panning, 2010). Once PRC1 recognizes and binds the H3K27me3 mark added by PRC2, it recruits additional proteins to establish the repressed chromatin configuration (Jones and Baylin, 2007). Gene promoters marked with H3K27me3 in ESCs are significantly more likely than other promoters to become methylated in cancer (Schlesinger et al., 2007). Moreover, the PcG targets in normal prostate cells are the same as those that become methylated in prostate cancer (Gal-Yam et al., 2008). Thus, altered chromatin structure does not always result in changes in gene expression associated with disease. Rather, disease results from the replacement of PcG repressive histone marks with methylation directly on DNA, which locks the chromatin in an inactive state, a process called epigenetic switching (Gal-Yam et al., 2008). Although the mechanism underlying predisposition of PcG targets to DNA methylation is not fully understood, the PRC1 component Cbx7 (chromobox homologue 7) was recently shown to interact directly with DNA (cytosine-5)-methyltransferase (DNMT)1 and DNMT3B at PcG target genes, establishing a link between histone and DNA methylation (Mohammad et al., 2009).

Among PcG proteins, the PRC1 component Bmi1 is a fundamental self-renewal regulator, being required for self-renewal of all postnatal stem cell populations studied to date (Molofsky et al., 2003; Park et al., 2003; van der Lugt et al., 1994). Bmi1 was originally described as a proto-oncogene that induces B and T cell leukemias (van Lohuizen et al., 1991), and is overexpressed in several human cancers, including mantle cell lymphoma, colorectal carcinoma, liver carcinomas, non-small-cell lung cancer, and cerebral tumors such as medulloblastomas (Martin-Perez et al., 2010). This evidence has strongly influenced cancer research, supporting the above-mentioned theory that cancer is essentially a stem cell disorder (Reya et al., 2001). The self-renewal function of Bmi1 in adult stem cells relies largely on the silencing of one of its targets, the locus encoding the p16INK4a and ARF tumor suppressors (Molofsky et al., 2006). Deletion of p16INK4a and/or ARF partially rescues the self-renewal defects observed in various stem cell populations from Bmi1-null mice. Nevertheless, as described by the authors, this rescue is incomplete and thus other major Bmi1 regulated genes must exist. Candidates for additional Bmi1 targets in the context of self renewal are the Hox (homeobox) genes. A subset of Hox genes has been implicated in mammalian brain development, and several of them are highly expressed in neurospheres formed in vitro from cultured neural stem cells of the subventricular zone of

PcG	Mouse	Human	Function	Hematopoietic defect
PRC1	Cbx2/M33 Cbx4/Mpc2 Cbx8/Pc3	CBX2/HPC1 CBX4/HPC2 CBX8/HPC3	Binds trimethylated H3K27	Hypoplasia of spleen and thymus, maturation arrest in T cell development
	Bmi1	BMI1	Co-factor of E3 ubiquitin ligase (RING1A/B) and compacts polynucleosome	Postnatal pancytopenia Impaired HSC self-renewal, hypoplasia of spleen and thymus. Maturation arrest in T and B cell development
	Ring1/Ring1a Rnf2/Ring1b	RING1/RING1A RNF2/RING1B	E3 ubiquitin ligase for H2AK119	Decreased bone marrow cells and increased myeloid progenitors
PRC2	Eed	EED	Stimulates histone methyltransferase activity of Ezh1/2	Myelo- and lymphoproliferative disease
	Suz12	SUZ12	Stimulates histone methyltransferase activity of Ezh1/2	Enhanced HSC activity
	Ezh1/Enx2 Ezh2/Enx1	EZH1 EZH2	Catalytic subunit of H3K27 histone methyltransferase	Maturation arrest of T cells at the early CD4, CD8 double negative stage in thymus and of B cells with impaired rearrangement of the IgH gene Ezh2$^{-/-}$ Lethal in HSC

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Table 1. Principcal components of the Polycomb Group Complexes and their hematopoietic defects in mutant mice.

Bmi-null mice (Molofsky et al., 2006). More recently, Bmi1 and Ring1A were shown to play essential roles in H2A ubiquitylation and Hox gene silencing. Knockout of Bmi1 results in significant loss of H2A ubiquitylation and an upregulation of HoxC13 expression, whereas Ezh2-mediated H3-K27 methylation is not affected (Cao et al., 2005). Similar findings have been described for the HoxC5 gene. However, considering that PcG proteins modify the chromatin of large sets of genes (Kirmizis et al., 2004), a great number of additional targets are likely to exist. For instance, both PRC2 and Bmi1 have recently been shown to play roles in the repression of E-cadherin expression (Yang et al., 2010). Interestingly, PcG genes have been shown to have a tumor suppressive function. In *Drosophila*, PcG proteins repress JAK/STAT and Notch signaling activity, whose activation drives disc cell overproliferation (Classen et al., 2009). Specifically, the *Drosophila* complex Psc (posterior sex combs), which includes Bmi1, and Suz12 (suppressor of zeste 12) play a tumor suppressive role mediated by Wnt repression in follicle stem cells(Li et al., 2010). In mammals, Eed (embryonic ectoderm development protein) displays tumor suppressive activity in the mouse hematopoietic system (Richie et al., 2002). Thus, PcG genes have been suggested to behave either as proto-oncogenes or as tumor suppressors depending on the tissue, cell context, developmental stage and gene dosage.

Bmi1 is regulated by Sonic Hedgehog, providing a direct connection between PcG and a major stem cell-specific pathway (Leung et al., 2004). Furthermore, activation of either Hedgehog or Notch signaling has been shown to increase Bmi1 expression, whereas siRNA knockdown of Bmi1 abrogates the effects of Hedgehog or Notch signaling on sphere formation, a functional readout of stemness. Thus the effects of Hedgehog and Notch signaling on stem cell self-renewal appear to be largely dependent on Bmi1. A complex regulation of Bmi1 is suggested by the fact that distinct Bmi1 regulators have been found in different types of cancer, for example Twist1 in head and neck squamous cell carcinoma and the Zeb1 (zinc finger E-box binding homeobox 1) – miR-200 pathway in pancreatic cancers (Wellner et al., 2009). Furthermore, a single PcG function can be regulated by multiple factors, for example Snail1 regulates E-cadherin silencing by PRC2, whereas the action of PRC1 on this target is regulated by Twist1 (Yang et al., 2010).

In summary, PcG proteins, in particular Bmi1, are essential for self-renewal and proliferative potential, which are crucial for the maintenance of stemness, acting as a critical failsafe mechanism against loss of stem cells in response to senescence signals. In turn, Bmi1 must be finely-regulated to prevent uncontrolled replicative expansion and tumor induction. Despite the importance of PcG proteins, we are only beginning to unravel how these master regulators are themselves regulated to achieve an appropriate balance between ensuring stem cell longevity and preventing tumorigenesis.

The tumor suppressors p16^{INK4a} and ARF. Cell-cycle regulators such as the *INK4/ARF* locus appear to play an important role in the reaction of adult stem cells to stress and aging. The *INK4/ARF* locus plays a central role in tumor suppression, reflected in its inactivation in almost 50% of human cancers (Sharpless, 2005). Indeed, this locus is regarded as one of the most important anti-oncogenic defenses of the mammalian genome, comparable in importance only to p53. The remarkable feature of the *INK4/ARF* locus is that it encodes three tumor suppressors in a genomic segment of about 50 kb: *p16^{INK4a}*, its related family member *p15^{INK4b}*, and *ARF* (called *p19^{ARF}* in mice and *p14^{ARF}* in humans). The actions of p16^{INK4a}, p15^{INK4b} and ARF are well understood. Both p16^{INK4a} and p15^{INK4b} inhibit the kinase

activity of CDK4/6-cycD complexes, thus contributing to the maintenance of the active, growth-suppressive form of the retinoblastoma (Rb) family of proteins. ARF contributes to the stability of p53 by inhibiting the p53-degrading activity of MDM2. Through the activation of Rb and p53, the *INK4/ARF* locus is able to induce cell senescence and cell death (Gil and Peters, 2006; Lowe and Sherr, 2003). These tumor suppressors have taken on additional importance given recent evidence that at least one product of the locus, p16[INK4a], also contributes to the decline in the replication potential of self-renewing cells during the aging of stem cells. The expression of p16[INK4a] is relatively low in the HSCs of young mice, but is upregulated with age or in response to cellular stresses (Janzen et al., 2006). Although the number of immunophenotypic HSCs increases with age in wild-type animals, HSC functionality is impaired. In particular, the HSC compartment of old animals is more rapidly exhausted by serial transplantation than that of young animals. In contrast, aging has the opposite effect on p16[INK4a]-/- HSCs, with p16[INK4a]-/- HSCs from old animals substantially outperforming young p16[INK4a]-/- HSCs in serial transplantation assays (Janzen et al., 2006). In fact, old p16[INK4a]-/- HSCs perform as well as young wild-type HSCs in this assay. Thus p16[INK4a] compromises HSC functionality in older mice. Similar results were obtained in studies of p16[INK4a]-/- neuronal stem cells and pancreatic islets (Krishnamurthy et al., 2006; Molofsky et al., 2006), revealing a general role for p16[INK4a] in the regulation of stem cell and progenitor cell aging. Therefore, on one face of this coin, p16[INK4a] acts as a potent tumor suppressor that promotes longevity by suppressing the development of cancer, while on the flipside, the increase of p16[INK4a] levels with age impairs the proliferation of stem or progenitor cells, ultimately reducing longevity. Thus, p16[INK4a] seems to balance an equilibrium reducing cancer incidence, but also contributing to aging by decreasing stem cell self-renewal and proliferation. These observations suggest the provocative but as yet unproven notion that mammalian aging results in part from the beneficial effects of tumor suppressor proteins (Figure 2).

The transcription factor p53. Besides p16[INK4a] tumor suppressor, p53 is also a tumor suppressor that influences stem cell self-renewal, tissue regenerative capacity, age-related disease, and cancer, which activity is lost in nearly half of all human cancers(Toledo and Wahl, 2006). The p53 protein is normally inactive, due in part to its rapid degradation by the specific ubiquitin ligase Mdm2. A multitude of stresses converge on p53 through complex, and partially understood, signaling pathways that stabilize and modify p53. The analysis of the effect of p53 in aging has revealed a dual role that seems to depend on the intensity of p53 activity. Overexpression of short isoforms of p53 in mice have greater protection against tumor development than wild-type mice, while at the same time they show signs of premature aging (Maier et al., 2004; Tyner et al., 2002). However, mouse models of increased wild-type p53 activity do not present premature aging. In particular, bacterial artificial chromosome transgenic mice that bear a third copy of the p53 locus show a decreased cancer incidence but normal longevity and normal onset of aging phenotypes (Garcia-Cao et al., 2002; Matheu et al., 2007; Matheu et al., 2004). An additional mouse model, the super-INK4a/ARF mice, with an extra copy of the entire *INK4a/ARF* locus (being ARF an activator of p53), show a significantly reduced incidence of cancer, although the mice aged normally (Matheu et al., 2004). To investigate whether the concomitant expression of both tumor suppressors had a synergistic effect, mice that bear a third copy of the p53 locus and a third copy of the *INK4/ARF* locus show increased longevity and delayed aging in a manner that cannot be explained by their reduced incidence of cancer (Matheu et al., 2007). Therefore,

and though the effects of p53 and *INK4/ARF* locus expression in aging are context and dosage dependent, these results suggest that under physiological aging (labeled by moderate increase of still regulated p53 activity), the damaged cells are eliminated by either triggering their self-destruction (by apoptosis) or by pulling them out of the proliferative pool (by inducing senescence). In contrast, by massive DNA damage, the presence of uncontrolled activity of p53 results in excessive elimination of cells by p53 that exhausts the capacity of tissue regeneration leading to premature aging.

The *INK4/ARF* locus and age-associated phenotypes. p16[INK4a] and ARF may also be broadly important to diseases of aging beyond their function in stem cells. Specifically, three research consortia that undertook genome-wide association studies across large, carefully annotated patient samples have reported an association between single nucleotide polymorphisms (SNPs) near to *INK4a/ARF* locus and frailty (Melzer et al., 2007), atherosclerotic heart disease (ASHD)(Helgadottir et al., 2007) (McPherson et al., 2007), and type-2 diabetes (Saxena et al., 2007; Zeggini et al., 2008) in large human cohorts. However, few of the associated SNPs near the locus, and associated with these phenotypes, are not in linkage disequilibrium with each other, which suggests that more than one polymorphism near the locus influences these aging phenotypes. Therefore, although these studies do not pinpoint specific polymorphisms that affect the risks of age-related diseases, there are only four genes in the vicinity of the mapped polymorphisms: p16[INK4a], ARF, p15[INK4b], and ANRIL (a noncoding RNA). More relative data suggest specific links: p16[INK4a] expression increases with age in pancreatic β cells, and p16[INK4a] deficiency increases β-cell regenerative capacity(Krishnamurthy et al., 2006), providing a mechanism by which polymorphisms that affect p16[INK4a] expression or activity might affect risk for type-2 diabetes. It remains unclear whether these polymorphisms influence the risk of frailty and heart disease through their effects on tissue regenerative capacity or by mechanisms that are completely independent of stem/progenitor cells. Nevertheless, in light of the murine genetic studies that link *INK4a/ARF* locus and stem cell function, proteins encoded by the locus are the strongest candidates to mediate the effects of these polymorphisms on the incidence of these common diseases that are associated with aging.

5. Conclusions

The regenerative capacity of many stem cells declines functionally with age and, this decline triggers in part many age-related symptoms, and the development of certain diseases. Recent evidences have demonstrated that certain tumor suppressors, like *p16[INK4a]*, also suppresses the proliferation of stem or progenitor cells in the bone marrow, pancreas and brain. Thus, p16[INK4a] seems to balance equilibrium reducing cancer incidence, which promotes longevity, but also decreasing stem cell self-renewal and proliferation, compromising tissue regeneration and repair, which are likely to reduce longevity. These observations allow us to suggest the provocative but unproved hypothesis that mammalian aging results in part from the beneficial efforts of tumor suppressor proteins to interdict cancer. In this stage, characterization of how stem cells age, such as **the characterization of reliable biomarkers,** deregulated signaling pathways, loss of self-renewal or acquisition of defects in differentiation of stem cells, will contribute to understand the age-associated pathophysiological decline. Likewise, it is also essential to figure out the cellular and molecular components of stem cell niches, how the niche changes during aging, and

whether senescent stem or support cells alter the niche. In summary, the rescue, treatment, or replacement of aged and dysfunctional adult stem and progenitor cells may provide novel avenues to treat diverse devastating premature aging and age-related disorders including hematopoietic and immune disorders, heart failure and cardiovascular diseases, neurodegenerative, muscular and gastrointestinal diseases, atherosclerosis and aggressive and lethal cancers.

6. Acknowledgement

7. Abbreviatons

PcG, Polycomb Group, PRC1, Polycomb repressive complex 1, PRC2, polycomb repressive complex 2.

8. References

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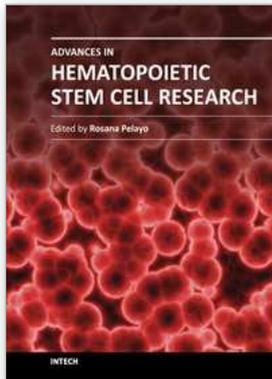
Advances in Hematopoietic Stem Cell Research

Edited by Dr. Rosana Pelayo

This book provides a comprehensive overview in our understanding of the biology and therapeutic potential of hematopoietic stem cells, and is aimed at those engaged in stem cell research: undergraduate and postgraduate science students, investigators and clinicians. Starting from fundamental principles in hematopoiesis, Advances in Hematopoietic Stem Cell Research assemble a wealth of information relevant to central mechanisms that may regulate differentiation, and expansion of hematopoietic stem cells in normal conditions and during disease.

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