Stem Cell Self-Renewal and Cancer Cell Proliferation Are Regulated by Common Networks That Balance the Activation of Proto-oncogenes and Tumor Suppressors

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Networks of proto-oncogenes and tumor suppressors that control cancer cell proliferation also regulate stem cell self-renewal and possibly stem cell aging. Proto-oncogenes promote regenerative capacity by promoting stem cell function but must be balanced with tumor suppressor activity to avoid neoplastic proliferation. Conversely, tumor suppressors inhibit regenerative capacity by promoting cell death or senescence in stem cells. For example, the polycomb family proto-oncogene, *Bmi-1*, is consistently required for the self-renewal of diverse adult stem cells, as well as for the proliferation of cancer cells in the same tissues. *Bmi-1* promotes stem cell self-renewal partly by repressing the expression of *Ink4a* and *Arf*, tumor suppressor genes that are commonly deleted in cancer. Despite ongoing *Bmi-1* expression, *Ink4a* expression increases with age, potentially reducing stem cell frequency and function. Increased tumor suppressor activity during aging therefore may partly account for age-related declines in stem cell function. Thus, networks of proto-oncogenes and tumor suppressors have evolved to coordinately regulate stem cell function throughout life. Imbalances within such networks cause cancer or premature declines in stem cell activity that resemble accelerated aging.

Mammals depend on stem cells in diverse tissues to replace cells throughout adult life and to repair tissues after injury or disease. For example, hematopoietic stem cells in the bone marrow produce millions of new blood cells daily, and stem cells in intestinal crypts constantly replace diverse types of gut epithelial cells. The depletion of stem cells from critical adult tissues, such as the hematopoietic system or gut epithelium, quickly leads to a loss of tissue integrity and death (for review, see Joseph and Morrison 2005). The persistence of stem cells throughout life in diverse tissues is therefore essential. The mechanism by which stem cells persist throughout life involves self-renewal, the process by which stem cells divide to form more stem cells (Morrison et al. 1997; Molofsky et al. 2004).

The persistence and continued mitotic activity of stem cells throughout life makes these cells a potential reservoir for the accumulation of oncogenic mutations (Reya et al. 2001). The self-renewal mechanisms that allow stem cells to persist consistently involve proto-oncogenic pathways such as Wnt, Shh, and Notch (Reya et al. 2001; Taipale and Beachy 2001). The activation of these pathways in stem cells throughout life may predispose these cells to neoplastic transformation, as it may take fewer mutations to constitutively activate such pathways in stem cells as compared to postmitotic cells in which pathway components are no longer expressed. There is evidence that some cancers arise from mutations that transform stem cells; however, the target cells for most cancers have not been rigorously identified, and many cancers may be capable of arising either from mutated

stem cells or from restricted progenitors/differentiated cells that acquire self-renewal capacity as a result of mutations (Sell and Pierce 1994; Reya et al. 2001; Pardal et al. 2003). In either case, the danger of neoplastic transformation from mutations that constitutively activate self-renewal pathways makes it critical to incorporate tumor suppressor mechanisms into this process.

Tumor suppressors come in two varieties: “caretakers,” such as ATM (ataxia telangiectasia mutated), that prevent mutations by detecting and promoting the repair of DNA damage, and “gatekeepers,” such as Rb and p53, that promote senescence or cell death when cells become mutated or stressed (Kinzler and Vogelstein 1997; Campisi 2005). Cellular senescence is a specialized form of terminal differentiation that is induced at the end of the replicative life of a cell, making the cell irreversibly postmitotic. These tumor suppressor functions take on added importance in stem cells as any mutations that occur in highly proliferative stem cells could be propagated throughout large numbers of progeny, increasing the probability of accumulating the additional mutations required for neoplastic transformation. Caretaker tumor suppressors would be expected to sustain normal stem cell activity by reducing the rate of mutagenesis. In contrast, gatekeeper tumor suppressors would be expected to reduce stem cell function by promoting cell death or senescence. Caretaking and gatekeeping tumor suppressors would thus be expected to have opposing effects on stem cell maintenance.

Tumor suppressors are also likely to influence stem cell aging. Tumor suppressors can induce cellular senescence in response to a variety of stimuli, including telomere shortening, oxidative stress, and oncogene activation—each of which activates tumor suppressors (Lowe and Sherr 2003; Itahana et al. 2004; Campisi 2005). Although the relationship between cellular senescence (which is typ-

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ically studied *in vitro*) and aging is not clear, it is thought that cellular senescence reflects some of the changes that occur during aging (Chang et al. 2004; Campisi 2005). Senescent cells have been reported to accumulate in aging human skin (Dimri et al. 1995), primate retina (Mishima et al. 1999), and human liver (Paradis et al. 2001). Senescent cells have also been detected at sites of age-related pathology (Vasile et al. 2001), and genes that overcome senescence can enhance the regenerative capacity of tissues exposed to chronic injury (Rudolph et al. 2000). These observations suggest that the senescence of progenitors in aging or damaged tissues may contribute to the age-related decline in the regenerative capacity of tissues.

The foregoing suggests that we have struck an evolutionary balance between proto-oncogenes that promote regeneration but also contribute to neoplastic proliferation, and tumor suppressors that inhibit carcinogenesis but also limit regenerative capacity. This raises the question of whether these pathways are coordinately regulated in stem cells, which are required for the regeneration of adult tissues, and which are thought to frequently be the targets of transforming mutations. Furthermore, aging is associated with decreased capacity for repair, increased incidence of degenerative disease, and increased incidence of cancer in many tissues that contain stem cells. This raises the additional question of whether the effects of proto-oncogenes and tumor suppressors on stem cells at least partially explain the changes observed in mammalian tissues with age. Recent evidence suggests that networks of proto-oncogenes and tumor suppressors coordinately regulate self-renewal and age-related changes in stem cells, as well as the generation and proliferation of cancer cells in the same tissues. This indicates that common networks of genes regulate stem cell self-renewal, cancer cell proliferation, and stem cell aging.

***Bmi-1* PROMOTES STEM CELL SELF-RENEWAL AND CANCER CELL PROLIFERATION**

Bmi-1 was first identified in 1991 as a proto-oncogene that cooperates with c-myc in oncogenesis (Haupt et al. 1991; van Lohuizen et al. 1991) and that causes leukemia when overexpressed in mice (Haupt et al. 1993). It is a member of the Polycomb group of proteins, transcriptional repressors that modify chromatin structure in a heritable way to maintain gene expression patterns established during prenatal development (Valk-Lingbeek et al. 2004). It has since been found to be overexpressed in multiple human cancers, including mantle cell lymphomas (Bea et al. 2001), non-small-cell lung cancer (Vonlanthen et al. 2001), and medulloblastomas (Leung et al. 2004).

Bmi-1-deficient mice are born in normal numbers and appear normal except for a relatively mild skeletal patterning abnormality (van der Lugt et al. 1994) that is presumably caused by the dysregulation of *Hox* gene expression upon loss of *Bmi-1* (Alkema et al. 1995). In contrast to their nearly normal prenatal development, *Bmi-1*^{-/-} mice exhibit progressive growth retardation postnatally and typically die by early adulthood with

hematopoietic failure, and neurological abnormalities including ataxia and seizures (van der Lugt et al. 1994).

The onset of growth retardation, hematopoietic failure, and neurological abnormalities correlates with the depletion of stem cells from every adult tissue yet examined in *Bmi-1*-deficient mice. Stem cells in the hematopoietic system and in the central and peripheral nervous systems form in normal numbers in the absence of *Bmi-1*, and appear to differentiate normally during fetal development, but exhibit a postnatal self-renewal defect that leads to their depletion by early adulthood (Fig. 1) (Lessard and Sauvageau 2003; Molofsky et al. 2003; Park et al. 2003). Overexpression of *Bmi-1* is also sufficient to promote the self-renewal of hematopoietic stem cells (Iwama et al. 2004). Interestingly, some restricted neural progenitors from the forebrain and gut proliferate normally in the absence of *Bmi-1*, indicating that *Bmi-1* is not generically required for the proliferation of all cells (Molofsky et al. 2003). These results indicate that *Bmi-1* is preferentially and consistently required for the postnatal maintenance of stem cells.

In addition to being essential for the maintenance of adult stem cells, *Bmi-1* is similarly required for the maintenance of cancer stem cells (Reya et al. 2001; Pardal et al. 2003). It is required for the maintenance of leukemic stem cells in a manner very similar to its requirement for the maintenance of normal hematopoietic stem cells (Lessard and Sauvageau 2003), and it is likely to be required for the proliferation of medulloblastoma cells as well (Leung et al. 2004). *Bmi-1* overexpression also promotes the generation/maintenance of cancer cells, as *Bmi-1* overexpression in lymphocytes leads to lymphoma (Haupt et al. 1993) and, in mammary epithelial cells, leads to their immortalization (Dimri et al. 2002). These data support the idea that cancer cells generally, and cancer stem cells in particular, depend on similar pathways as normal stem cells for their proliferation/self-renewal.

Figure 1. CNS stem cells require *Bmi-1* to self-renew postnatally. The photos depict typical neurospheres (neural stem cell colonies that arise from single cells in nonadherent cultures) that formed after 10 days in culture from CNS subventricular zone cells. By postnatal day 30, the frequency of CNS subventricular zone cells that formed multipotent neurospheres in culture was significantly lower in the absence of *Bmi-1*, and the self-renewal of these cells in culture was also significantly reduced (*, $p < 0.05$). Self-renewal is expressed as the number of secondary neurospheres generated per primary neurosphere upon subcloning. Similar results were obtained for multipotent neural crest stem cells from the peripheral nervous system (data not shown). (Photos reprinted, with permission, from Molofsky et al. 2003 [©Nature Publishing Group].)

OTHER PROTO-ONCOGENES ALSO PROMOTE STEM CELL SELF-RENEWAL

Bmi-1 is not unusual among proto-oncogenes in promoting the self-renewal of normal stem cells and the proliferation of cancer cells from the same tissues (Reya et al. 2001). The Wnt/ β -catenin signaling pathway promotes the self-renewal of intestinal epithelial stem cells, and mutations that increase signaling through this pathway promote the generation and proliferation of colorectal cancer cells (Kinzler and Vogelstein 1996; Batlle et al. 2002; van de Wetering et al. 2002). This pathway also promotes normal stem cell self-renewal and tumorigenesis in other tissues, including the skin and the hematopoietic system (for review, see Kleber and Sommer 2004; Reya and Clevers 2005). Similarly, Sonic Hedgehog signaling is necessary for the maintenance of neural stem cells in the central nervous system (Lai et al. 2003; Machold et al. 2003), and overactivation of this pathway is involved in the generation of diverse types of brain tumors (Ruiz i Altaba et al. 2002). These are only a few of many examples of pathways that promote normal stem cell self-renewal and which lead to tumorigenesis upon overactivation. These results are consistent with the idea that mutations frequently cause cancer by inappropriately activating self-renewal mechanisms in stem cells or other cells.

THE TUMOR SUPPRESSORS *Ink4a* AND *Arf* INHIBIT CANCER CELL PROLIFERATION AND STEM CELL SELF-RENEWAL

To avoid neoplastic proliferation, the activities of proto-oncogenes are balanced against tumor suppressors. Tumor suppressor activity can be induced by inappropriate mitogenic stimuli and can inhibit proliferation by promoting cellular senescence or cell death. The *Ink4a-Arf* locus encodes two gatekeeper tumor suppressors that activate critical senescence pathways (Sherr 2001; Campisi 2005). *Ink4a* encodes p16^{Ink4a}, a cyclin-dependent kinase inhibitor that promotes Rb activation by disrupting cyclin D-cdk4/6 complexes. *Arf* encodes p19^{Arf}, which promotes p53 activation by inactivating Mdm2. Induction of p16^{Ink4a} and/or p19^{Arf} expression in cultured primary cells leads to cellular senescence via the activation of these Rb and p53 pathways (for review, see Campisi 2005). *Bmi-1* overexpression, in contrast, can bypass senescence and extend the replicative life span of primary cells by reducing p16^{Ink4a} and p19^{Arf} expression (Jacobs et al. 1999a; Dimri et al. 2002; Itahana et al. 2003).

Inactivation of these senescence pathways contributes strongly to carcinogenesis. *Ink4a* deletion in mice and humans is associated with lymphoma, lung adenoma, brain tumors, melanoma, and other cancers (Krimpenfort et al. 2001; Sharpless et al. 2001; Sherr and McCormick 2002). *Arf* deletion in mice leads to an increased incidence of sarcomas, lymphomas, and gliomas, as well as other types of cancers (Kamijo et al. 1999). Combined loss of *Ink4a* and *Arf* is often observed in human tumors (for review, see Ruas and Peters 1998; Sherr 1998). These data indicate that p16^{Ink4a} and p19^{Arf} are critical tumor suppressors in diverse tissues.

p16^{Ink4a} and p19^{Arf} also inhibit the self-renewal of at least some types of stem cells. Two of the major mechanisms by which *Bmi-1* promotes neural stem cell self-renewal are inhibiting *Ink4a* and *Arf* expression (Molofsky et al. 2003, 2005; Bruggeman et al. 2005). *Bmi-1* directly or indirectly represses transcription at the *Ink4a-Arf* locus (Jacobs et al. 1999a,b; Itahana et al. 2003). Deletion of *Ink4a-Arf* rescues the ability of *Bmi-1*^{-/-} mouse embryonic fibroblasts to proliferate in culture and partially rescues cerebellum development in *Bmi-1*^{-/-} mice (Jacobs et al. 1999a). Although p16^{Ink4a} and p19^{Arf} are not generally expressed by normal cells in young mice in vivo (Zindy et al. 1997), these proteins become strongly expressed in stem cells and other progenitors in the absence of *Bmi-1* (Molofsky et al. 2003, 2005; Park et al. 2003). Deletion of either *Ink4a* or *Arf* from *Bmi-1*-deficient mice substantially, although only partially, rescues neural stem cell self-renewal, neural stem cell frequency, and various aspects of

Figure 2. Deletion of *Ink4a* or *Arf* significantly rescues stem cell frequency and proliferation in the forebrain subventricular zone (SVZ) of *Bmi-1*^{-/-} mice but exhibits differential effects on cerebellum rescue. *Ink4a* deficiency (A) or *Arf* deficiency (B) partially rescues the percentage of SVZ cells from *Bmi-1*^{-/-} mice that form multipotent stem cell colonies in culture. The rate of proliferation (percentage of cells that incorporate a pulse of BrdU) in the forebrain SVZ of *Bmi-1*^{-/-} mice is also significantly increased by *Ink4a* deficiency (C) or by *Arf* deficiency (D). (E) Hematoxylin and eosin-stained sagittal sections of adult cerebellum show that deletion of *Arf*, but not *Ink4a*, partially rescues the overall cerebellum size in *Bmi-1*^{-/-} mice. Thickness of the cerebellum granule cell layer (GL) and cell density in the molecular layer (ML) for each genotype is quantified as a percentage of wild-type. * indicates significantly different ($p < 0.05$ by t -test) from wild-type, # indicates significantly different from *Bmi-1*^{-/-} *Ink4a*^{+/+} or *Bmi-1*^{-/-} *Arf*^{+/+}, and \$ indicates significantly different from *Bmi-1*^{+/+} *Ink4a*^{-/-} or *Bmi-1*^{+/+} *Arf*^{-/-}.

Figure 3. Networks of proto-oncogenes (purple) and tumor suppressors (orange) control stem cell self-renewal. The ability of adult stem cells to self-renew depends on a network of proto-oncogenes that activate cell cycle entry, and tumor suppressors that block cell cycle progression. External stimuli like mitogen activation promote cell cycle entry, whereas oncogene activation, telomere attrition, or DNA damage can promote senescence or cell death via p53 activation.

neural development (Fig. 2) (Molofsky et al. 2003, 2005; Bruggeman et al. 2005). These results indicate that the *Ink4a* and *Arf* senescence pathways must be repressed in order to maintain neural stem cells throughout adult life. Adult stem cell self-renewal thus reflects a balance in which proto-oncogene activity promotes self-renewal and tumor suppressor activity inhibits self-renewal (Fig. 3). Mutational overactivation of proto-oncogenes can cause cancer, whereas substantial increases in tumor suppressor activity can cause premature senescence of stem cells, potentially impairing tissue growth and regeneration (Fig. 4).

Figure 4. Adult stem cell self-renewal represents a balance between proto-oncogenes that promote stem cell self-renewal but which can cause cancer when overactivated, and gatekeeper tumor suppressors that keep self-renewal in check but which can lead to premature depletion of stem cells when overactivated. Tissue regeneration is likely favored by the activation of proto-oncogene pathways whereas the activation of gatekeeper tumor suppressors may contribute to reduced regenerative capacity, increased degenerative disease, and perhaps aging.

THE *Ink4a* TUMOR SUPPRESSOR MAY ALSO PROMOTE STEM CELL AGING

A central feature of aging in mammals is the reduced capacity for regeneration in tissues that contain stem cells. Stem cell function declines with age in diverse tissues, including the hematopoietic system (Morrison et al. 1996b; Chen et al. 2000), muscle (Conboy et al. 2003, 2005), and brain (Kuhn et al. 1996; Maslov et al. 2004). Indeed, differences among mouse strains in the frequency and proliferation of hematopoietic stem cells during aging correlate with differences in life span, suggesting that stem cell aging is regulated by mechanisms that also determine life span (de Haan et al. 1997). These observations raise the possibility that certain aspects of mammalian aging are caused by age-related reductions in stem cell function.

The expression of p16^{Ink4a} and p19^{Arf} increases substantially with age in multiple mouse tissues (Zindy et al. 1997; Krishnamurthy et al. 2004). This raises the question of whether these increases in p16^{Ink4a} and p19^{Arf} expression cause age-related declines in tissue function (Sharpless 2004). Although moderately increased expression of p16^{Ink4a} and p19^{Arf} in transgenic mice did not detectably accelerate aging or change life span (Matheu et al. 2004), the increase in p16^{Ink4a} and p19^{Arf} expression in these mice was small relative to the increase observed in old mice. The levels of p16^{Ink4a} and p19^{Arf} that are required to promote aging may be qualitatively higher than the levels that are required to inhibit cancer. To assess the physiological role of these proteins in normal aging, it will therefore be necessary to examine mice that are deficient for *Ink4a* and/or *Arf* (Fig. 5).

Although *Ink4a* may regulate stem cell aging, the relationship between stem cell aging and overall organismal aging or life span remains unclear. The age-related decline in stem cell function may be a major cause of the decline in regenerative capacity and the increase in degenerative disease that are observed in many aging tissues. On the other hand, increases in the death or dysfunction of mature cells in many aging tissues must also contribute to age-related morbidity. It is similarly unknown whether physiological differences in the rate at which stem cell activity declines with age have a detectable impact on longevity. It is likely that there will be important differences between tissues, and perhaps between stem cells and differentiated cells, in terms of the genes that regulate

Figure 5. Stem cell self-renewal, stem cell aging, and cancer cell proliferation may be coordinately regulated by pathways that balance the activation of proto-oncogenes like *Bmi-1* and tumor suppressors like *Ink4a* and *Arf*.

the aging process. Although many of these big picture questions remain unanswered, it may be possible to gain important new insights into the aging process at a cellular level by studying individual cell types that have known physiological functions in vivo, such as hematopoietic or neural stem cells.

OTHER TUMOR SUPPRESSORS MAY ALSO REGULATE AGING

Other tumor suppressors also regulate aging in mice, although few studies have specifically examined their ability to promote age-related changes in stem cells. p53 is a powerful gatekeeping tumor suppressor that responds to a variety of cellular stresses, including DNA damage, hypoxia, and oncogene activation, to induce cell death or cell cycle arrest (Levine 1997; Serrano et al. 1997; Giaccia and Kastan 1998). p53 is also one of the most commonly deleted genes in human cancer (Lozano and Elledge 2000; Sherr and McCormick 2002). Recent reports about genetically engineered mice with altered longevity phenotypes implicate p53 as a mediator of aging (Migliaccio et al. 1999; Vogel et al. 1999; Lim et al. 2000). Mice expressing a mutant form of p53 that augments wild-type p53 activity exhibit enhanced resistance to spontaneous tumors and display an early onset of phenotypes associated with aging (Tyner et al. 2002). The short isoform of p53, p44, promotes IGF-1 signaling (Maier et al. 2004), a pathway that controls both aging and cancer cell proliferation in mammals (Holzenberger et al. 2003; Pollak et al. 2004). Mice overexpressing p44 exhibit phenotypes consistent with accelerated aging (Maier et al. 2004). Moderate overexpression of p53 in BAC transgenic mice increased cancer resistance but did not accelerate aging (Garcia-Cao et al. 2002), suggesting that aging requires higher levels of p53 activity than tumor suppression. This raises the question of whether physiological levels of p53 expression regulate aging; the levels of p53 activation that are required to accelerate aging may never be achieved under physiological circumstances. Nonetheless, p53 is likely to regulate the self-renewal of stem cells because p53 activation promotes p21^{Cip1} expression, and p21^{Cip1} regulates stem cell self-renewal in diverse tissues (Cheng et al. 2000; Kippin et al. 2005).

Telomere length is another crucial checkpoint that regulates neoplastic proliferation, as well as stem cell function and aging (Sharpless and DePinho 2004). Telomeres are repetitive DNA sequences at the ends of eukaryotic chromosomes that prevent the fusion of chromosomes (McEachern et al. 2000). In most somatic tissues, telomeric DNA undergoes progressive shortening with each round of cell division, resulting from incomplete replication by DNA polymerases (McEachern et al. 2000). Telomere shortening to a critical length can activate DNA damage pathways that trigger cell cycle arrest or apoptosis (Chiu and Harley 1997). Thus, telomere attrition limits the number of times that progenitors can divide in the absence of mechanisms like telomerase expression that maintain or lengthen telomeres.

Stem cells express telomerase and depend on it to

maintain their tremendous self-renewal potential (Morrison et al. 1996a; Lee et al. 1998; Allsopp et al. 2003a); however, telomere length in stem cells still declines with age and can limit stem cell proliferation after repeated injury (Chiu et al. 1996; Rudolph et al. 2000; Allsopp et al. 2003b). Inbred laboratory mice have hyper-long telomeres (Starling et al. 1990) and therefore take three generations to critically deplete telomeres in the absence of telomerase; however, upon reaching this point, telomerase-deficient mice exhibit proliferation defects in a variety of tissues and show signs of premature aging (Blasco et al. 1997; Lee et al. 1998). These phenotypes are rescued to a considerable extent by p53 deficiency, indicating that telomere attrition causes senescence via p53 activation (Chin et al. 1999). By regulating the number of times a cell can divide before triggering senescence, telomeres and telomerase can inhibit neoplastic proliferation and determine the replicative life span of normal stem cells. Since humans have a much longer life span and much shorter telomeres than inbred mice, these observations raise the possibility that the proliferation of some human cells could be limited by telomere erosion during normal aging in vivo.

Although gatekeeper tumor suppressors promote aging phenotypes, other tumor suppressors can slow the aging process while linking stem cell self-renewal and cancer cell proliferation. ATM is a caretaker tumor suppressor that is activated in response to oxidative stress, DNA damage, or telomere instability, and which can promote DNA damage repair as well as cellular senescence (Shiloh 2003). Mutational inactivation of *Atm* causes ataxia telangiectasia, a recessive disorder characterized by neuronal degeneration, premature aging, and high cancer incidence (Shiloh 2003). Loss of both *Atm* and telomerase function in mice leads to premature aging with multiple stem cell populations apparently affected (Wong et al. 2003). ATM also regulates the maintenance of hematopoietic stem cells (Ito et al. 2004). In the absence of *Atm*, an increase in reactive oxygen species leads to activation of p16^{ink4a} and to the depletion of hematopoietic stem cells, which could be rescued by treatment with antioxidants or by overexpression of Bmi-1. ATM therefore slows the aging process and avoids carcinogenesis by reducing DNA damage and other oxidative damage in diverse cells, including stem cells.

The tumor suppressor PTEN negatively regulates signaling through the PI3 kinase pathway, which promotes cell growth, proliferation, and survival (Stiles et al. 2004). PTEN negatively regulates the self-renewal of fetal CNS stem cells (Backman et al. 2001; Groszer et al. 2001) as well as the proliferation of CNS and other cancer cells (Suzuki et al. 1998; Di Cristofano and Pandolfi 2000; Wechsler-Reya and Scott 2001). PTEN negatively regulates signaling through the insulin/insulin-like growth factor pathway, which promotes aging in an evolutionarily conserved manner (Tatar et al. 2003), and the *Caenorhabditis elegans* homolog of Pten, Daf-18, promotes life span extension in nematodes (Mihaylova et al. 1999; Solari et al. 2005). Human *Pten* complements the Daf-18 mutation in worms (Solari et al. 2005), raising the

question of whether PTEN promotes life span extension, or at least maintenance of adult stem cell activity, in mammals as well.

CONCLUSIONS: AN EVOLVED BALANCE BETWEEN PROTO-ONCOGENES AND TUMOR SUPPRESSORS

Stem cells must self-renew throughout life to promote tissue maintenance and repair. This makes these cells particularly susceptible to the accumulation of potentially transforming mutations. To promote tissue regeneration while avoiding malignant transformation, a tightly regulated balance between the expression of proto-oncogenes and tumor suppressors has evolved. Proto-oncogenes promote stem cell self-renewal and tissue regeneration, but mutations that activate these pathways can lead to cancer. Gatekeeping tumor suppressors are activated by mutations and prevent neoplastic proliferation by promoting cellular senescence. This reduces cancer incidence but also contributes to aging by reducing the regenerative capacity of tissues. Hence, aging is in some ways a by-product of mechanisms that evolved to prevent the neoplastic transformation of stem cells and other progenitors.

The balance of proto-oncogene and tumor suppressor activity in stem cells changes throughout life (Fig. 6). Fetal development is a time of rapid tissue growth before cells have an opportunity to accumulate mutations. As a result, proto-oncogene activity dominates tumor suppressor activity in stem cells during fetal development to promote rapid proliferation. In contrast, most adult stem cells are quiescent most of the time (Morshead et al. 1994; Cheshier et al. 1999). Whereas this quiescence is likely critical for stem cell maintenance and probably reflects the increased influence of tumor suppressors during adult life (Cheng et al. 2000), the regulation of stem cell quies-

cence remains poorly understood. In concert with these developmental changes in stem cell function, adult mammals also exhibit an increased incidence of cancer in all proliferative tissues that contain stem cells. Whether because of accumulating damage/dysfunction or because of a developmentally programmed senescence process, tumor suppressors such as p16^{Ink4a} appear to exhibit increasing activity in aging stem cells. This could contribute to age-related morbidity by reducing the regenerative capacity of aging tissues, perhaps increasing the incidence of degenerative disease.

These observations raise the question of whether polymorphisms that cause partial increases or decreases in the activity of proto-oncogenes and tumor suppressors cause physiological variations in tissue regenerative capacity or aging just as such polymorphisms are already known to affect cancer predisposition. A human polymorphism that reduces p53 activity increases cancer risk but may also be associated with significantly increased survival into old age, despite the increased cancer risk (van Heemst et al. 2005). More studies confirming findings of this type could greatly increase our understanding of how relatively small functional changes in tumor suppressor function could lead to natural variations in human longevity and regenerative capacity (Donehower 2005). A key question is whether by better understanding these networks of proto-oncogenes and tumor suppressors it will be possible to pharmacologically enhance tissue regeneration or delay changes associated with aging without increasing the risk of cancer and vice versa.

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Figure 6. Developmental changes in the balance between proto-oncogenes and tumor suppressors. Stem cells proliferate rapidly during fetal development to accomplish the necessary tissue growth. This suggests that pathways which favor proliferation are strongly activated during fetal development and may not be subject to some of the gatekeeping tumor suppressor mechanisms that limit the proliferation of adult cells. Evolutionarily it may be possible to promote rapid fetal growth by removing tumor suppressor mechanisms because there is little opportunity to accumulate carcinogenic mutations during fetal development. In contrast, adult stem cells are quiescent most of the time, and appear to be subject to many more constraints upon their rate and extent of proliferation. This suggests that more tumor suppressor mechanisms are expressed in adult cells, which are at risk of accumulating transforming mutations.

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