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Recent insights into the molecular mechanisms involved in aging and the malignant transformation of adult stem/progenitor cells and their therapeutic implications

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Abstract

Recent advancements in tissue-resident adult stem/progenitor cell research have revealed that enhanced telomere attrition, oxidative stress, ultraviolet radiation exposure and oncogenic events leading to severe DNA damages and genomic instability may occur in these immature and regenerative cells during chronological aging. Particularly, the alterations in key signaling components controlling their self-renewal capacity and an up-regulation of tumor suppressor gene products such as p16^{INK4A}, p19^{ARF}, ataxia-telangiectasia mutated (ATM) kinase, p53 and/or the forkhead box O (FOXOs) family of transcription factors may result in their dysfunctions, growth arrest and senescence or apoptotic death during the aging process. These molecular events may culminate in a progressive decline in the regenerative functions and the number of tissue-resident adult stem/progenitor cells, and age-related disease development. Conversely, the telomerase re-activation and accumulation of numerous genetic and/or epigenetic alterations in adult stem/progenitor cells with advancing age may result in their immortalization and malignant transformation into highly leukemic or tumorigenic cancer-initiating cells and cancer initiation. Therefore, the cell-replacement and gene therapies and molecular targeting of aged and dysfunctional adult stem/progenitor cells including their malignant counterpart, cancer-initiating cells, hold great promise for treating and even curing diverse devastating human diseases. These diseases include premature aging diseases, hematopoietic, cardiovascular, musculoskeletal, pulmonary, ocular, urogenital, neurodegenerative and skin disorders and aggressive and recurrent cancers.

Keywords

Adult stem/progenitor cells; Senescence; Aging; Cancer-initiating cells; Anti-aging therapies; Cancer therapies

1. Introduction

Major advances in the field of adult stem/progenitor cell biology have indicated that these immature cells endowed with high self-renewal and multilineage differentiation capacities provide critical functions in maintaining tissue homeostasis and repair after severe injuries along the lifespan of individuals (Arai and Suda, 2007; Bryder et al., 2006; Dhawan and Rando, 2005; Kim et al., 2005; Leri et al., 2005; Mimeault and Batra, 2006, 2008a; Mimeault et al., 2007a; Reya and Clevers, 2005; Rizo et al., 2006; Wilson and Trumpp, 2006; Zhao et al., 2008). Recent accumulating lines of evidence, however, have revealed that the molecular and biochemical changes may occur in the tissue-resident stem/progenitor cells and their specialized microenvironments, niches during the chronological aging, and have severe pathophysiological consequences (Anversa et al., 2006; Aubert and Lansdorp, 2008; Ballard and Edelberg, 2008; Galvan and Jin, 2007; Gopinath and Rando, 2008; Gorbunova et al., 2007; Kenyon and Gerson, 2007; Rossi et al., 2007; Ruzankina et al., 2008; Sharpless and DePinho, 2007; Zhao et al., 2008). Telomere shortening, DNA repair defects, genotoxic stress, chromosomal instability and the accumulation of genetic and/or epigenetic alterations occurring in the adult stem/progenitor cells and their progenies as well as in the changes in their external tissue environment with the passage of time may lead to their dysfunction or loss *via* the senescence or apoptotic death (Figs. 1–3) (Calado and Young, 2008; Carlson and Conboy, 2007; Degens, 2007; Droge and Schipper, 2007; Galvan and Jin, 2007; Gorbunova et al., 2007; Jie et al., 2008; Naka et al., 2008; Ruzankina et al., 2008; Sharpless and DePinho, 2007). This progressive age-dependent decline in the functional properties and the number of adult stem/progenitor cells due to the intrinsic aging and/or extrinsic changes in the key niche elements, has been associated with an impairment of the homeostatic mechanisms of tissue regeneration and repair after injuries, and the development of diverse human disorders. Among the age-related disorders, there are a gradual loss of hematological, immune, cardiovascular, musculoskeletal, pulmonary, gastrointestinal, urogenital, ocular, brain and skin functions resulting in an enhanced occurrence of diverse diseases such as bone marrow (BM) and heart failures, atherosclerosis, diabetes mellitus, neurodegenerative and skin disorders (Brack et al., 2007; Galvan and Jin, 2007; Jie et al., 2008; Ju et al., 2007; Kwon et al., 2008; Mimeault et al., 2007a; Nishimura et al., 2005; Pignolo et al., 2008; Rossi et al., 2005; Satoh et al., 2008; Schipper et al., 2008). Therefore, the cell-replacement and gene therapies to alleviate the age-related dysfunctions occurring in the tissue-resident stem/progenitor cells and their progenies offer great promise in reducing the detrimental metabolic and physiological consequences of pathological aging, and thereby improve the lifespan of individuals (Ballard and Edelberg, 2008; Bellantuono and Keith, 2007; Gonzalez et al., 2008; Leri et al., 2005; McCullough and Kelly, 2006; Mimeault and Batra, 2006, 2008a; Mimeault et al., 2007a; Rossi et al., 2007).

In addition, a growing body of experimental evidence has indicated that the tissue-resident adult stem/progenitor cells could be at the origin of the most aggressive human cancers including age-related cancer types (Aubert and Lansdorp, 2008; Bapat et al., 2005; Ginestier et al., 2007; Kim et al., 2005; Matsui et al., 2008; Mimeault and Batra, 2008a,c; Mimeault et al., 2007b, 2008b; Nicolis, 2007; Nijhof et al., 2007; Rizo et al., 2006; Vaish, 2007). Particularly, the high longevity and proliferative capacity of adult stem/progenitor cells may allow them to accumulate the genetic and/or epigenetic alterations that may subsequently culminate in their dysfunction and malignant transformation into cancer stem cells (CSCs) and cancer initiation and progression with advancing age (Figs. 1 and 4). New concepts on CSCs suggest that these highly leukemic or tumorigenic cancer cells or their malignant progenies endowed with a high self-renewal potential and aberrant differentiation ability, also designated as cancer- or tumor-initiating cells, can provide critical roles for primary tumor growth, metastases at distant tissues and organs, resistance to current conventional

therapies and disease relapse (Bao et al., 2006; Eramo et al., 2008; Fillmore and Kuperwasser, 2008; Ginestier et al., 2007; Hermann et al., 2007; Hope et al., 2004; Jamieson et al., 2004; Liu et al., 2006; Matsui et al., 2008; Mimeault et al., 2007a,b; Nicolis, 2007; Schatton et al., 2008; Singh et al., 2004; Wright et al., 2008; Yang et al., 2008b; Young et al., 2008; Zhang et al., 2008c). Therefore, the molecular targeting of these cancer-initiating cells and their local microenvironment, niche may represent a promising strategy for improving the current cancer therapies. In regard with this, we described the unique intrinsic and functional properties of tissue-resident adult stem/progenitor cells that may contribute to their high longevity. We also reviewed the deregulated signaling pathway elements, including the signals from their niches and molecular mechanisms that may contribute to trigger their dysfunction, senescence or apoptotic cell death throughout the aging process, and malignant transformation during cancer progression. Interestingly, we also discussed the new therapeutic strategies that have been designed for treating age-related disorders and improving the current clinical therapies against aggressive and recurrent cancers.

2. Phenotypic and functional properties of tissue-resident adult stem/progenitor cells

The small pools of immature adult stem/progenitor cells possessing high self-renewal and multilineage differentiation capacities, and which have generally a smaller size relative to the terminally differentiated cells, have been identified and isolated from most tissues and organs in human (Arai and Suda, 2007; Brittan and Wright, 2002; Bryder et al., 2006; Dhawan and Rando, 2005; Kim et al., 2005; Leri et al., 2005; Mimeault and Batra, 2006, 2008a; Mimeault et al., 2007a; Reya and Clevers, 2005; Rizo et al., 2006; Wilson and Trumpp, 2006; Zhao et al., 2008). Among the tissues and organs harboring a very small subpopulation of adult stem/progenitor cells, corresponding to about 0.1–3% from the total cell mass, there are BM, vascular walls, heart, brain, skeletal muscles and adipose tissues as well as the epithelium of the skin, eye, lung, liver, digestive tract, pancreas, breast, ovary, uterus, prostate and testis (Fig. 3). In general, the poorly differentiated tissue-resident adult stem/progenitor cells, are localized in the specific anatomic localizations within a specialized microenvironment designated as niches consisting of the neighboring cells such as fibroblasts, endothelial cells and/or stromal components that tightly regulate their functions through the direct interactions and release of specific soluble factors (Arai and Suda, 2007; Brittan and Wright, 2002; Bryder et al., 2006; Lim et al., 2007; Mimeault et al., 2007a; Mimeault and Batra, 2006, 2008b; Rizo et al., 2006; Watts et al., 2005; Wilson and Trumpp, 2006). All of the multipotent or bi-potent adult stem/progenitor cells can give rise to the mature and specialized cell types of distinct lineages in the tissues and organs from which they originate during tissue regeneration in homeostatic conditions and after intense injuries (Brittan and Wright, 2002; Bryder et al., 2006; Gopinath and Rando, 2008; Griffiths et al., 2005; Herrera et al., 2006; Hope et al., 2004; Kim et al., 2005; Lavker et al., 2004; Leri et al., 2005; Lim et al., 2007; Mimeault and Batra, 2006, 2008a; Mimeault et al., 2007a; Rizo et al., 2006; Schaffler and Buchler, 2007; Watts et al., 2005). Although certain adult stem/progenitor cells such as them found in BM, skin and gastrointestinal tract typically display a rapid turnover to replenish the cell loss along lifespan, other adult stem/progenitor cell types remain under a quiescent state and rarely divide in normal conditions, and undergo only a sustained proliferation after intense tissue injuries (Brittan and Wright, 2002; Bryder et al., 2006; Mimeault and Batra, 2006, 2008a; Mimeault et al., 2007a; Moore and Lemischka, 2006; Potten and Ellis, 2006; Rizo et al., 2006). The expansion of adult stem/progenitor cell pool within niche is generally accomplished through a symmetric cell division that gives rise to two identical stem cell daughters. The generation of differentiated cell lineages rather generally implicates an asymmetric division of a stem cell that gives rise to one stem cell daughter and one cell termed early transit-amplifying (TA)/intermediate cell

(Brittan and Wright, 2002; Griffiths et al., 2005; Mimeault and Batra, 2006, 2008a; Mimeault et al., 2007a; Moore and Lemischka, 2006; Watts et al., 2005; Wilson and Trumpp, 2006). The TA cells, in turn, can give rise to a heterogeneous population of poorly, moderately and terminally differentiated cells constituting the tissues in which they originate (Brittan and Wright, 2002; Mimeault and Batra, 2006, 2008a,c; Mimeault et al., 2007a, 2008b; Watts et al., 2005). More particularly, the early TA cells, which possess a high proliferative potential and migratory ability, may exit the stem cell niche and give rise to late TA cells. The migration of late TA cells at distant sites within the tissues from which they originate or more distant compartments concomitant with the changes in their local microenvironment may also result to a populational asymmetry and generation of differentiated cells endowed with different phenotypic properties characterizing each tissue and organ (Mimeault and Batra, 2006, 2008a,c; Mimeault et al., 2007a, 2008b; Urbanek et al., 2006). For instance, the corneal epithelial stem cells (CESCs) also designated as limbal stem cells, which are located in basal layer of the limbal epithelium, can give rise to the TA cells that migrate from limbus to a distant compartment, the corneal basal cell layer where they can generate the corneal epithelial cell precursors that contribute to corneal epithelium regeneration process (Imanishi et al., 2000; Lavker et al., 2004; Mimeault and Batra, 2008a).

The replenishment of differentiated cells mediated *via* adult stem/progenitor cells during hematopoiesis and tissue regeneration is usually accompanied by microenvironmental changes in the niche including their interactions with host supporting cells and extra-cellular matrix (ECM) components, and orchestrated by several growth factors, cytokines and chemokines through their cognate receptors (Altaba et al., 2007; Arai and Suda, 2007; Brittan and Wright, 2002; Bryder et al., 2006; Chambers and Goodell, 2007; Gopinath and Rando, 2008; Imanishi et al., 2000; Mimeault and Batra, 2006, 2008a; Mimeault et al., 2007a; Reya and Clevers, 2005; Rizo et al., 2006; Watts et al., 2005; Wilson and Trumpp, 2006). Diverse soluble factors released by activated tissue-resident stem/progenitor cells and stromal cells including the myofibroblasts, endothelial cells and immune cells such as macrophages attracted at the injured areas may participate to the stringent regulation of adult stem/progenitor cell behavior. Among them, there are the signaling cascades activated by fibroblast growth factor (FGF)–FGFR, epidermal growth factor (EGF)–EGFR, sonic hedgehog (SHH)–PTCH, Wnt/ β -catenin, Notch, bone morphogenic proteins (BMPs), stromal cell-derived factor-1 (SDF-1)/CXCR4 chemokine receptor 4 (CXCR4), ECM components/integrins and/or the members of the Polycomb group of genes (PcGs) such as BMI-1 (Fig. 4) (Altaba et al., 2007; Arai and Suda, 2007; Brittan and Wright, 2002; Bryder et al., 2006; Chambers and Goodell, 2007; Gopinath and Rando, 2008; Imanishi et al., 2000; Mimeault and Batra, 2006, 2008a; Mimeault et al., 2007a; Nicolis, 2007; Reya and Clevers, 2005; Rizo et al., 2006; Watts et al., 2005; Wilson and Trumpp, 2006). The changes in local microenvironment and stimulation of these distinct developmental signaling pathways in the tissue-resident adult stem/progenitor cells may contribute to promote their rate of proliferation and/or differentiation under specific homeostatic and pathological conditions. In addition, most of the tissue-resident adult stem/progenitor cells also possess unique intrinsic properties and resistance mechanisms that confer them with a higher longevity as compared to their differentiated progenies.

2.1. Intrinsic properties associated with the high longevity of tissue-resident adult stem/progenitor cells

The persistence of tissue-resident adult stem/progenitor cells along the lifespan has been associated with several intrinsic properties of these immature cells. Among the molecular mechanisms that may contribute to the extension of the longevity of adult stem/progenitor cells, there are their high telomerase activity, slow division and high resistance to internal and external damages (Arai and Suda, 2007; Aubert and Lansdorp, 2008; Bayne and Liu,

2005; Calado and Young, 2008; Flores et al., 2008; Gonzalez et al., 2008; Hiyama and Hiyama, 2007; Mimeault and Batra, 2008a; Mimeault et al., 2007a; Rizo et al., 2006; Schneider, 2006; Serakinci et al., 2008). More specifically, the telomerase is a ribonucleoprotein complex consisting of a RNA primer sequence designated as TR or TERC, which acts as a template for a reverse transcriptase component TERT (telomerase reverse transcriptase) (Fig. 2). Telomerase catalyzes the addition of hexameric tandem repeats (TTAGGG)_n designated as telomeres at the linear chromosome ends that provide important functions for the chromosomal stability, and which shorten during the cellular replication (Aubert and Lansdorp, 2008; Calado and Young, 2008; Granger et al., 2002; Hiyama and Hiyama, 2007). The highly proliferative adult stem/progenitor cells of self-renewing organs, which require extensive cell division, and the germinal stem cells in ovaries and testis generally display a significant telomerase activity, while most somatic and differentiated cells express low to undetectable levels of TERT and telomerase activity (Aubert and Lansdorp, 2008; Bayne and Liu, 2005; Calado and Young, 2008; Flores et al., 2008; Gonzalez et al., 2008; Hiyama and Hiyama, 2007; Serakinci et al., 2008; Shin et al., 2006). Hence, in the absence of a sufficient telomerase activity, the telomere length generally shortens at each cell division in the most normal somatic cells, and this molecular event may ultimately lead to a critical length of telomere that triggers DNA damage responses and dysfunctions and the loss of specialized and mature cells during aging (Aubert and Lansdorp, 2008; Blasco, 2005; Calado and Young, 2008; Deng and Chang, 2007; Granger et al., 2002; Hiyama and Hiyama, 2007; Serakinci et al., 2008; Shay and Wright, 2007; Shin et al., 2006). Therefore, the active telomerase detected in most human adult stem/progenitor cells may help to maintain their telomere length, chromosomal structure integrity, self-renewal and viability during chronological aging as compared to their differentiated progenies. Consistently, using confocal telomere quantitative fluorescence *in situ* hybridization (telomapping), it has been observed that the longest telomeres were detected in adult stem/progenitor cell compartments within the hair follicle, small intestine, testis, cornea, and brain of the mouse (Flores et al., 2008). Although a low telomerase activity is typically detected in the primitive adult stem/progenitor cells in the quiescent state, an enhanced expression of TERT concomitant with high telomerase activity may occur following their activation in response to different growth factor stimulus. In addition to its function in telomere maintenance, it has also been reported that the telomerase catalytic subunit, TERT may directly promote the entrance of quiescent adult stem/progenitor cells including hematopoietic, skin and gastrointestinal stem/progenitor cells into the cell cycle through non-canonical pathways (Choi et al., 2008; Rajaraman et al., 2007; Sarin et al., 2005). For instance, TERT-induced transcriptional response in tissue-resident stem/progenitor cells, such as activated hair follicle stem/progenitor cells, may be mediated *via* an up-regulation of developmental pathways such as Wnt/ β -catenin and Myc (Choi et al., 2008).

On the other hand, the adult stem/progenitor cells in several tissues exist under a quiescent and less metabolically active state in homeostatic conditions which is strictly regulated by their specialized microenvironment, niche (Arai and Suda, 2007; Dhawan and Rando, 2005; Rizo et al., 2006; Rossi et al., 2007; Tavernarakis, 2008; Wilson and Trumpp, 2006). Thereby, these rare regenerative cells may be subjected less to telomere attrition and accumulation of highly toxic secondary metabolic products including reactive oxygen species (ROS) that can cause severe damages to nuclear and mitochondrial DNA, membranes and/or proteins. In this matter, some recent studies have revealed that the caloric restriction by limiting dietary energy intake may improve the resistance mechanisms of adult stem/progenitor cells and their progenies in response to metabolic and oxidative stresses, and thereby lengthens lifespan (Ertl et al., 2008; Mantel and Broxmeyer, 2008; Trapp and Jung, 2006). Particularly, the caloric restriction may extend the lifespan through an up-regulation of a member of nicotinamide adenine dinucleotide (NAD⁺)-dependent protein

deacetylase family termed sirtuin-1 (silent mating type information regulation 2 homolog 1, SIRT1) in adult stem/progenitor cells, whose enzyme can regulate the mitochondrial biogenesis and response to cellular stress (Mantel and Broxmeyer, 2008). Additionally, the tissue-resident adult stem/progenitor cells are usually characterized by high levels of expression and/or activity of ATP-binding cassette (ABC) multi-drug transporters and anti-apoptotic factors such as Bcl-2, Bcl-xL and survivin that may contribute to their resistance to cytotoxic insults (Krishnamurthy and Schuetz, 2006; Mimeault and Batra, 2008a; Mimeault et al., 2007a,b).

Hence, all of these aforementioned intrinsic properties common to a large variety of tissue-resident adult stem/progenitor cells may provide them with survival advantages and a greater longevity as compared to their differentiated progenies. Nevertheless, an accumulation of genetic abnormalities in these immature and self-renewing cells concomitant with the changes in their local microenvironment, niche with advancing age may lead to the development of particular human disorders. In this matter, we reviewed the molecular mechanisms that are frequently deregulated in adult stem/progenitor cells during chronological aging, and which may contribute to age-related disorders and carcinogenesis.

3. Molecular mechanisms associated with dysfunctions, senescence and the apoptotic death of tissue-resident adult stem/progenitor cells and their progenies during chronological aging

Normal human aging is a complex biological process that results from gradual phenotypic and functional changes of cells, which may be influenced by their tissue microenvironment, that occurs with the passage of time. The age-associated pathophysiological changes typically lead to an imbalance that favors the mechanisms of replicative senescence and programmed cell death (apoptosis) to the detriment of the DNA repair mechanisms and survival signaling pathways (Figs. 1 and 2). Although most tissue-resident adult stem/progenitor cells have a long lifespan, the genetic and/or epigenetic alterations in these immature cells as well as their deregulated interactions with the niche components may result in their acquisition of a dysfunctional behavior or loss during chronological aging (Figs. 1–3) (Anversa et al., 2006; Aubert and Lansdorp, 2008; Calado and Young, 2008; Chambers and Goodell, 2007; Fraga and Esteller, 2007; Gopinath and Rando, 2008; Granger et al., 2002; Hiyama and Hiyama, 2007; Ito et al., 2006; Kenyon and Gerson, 2007; Mimeault and Batra, 2008a; Molofsky et al., 2006; O'Driscoll and Jeggo, 2008; Schlessinger and Van Zant, 2001; Sharpless and DePinho, 2007). Particularly, a cumulative loss of telomeric DNA, defects in DNA repair mechanisms, oxidative stress- or ultraviolet (UV) radiation-induced DNA damages and chromosomal instability during the aging of adult stem/progenitor cells may trigger different cell cycle checkpoint mechanisms initiated through different signaling elements (Figs. 1 and 2) (Deng and Chang, 2007; Fraga and Esteller, 2007; Fuss and Cooper, 2006; Hiyama and Hiyama, 2007; Kenyon and Gerson, 2007; Naka et al., 2008; O'Driscoll and Jeggo, 2008; Rajaraman et al., 2007; Ruzankina et al., 2008; Satoh et al., 2008; Sharpless and DePinho, 2007; Shay and Wright, 2005b; Shay and Wright, 2007; Shin et al., 2006; Vaish, 2007). These mechanisms comprise an up-regulation of tumor suppressor gene products including two alternatively spliced proteins, p16^{INK4A} and p19^{ARF} (also designated as p14^{ARF} in mice) encoded by CDKN2A/ARF locus on human chromosome 9p21, ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) protein kinases, p53 and/or the forkhead box O (FOXOs) family of transcription factors. The activation of p16^{INK4A}/pRb, p53/p21^{CIP1/WAF1} and/or FOXOs/p27^{KIP1}/p57^{KIP2} signaling pathways may result in an inhibition of activities of cyclin-dependent kinase (CDK)/cyclin complexes, repression of the free E2F transcription factor-induced gene products, and thereby lead to a cell growth

inhibition or senescence (Figs. 1 and 2) (Dansen and Burgering, 2008; Hinkal and Donehower, 2008; Ito et al., 2004, 2006; Janzen et al., 2006; Kim and Sharpless, 2006; Krishnamurthy et al., 2004; Krishnamurthy et al., 2006; Maurelli et al., 2006; Molofsky et al., 2006; Naka et al., 2008; Yang et al., 2008a). Alternatively, the activation of the p53 transcription factor may also trigger the apoptotic death program in adult stem/progenitor cells and their progenies. Among the potential p53-induced apoptotic death mechanisms, there are an up-regulation of diverse pro-apoptotic factors such as Bax and Bak proteins, down-regulation of anti-apoptotic proteins like Bcl-2 and Bcl-xL or an enhanced expression of p53 up-regulated modulator of apoptosis (PUMA) and Noxa (Fig. 2) (Ito et al., 2004; Lowe et al., 2004; Ungewitter and Scrable, 2008). Importantly, the inhibition of growth factor-induced PI₃K/Akt (also designated as protein kinase B, PKB) by the PTEN tumor suppressor protein and/or activation of the aforementioned tumor suppressing pathways in response to oncogenic events such as activating mutations in Ras and Myc oncoproteins may also help prevent cancer initiation (Figs. 1 and 2) (Collado et al., 2005; Cosme-Blanco et al., 2007; Courtois-Cox et al., 2006; Dansen and Burgering, 2008; Gray-Schopfer et al., 2006; Kim and Sharpless, 2006; Lowe et al., 2004; McDermott et al., 2006; Michaloglou et al., 2005; Shay and Wright, 2005b; Shay and Wright, 2007; Ungewitter and Scrable, 2008).

Numerous *in vivo* studies carried out in animal models have provided experimental data supporting the dual functions of the telomere shortening and/or activation of tumor suppressor gene products in the loss of endogenous pools of functional adult stem/progenitor cells with the chronological aging *versus* their beneficial effect in preventing cancer initiation (Calado and Young, 2008; Cosme-Blanco et al., 2007; Gonzalez-Suarez et al., 2000; Hinkal and Donehower, 2008; Ito et al., 2004, 2006; Janzen et al., 2006; Krishnamurthy et al., 2006; Molofsky et al., 2006; Pellegrini et al., 2004; Rajaraman et al., 2007; Shay and Wright, 2007). For instance, in support with the critical function of the p16^{INK4A} protein in cell aging, it has been shown that the down-regulation of p16^{INK4A} was associated with an enhanced self-renewal capacity, proliferation and a regenerative potential of multipotent hematopoietic stem cells (HSCs) and neural stem cells (NSCs) and unipotent pancreatic progenitor cells, while p16^{INK4A} overexpression induced the anti-proliferative effects in these regenerative cells (Janzen et al., 2006; Krishnamurthy et al., 2006; Molofsky et al., 2006). Moreover, it has been noticed that telomere uncapping occurred in gastrointestinal progenitors of *TERT*^{3/3} mice, which are deficient in telomerase and have short telomeres, in a S-phase-dependent manner, and this event ultimately triggered a p53-induced apoptotic cell death (Rajaraman et al., 2007). Conversely, an ectopic expression of telomerase catalytic subunit, TERT may lead to an activation of telomerase, maintaining of telomeres, and extend the lifespan of human adult stem/progenitor cells and their progenies (Pellegrini et al., 2004; Shay and Wright, 2007). Importantly, the characterization of *TERC*^{-/-}p53^{R172P} mice, which are unable to trigger the apoptosis, has revealed that an induction of p53/p21^{CIP1/WAF1} signaling cascade and an expression of the senescence-associated β -galactosidase marker occurred in numerous tissues such as skin, lung, kidney, liver, spleen, intestine and testes (Cosme-Blanco et al., 2007; Gonzalez-Suarez et al., 2000). These mice were also resistant to spontaneous tumorigenesis (Cosme-Blanco et al., 2007; Gonzalez-Suarez et al., 2000).

Hence, it appears that a stimulation of tumor suppressor gene product-induced senescence or apoptotic cell death in tissue-resident adult stem/progenitor cells during chronological aging may constitute a barrier to cancer initiation (Figs. 1 and 2). In counterpart, the activation of these same tumor-suppressing cascades in the immature and regenerative cells, may also contribute to their loss and age-associated disease development. Moreover, the telomerase re-activation and inactivation of tumor suppressor gene products in adult stem/progenitor cells and their progenies during chronological aging may lead to a bypass of the senescence or apoptotic cell death programs, and thereby promote cancer initiation.

4. New concepts on the critical implications of malignant transformation of tissue-resident adult stem/progenitor cells into cancer-initiating cells in cancer progression and treatment resistance

Numerous lines of experimental evidence have revealed that the occurrence of aberrant genetic abnormalities in tissue-resident adult stem cells, or their more committed progenies endowed with a self-renewal potential concomitant with the changes in their niches, may result in their malignant transformation into leukemic or tumorigenic CSCs or progenitor cells also designated as cancer- or tumor-initiating cells (Aubert and Lansdorp, 2008; Bapat et al., 2005; Ginestier et al., 2007; Huntly et al., 2004; Kim et al., 2005; Matsui et al., 2008; Mimeault and Batra, 2008a,c; Mimeault et al., 2007b, 2008b; Nicolis, 2007; Nijhof et al., 2007; Rizo et al., 2006; Vaish, 2007; Young et al., 2008). The critical functions of cancer-initiating cells in cancer development is notably supported by the identification and isolation of small subpopulations of immature cells with stem cells-like properties, comprising about 0.1–3% of total cancer cell mass, from malignant patient's tissues and established cancer cell lines (Al-Hajj and Clarke, 2004; Bapat et al., 2005; Eramo et al., 2008; Fang et al., 2005; Fillmore and Kuperwasser, 2008; Galli et al., 2004; Ginestier et al., 2007; Hemmati et al., 2003; Hermann et al., 2007; Hirschmann-Jax et al., 2004; Hope et al., 2004; Huang et al., 2008; Jamieson et al., 2004; Kim et al., 2005; Liu et al., 2006; Maitland et al., 2006; Matsui et al., 2004; Mimeault et al., 2007b; Ponti et al., 2005; Prince et al., 2007; Ricci-Vitiani et al., 2007; Salmaggi et al., 2006; Schatton et al., 2008; She et al., 2008; Shi et al., 2008; Singh et al., 2004; Wei et al., 2007; Wright et al., 2008; Yang et al., 2008b; Yu et al., 2008; Yuan et al., 2004; Zhang et al., 2008b; Zhong et al., 2007). Among the malignant tissues harboring a very small subpopulation of cancer-initiating cells, there are leukemias, lymphomas, sarcomas, brain cancers, melanoma, retinoblastoma and a variety of epithelial cancers including skin, head and neck, thyroid, lung, cervical, renal, hepatic, esophageal, gastrointestinal, colon, bladder, pancreatic, prostatic, mammary and ovarian cancers. Cancer-initiating cells typically expressed different stem cell-like markers such as telomerase, CD133, CD44, stem cell factor (SCF) receptor KIT, aldehyde dehydrogenase (ADHT) and/or ABC multidrug transporters but lacked differentiation marker expression. It has also been shown that the highly leukemic or tumorigenic cancer-initiating cells with stem cell-like properties isolated from malignant patient's tissues or established cancer cell lines were able to give rise to the total bulk mass of differentiated cancer cells *in vitro* and recapitulated the complex morphological characteristics and heterogeneous phenotype of the original patient's cancers in animal models *in vivo* (Al-Hajj and Clarke, 2004; Bapat et al., 2005; Eramo et al., 2008; Fang et al., 2005; Fillmore and Kuperwasser, 2008; Galli et al., 2004; Ginestier et al., 2007; Hemmati et al., 2003; Hermann et al., 2007; Hirschmann-Jax et al., 2004; Hope et al., 2004; Huang et al., 2008; Kim et al., 2005; Maitland et al., 2006; Ponti et al., 2005; Prince et al., 2007; Ricci-Vitiani et al., 2007; Salmaggi et al., 2006; Schatton et al., 2008; She et al., 2008; Shi et al., 2008; Singh et al., 2004; Wei et al., 2007; Wright et al., 2008; Yang et al., 2008b; Yu et al., 2008; Yuan et al., 2004; Zhang et al., 2008b; Zhong et al., 2007).

In addition, the cancer progression is generally accompanied by a progressive accumulation of distinct malignant transforming events in cancer-initiating cells and their progenies concomitant with the changes in their microenvironment that may confer to them a more aggressive phenotype and the survival advantages (Bapat et al., 2005; Brabletz et al., 2005; Chiba et al., 2008; Gray-Schopfer et al., 2007; Hermann et al., 2007; Ma et al., 2008b; Mimeault and Batra, 2007a,b; Mimeault et al., 2007b, 2008a; Nicolis, 2007; Rich, 2007; Sato et al., 2007; Sengupta et al., 2007; Tso et al., 2006; Yang et al., 2008b). In this regard, the long lifespan of adult stem/progenitor cells may notably allow them to accumulate

distinct genetic and/or epigenetic alterations that are necessary for their malignant transformation in cancer-initiating cells and development of certain age-related cancer types.

4.1. Model of age-related carcinogenesis

A growing body of experimental evidence has revealed that an increased incidence of certain cancer types including myeloblastic leukemias, glial brain tumors and epithelial cancers may occur with advancing age in humans (Bell and Van Zant, 2004; DePinho, 2000; Jamieson et al., 2004; Michotte et al., 2004; Mimeault et al., 2007b; Rossi et al., 2007; Sengupta et al., 2007; Ysebaert et al., 2006). More specifically, enhanced inflammation and oxidative stress, telomere shortening or accumulation of particular oncogenic events in adult stem/progenitor cells during chronological aging may lead to genomic instability that may promote their transformation into precancerous stem/progenitor cells (Fig. 1). This early stage of genomic instability leading to pre-malignant lesion formation may be followed by an increase of telomerase activity (immortalization) and the inactivation of tumor suppressor gene products such as p16^{INK4A}, pRb, p53 and/or PTEN in these immature precancerous cells that allow them to bypass the replicative senescence or apoptotic death process (Fig. 1) (Aubert and Lansdorp, 2008; Deng and Chang, 2007; Jarrard et al., 2002; Marusyk and DeGregori, 2007; Maurelli et al., 2006; Pacifico et al., 2008; Schwarze et al., 2002; Serakinci et al., 2008; Shay and Wright, 2005b; Shin et al., 2006; Shiras et al., 2007; Tchernev and Orfanos, 2007; Vaish, 2007; Zhou et al., 2007c). Hence, the subsequent accumulation of numerous oncogenic events such as the activation of distinct growth factor signaling pathways in precancerous stem/progenitor cells may culminate to their malignant transformation into highly leukemic or tumorigenic CSCs or progenitor cells, cancer initiation and progressions during chronological aging (Fig. 1) (Bell and Van Zant, 2004; DePinho, 2000; Marusyk and DeGregori, 2008; Mimeault et al., 2007b; Rizo et al., 2006; Vaish, 2007).

In support with this model of age-related carcinogenesis, several studies have revealed that the human cells in pre-cancerous epithelial lesions such as ductal breast carcinoma *in situ* and prostatic, pancreatic, colorectal and cervical intraepithelial neoplasias (PINs) are usually characterized by low telomerase activity and shortened telomeres (Engelhardt et al., 1997; Hashimoto et al., 2008; Meeker et al., 2004; Shay and Wright, 2007). In contrast, an up-regulation or re-activation of TERT expression and telomerase activity and inactivation of tumor suppressor genes such as p16^{INK4A}, pRb, p53 and/or PTEN frequently occur during the progression of these pre-malignant epithelial lesions to carcinomas (Fig. 1) (Deng and Chang, 2007; Engelhardt et al., 1997; Hashimoto et al., 2008; Li et al., 2000; Melo and Barnes, 2007; Rasoul et al., 2004; Rudolph et al., 2001; Shay and Wright, 2005b, 2007; Shin et al., 2006; Zhou et al., 2007c). In fact, high TERT expression levels and telomerase activity are generally detected in cancer cells in most human cancers including leukemias, melanoma, skin, brain, bladder, renal, gastrointestinal, hepatic, pancreatic, testis, prostatic, breast and ovarian cancers (Deng and Chang, 2007; Engelhardt et al., 1997; Granger et al., 2002; Hashimoto et al., 2008; Li et al., 2000; Melo and Barnes, 2007; Ohyashiki et al., 2000; Rasoul et al., 2004; Rudolph et al., 2001; Shay and Wright, 2005b, 2007; Shin et al., 2006). Thereby, the telomere maintenance in cancer cells including cancer-initiating cells may contribute to their immortality and high proliferative capacity. For instance, it has been reported that a progressive telomere attrition in successive generations of ApcMin *TERC*^{-/-} mice, promoted a chromosomal instability that led to the occurrence of early microscopic precancerous lesions associated with the colorectal cancer initiation (Rudolph et al., 2001). Moreover, a subsequent telomerase re-activation restored the genomic stability and initiated the transition of these early pre-cancerous lesions to well-established macroscopic adenocarcinomas (Rudolph et al., 2001). It has been observed that the inactivation of p16^{INK4A} resulted in an immortalization of holoclones, which are considered to be

representative of epithelial stem/progenitor cell fraction in primary human keratinocytes in culture, while this molecular event does not induce the replicative bypass in transit amplifying keratinocytes (Maurelli et al., 2006). The p16^{INK4A} inactivation-induced senescence bypass in primary human keratinocytes was also accompanied by a re-activation of BMI-1 expression and telomerase activity (Maurelli et al., 2006). Similarly, the inactivation of the p53 gene product may also contribute to the bypass of senescence and the apoptotic death of cancer cells and malignant neoplasm formation as well as the development of chemoresistance mechanisms (Marusyk and DeGregori, 2007; Zhou et al., 2007c).

In addition, the cancer progression to locally invasive and metastatic disease stages frequently implicates an aberrant activation of distinct developmental cascades that provide critical roles in stringent regulation of the self-renewal and/or differentiation of adult stem/progenitor cells such as hedgehog, EGFR, Wnt/ β -catenin, NOTCH, SDF-1/CXCR4 and/or polycomb group BMP-1 in cancer-initiating cells and their progenies (Bapat et al., 2005; Chiba et al., 2008; Glinsky, 2008; Haraguchi et al., 2006; Hermann et al., 2007; Katoh, 2007; Liu et al., 2006; Mimeault and Batra, 2007a,b, 2008c,d; Mimeault et al., 2007b, 2008b; Rizo et al., 2006; Sato et al., 2007; Sengupta et al., 2007; Tso et al., 2006; Yang et al., 2008b). The stimulation of these growth factor signaling pathways may contribute to the sustained growth, survival, invasion and/or metastatic spread of cancer-initiating cells and their progenies to distant sites (Figs. 1 and 4). Especially, the development of aggressive and recurrent cancer subtypes is usually accompanied by acquisition of a migratory phenotype by tumorigenic cancer-initiating cells and their progenies during the epithelial-mesenchymal transition (EMT) program (Bapat et al., 2005; Brabletz et al., 2005; Hermann et al., 2007; Mimeault and Batra, 2007a,b, 2008c,d; Mimeault et al., 2007b, 2008b; Shipitsin et al., 2007; Thiery, 2002; Tso et al., 2006; Turley et al., 2008; Wang et al., 2007b; Zhou and Hung, 2005). The gene products that are often altered in cancer cells during EMT program include the down-regulation of E-cadherin and up-regulated expression of N-cadherin, snail, slug, twist and NF- κ B. These deregulated signaling elements may promote the invasion of tumorigenic and migrating cancer-initiating cells from primary neoplasms, formation of metastases at distant sites, treatment resistance and disease relapse.

4.2. Intrinsic and acquired resistance of cancer-initiating cells to current therapeutic treatments

A growing body of evidence has also indicated that the highly leukemic or tumorigenic cancer-initiating cells isolated from malignant patient's tissues or established cancer cell lines may be more resistance than their differentiated progenies to current anti-hormonal therapies, radiation therapies or chemotherapies (Bao et al., 2006; de Jonge-Peeters et al., 2007; Dean et al., 2005; Fillmore and Kuperwasser, 2008; Friel et al., 2008; Haraguchi et al., 2006; Hermann et al., 2007; Hirschmann-Jax et al., 2004; Huang et al., 2008; Levina et al., 2008; Liu et al., 2006, 2007; Loebinger et al., 2008; Maitland et al., 2006; Matsui et al., 2008; Mimeault et al., 2007a,b, 2008a; Phillips et al., 2006; Schatton et al., 2008; She et al., 2008; Shi et al., 2008; Sung et al., 2008; Todaro et al., 2007; Wang et al., 2007a; Wright et al., 2008; Zhang et al., 2008c; Zhou et al., 2007a,b, 2008a). Particularly, the cancer-initiating cells often exist under a quiescent state and they are characterized by high expression levels and/or activity of diverse ABC multidrug efflux pumps, active DNA repair and intracellular detoxifying enzymes and anti-apoptotic signaling factors such as Bcl-2, survivin, and NF- κ B (Bao et al., 2006; Birnie et al., 2008; Chen et al., 2008; de Jonge-Peeters et al., 2007; Dean et al., 2005; Dylla et al., 2008; Frank et al., 2005; Hirschmann-Jax et al., 2004; Ho et al., 2007; Johannessen et al., 2008; Kang and Kang, 2007; Liu et al., 2006, 2007; Matsui et al., 2008; Mimeault and Batra, 2008d; Mimeault et al., 2007b, 2008a; Rich, 2007; Salmaggi et al., 2006; Shervington and Lu, 2008; Widera et al., 2008; Xu et al., 2007). These distinctive

features of cancer-initiating cells may contribute to their resistance to current therapeutic treatments and disease recurrence. For instance, CD133⁺ brain tumor stem cells (BTSCs) isolated from primary cell lines established from glioblastoma patients, which expressed higher levels of CD90, CD44, CXCR4, Nestin, Msi1 and MELK relative to CD133⁻ cancer cells, were resistant to diverse chemotherapeutic drugs such as temozolomide, carboplatin, etoposide and paclitaxel (Liu et al., 2006). In the same pathway, the CD133⁺ BTSCs from glioblastomas were also enriched after ionizing radiation treatment (Bao et al., 2006). It has been proposed that the high radioresistance of BTSCs may be associated with a preferential activation of the DNA damage checkpoint response concomitant with an increase in DNA repair capacity relative to the CD133⁻ cell fraction (Bao et al., 2006).

Altogether, these observations suggest that telomere attrition and genotoxic stress occurring in adult stem/progenitor cells during aging may promote chromosomal instability, which in turn, may trigger the early stage of pre-cancerous lesions. This early stage of chromosomal instability, as a pre-disposition to the carcinogenesis, could ultimately culminate in an up-regulation of telomerase activity plus an accumulation of other genetic and/or epigenetic alterations in the precancerous stem/progenitor cells during chronological aging. Thereby, these molecular events may contribute to their malignant transformation in cancer-initiating cells and cancer initiation and the progression to invasive and metastatic disease stages with advancing age (Figs. 1 and 3). Hence, the persistence of cancer-initiating cells after treatment with current therapies may then provide critical roles for leukemia recurrence or tumor re-growth and disease relapse.

5. Implications of tissue-resident adult stem/progenitor cell dysfunctions and loss in the development of premature aging disorders and age-related pathologies and cancers

Since the tissue-resident adult stem/progenitor cells provide critical roles in tissue regeneration and homeostasis, the occurrence of age-dependent stem/progenitor cell dysfunctions or their progressive tissue depletion may play a central role in the etiopathogenesis of diverse age-related disorders. Among them, there are premature aging diseases, hematopoietic, immune, cardiovascular, ocular, musculoskeletal, pulmonary, gastrointestinal, urogenital, neurodegenerative and skin disorders and cancers (Brack et al., 2007; Galvan and Jin, 2007; Jie et al., 2008; Ju et al., 2007; Kwon et al., 2008; Mimeault et al., 2007a; Nishimura et al., 2005; Pignolo et al., 2008; Rossi et al., 2005; Satoh et al., 2008; Schipper et al., 2008). In this matter, we reviewed here the consequences of genetic abnormalities, dysfunctions or loss of tissues-resident adult stem/progenitor cells and their progenies on the development of specific premature aging disorders and age-related diseases and cancers.

5.1. Premature aging disorders

Numerous inherited or sporadic genomic abnormalities or epigenetic alterations, which may cause severe dereglements in normal aging mechanisms, such as a greatly accelerated telomere attrition, and impairment of nuclear architecture, cell cycle regulation and/or DNA repair or replication, may result to development of different premature aging disorders (Calado and Young, 2008; Capell and Collins, 2006; Crabbe et al., 2007; Fraga and Esteller, 2007; Hiyama and Hiyama, 2007; Kenyon and Gerson, 2007; O'Driscoll and Jeggo, 2008; Shin et al., 2006; Wong et al., 2003). These devastating premature aging diseases include the progeroid syndromes such as Hutchinson–Gilford progeria syndrome (HGPS), Werner syndrome (WS), Bloom's syndrome (BS), and ataxia telangiectasia (AT) as well as dyskeratosis congenital (DC), Shwachman–Diamond syndrome (SDS), idiopathic pulmonary fibrosis, Fanconi anemia (FA), aplastic anemia (AA), xeroderma pigmentosum

(XP), Cockayne syndrome, and trichothiodystrophy (Armanios et al., 2007; Bergoglio and Magnaldo, 2006; Calado and Young, 2008; Crabbe et al., 2007; Davis and Kipling, 2006; Fuss and Cooper, 2006; Marrone et al., 2007; Meshorer and Gruenbaum, 2008; Plasilova et al., 2004; Risitano et al., 2007; Scaffidi and Misteli, 2008; Vulliamy et al., 2006; Wong et al., 2003; Yamamoto et al., 2008; Young et al., 2008). In general, most of the patients diagnosed with rare premature aging diseases are characterized by an accelerated apparition of certain abnormal phenotypes and pathological symptoms associated with normal chronological aging mechanisms, and therefore they appear much older than their chronological age. These disorders are typically caused by the inherited or sporadic genetic mutations in key gene products regulating the cellular lifespan that may result in detrimental nuclear lamina alterations (lamin A or its processing enzyme, metalloprotease Zmpste24 mutations), an accelerated telomere attrition (WRNp helicase, TERT and/or TERC mutations) and/or DNA repair defects (WRNp helicase, FA or XP gene mutations) (Armanios et al., 2007; Bergoglio and Magnaldo, 2006; Bernardes de Jesus et al., 2008; Calado and Young, 2008; Capell and Collins, 2006; Chigancas et al., 2008; Fraga and Esteller, 2007; Hiyama and Hiyama, 2007; Kenyon and Gerson, 2007; Marrone et al., 2007; O'Driscoll and Jeggo, 2008; Plasilova et al., 2004; Redondo et al., 2008; Scaffidi and Misteli, 2008; Shin et al., 2006; Vulliamy et al., 2006; Wong et al., 2003; Yamamoto et al., 2008). These genetic abnormalities may lead to a genomic instability and functional defects or loss of adult stem/progenitor cells and their progenies, serious illnesses, a decreased longevity and enhanced incidence of certain cancer types in the patients.

Among the premature aging disorders, there are a group of progeroid syndromes. Specifically, HGPS is a rare progeroid disorder affecting children commonly characterized by the mutations in the lamin gene (LMNA) which generates a truncated form of the nuclear lamin A protein termed progerin lacking the second Zmpste24 cleavage site (Capell and Collins, 2006; Fraga and Esteller, 2007; Kudlow et al., 2007; Meshorer and Gruenbaum, 2008; Plasilova et al., 2004; Scaffidi and Misteli, 2008). The production of progerin in human adult stem/progenitor cells and their progenies, and more particularly in mesenchymal stem cells (MSCs), may alter the normal functions of lamin A, which is a mean component of the nuclear lamina, a scaffold-like structure that lines the inner surface of the nuclear membrane (Capell and Collins, 2006; Meshorer and Gruenbaum, 2008; Plasilova et al., 2004; Scaffidi and Misteli, 2008). Hence, the lamina alterations may lead to extensive nuclear defects, including abnormal chromatin structure organization, increased DNA damage and deregulation of diverse signaling cascades such as Wnt and Notch in adult stem/progenitor cells and their progenies, loss of cell functions and progressive deterioration of physiological functions of diverse tissues (Capell and Collins, 2006; Meshorer and Gruenbaum, 2008; Plasilova et al., 2004; Scaffidi and Misteli, 2008). These molecular events may ultimately culminate to a premature cellular senescence and diverse pathological symptoms in HGPS patients such as a growth retardation, impaired or absence of sexual maturation, diffuse fronto-temporo-occipital alopecia, loss of hair and subcutaneous fat, scleroderma-like skin changes and severe atherosclerotic lesions leading to the death at a mean age of about 13.5 years (Capell and Collins, 2006; Meshorer and Gruenbaum, 2008; Plasilova et al., 2004; Sarkar and Shinton, 2001). HGPS also pre-disposes to development of diverse hematological malignancies. In this regard, it has also been noticed that the repression of lamin A/C expression *via* the hypermethylation of its promoter may occur in certain types of leukemias and lymphomas such as diffuse large B-cell lymphomas, and this molecular event could be associated with a poor cancer patient survival (Agrelo et al., 2005). Moreover, the lamin gene mutations may also be detected in certain cases of atypical WS form (Capell and Collins, 2006; Plasilova et al., 2004). In fact, WS also referred as a progeroid syndrome, is a very rare autosomal recessive disorder, which is characterized in the majority of cases by loss-of-function mutations in *WRN* gene encoding a RecQ family member with both DNA helicase and exonuclease activities, WRNp nuclear protein that

leads to DNA repair defects and a maintenance of shorter-than-normal telomere length (Crabbe et al., 2007; Davis and Kipling, 2006; Fraga and Esteller, 2007; Kenyon and Gerson, 2007; Kudlow et al., 2007; Pignolo et al., 2008). This premature aging disorder is usually manifest in young adult and accompanied by an acceleration of growth arrest and acquisition of aging phenotypes causing a short stature, skin atrophy, ulceration and hair graying (Crabbe et al., 2007; Davis and Kipling, 2006; Pignolo et al., 2008). The patients with WS have an increased incidence to develop diverse age-related diseases such as cataracts, type 2 diabetes mellitus, premature osteoporosis, soft-tissue calcification, atherosclerosis and mesenchymal and epithelial cancers (Crabbe et al., 2007; Kenyon and Gerson, 2007; Pignolo et al., 2008). Importantly, the epigenetic inactivation of WRN may also lead to the loss of WRN-associated exonuclease activity and increased chromosomal instability in normal individuals (Agrelo et al., 2006). This molecular event has been associated with a higher pre-disposition to develop the malignant neoplasms of epithelial origin than mesenchymal cancers as compared to a greater prevalence of the occurrence of mesenchymal cancers in WS patients (Agrelo et al., 2006).

In addition, the autosomal common and X-linked forms of DC, which are rare hereditary accelerated aging disorders, may be caused respectively by mutations in *TERC* or *TERT* and *DKC1* encoding a nucleolar protein termed dyskerin which is involved in both ribosome biogenesis and telomere maintenance (Armanios et al., 2007; Dokal and Vulliamy, 2003; Goldman et al., 2008; Marrone et al., 2007; Mason et al., 2005; Pignolo et al., 2008; Vulliamy et al., 2006; Westin et al., 2007). DCs are associated with the defects in telomere maintenance that result in the shortened telomeres in the adult stem/progenitor cells and their progenies in several tissues. The telomere uncapping in DC patients progressively leads to severe failures in BM, skin, gastrointestinal tract and lungs, premature hair loss and graying and nail dystrophy as well as a predisposition to develop the hematopoietic system disorders, premature osteoporosis, oral mucosa, and skin cancers (Mason et al., 2005). In the most of cases, DC culminates to a premature death of patients, which is often associated with the occurrence of AA and pulmonary fibrosis (Armanios et al., 2007). In the same way, the FA syndrome and other forms of congenital and acquired AAs, have also been associated with the mutations in gene products that may cause the defects in cell cycle regulation, DNA repair and replication and/or abnormal telomere maintenance. These molecular events may lead a high genomic instability characterized by an enhanced cellular sensitivity to DNA damages and accelerated aging process in the patients (Aubert and Lansdorp, 2008; Calado and Young, 2008; Cohn and D'Andrea, 2008; Collis et al., 2008; Kalb et al., 2006; Kenyon and Gerson, 2007; Kim et al., 2008; Levitus et al., 2006; Nijnik et al., 2007; Risitano et al., 2007; Sii-Felice et al., 2008; Wang et al., 2008; Yamamoto et al., 2008; Young et al., 2008). These defects may notably occur in certain adult stem/progenitor cells such as BM-resident HSCs, NSCs and/or germinal stem cells. These premature aging diseases may result in the occurrence of skin, thumb and kidney abnormalities, hematological and neurological disorders, BM failure and an increased incidence of leukemia, brain cancer and diverse other solid tumors such as squamous cell carcinoma of the head and neck (HNSCC) and cervix, gastrointestinal and gynecological cancers (Aubert and Lansdorp, 2008; Calado and Young, 2008; Kalb et al., 2006; Kenyon and Gerson, 2007; Mantel and Broxmeyer, 2008; Nijnik et al., 2007; Risitano et al., 2007; Sii-Felice et al., 2008; Young et al., 2008; Zhang et al., 2008a). Other accelerated aging disorders also include XP, Cockayne syndrome and trichothiodystrophy, which implicate the mutations in a group of XP genes encoding proteins that are essential components of DNA nucleotide excision repair (NER) complex (Bergoglio and Magnaldo, 2006; Bernardes de Jesus et al., 2008; Chigancas et al., 2008; Redondo et al., 2008). The patients with these premature aging disorders may be characterized by brittle hair and scaly skin and stunted growth as well as a high incidence to develop the ultraviolet light-induced skin cancers in the case of XP patients.

5.2. Age-related pathologies and cancers

Some studies have also revealed that the chronological aging may be accompanied by an enhanced oxidative stress and ROS production, telomere attrition and genomic instability leading to dysfunctions or loss of tissue-resident adult stem cells. Especially, accumulating lines of evidence have indicated that the functional dereglements may occur in human BM-resident HSCs and the hematopoietic cell lineages with advancing age (Figs. 1–3) (Arai and Suda, 2007; Aubert and Lansdorp, 2008; Calado and Young, 2008; Chambers and Goodell, 2007; Chen, 2005; Jie et al., 2008; Jung et al., 2008; Naka et al., 2008; Rando, 2006; Rossi et al., 2007; Schlessinger and Van Zant, 2001). This pathological aging process of HSCs typically leads to a decline in the number of common lymphoid progenitors and lymphoid cell lineages (T, B- and NK-cells) and immune function concomitant with an accumulation of common myeloid progenitors and myeloid cell lineages (erythrocytes, megakaryocytes, platelets, granulocytes, monocytes and macrophages) (Fig. 3). These cellular events may be accompanied by an enhanced incidence of BM failure, immune system defects including an impaired immune response to infectious diseases, and increased hematological disorders such as anemia and myeloblastic leukemogenesis in aged individuals (Arai and Suda, 2007; Aubert and Lansdorp, 2008; Calado and Young, 2008; Chambers and Goodell, 2007; Jamieson et al., 2004; Melo and Barnes, 2007; Mimeault et al., 2007a; Rizo et al., 2006; Rossi et al., 2007; Young et al., 2008). Additionally, the dysfunctions or loss of BM-resident MSCs with aging may substantially impair the osteogenesis as well as the microenvironment and functions of HSCs in normal hematopoiesis and lead to the development of diseases such as osteoporosis, hematopoietic disorders and fibrosarcomas (Fig. 3) (Hilton et al., 2008; Jiang et al., 2008; Ju et al., 2007; Jung et al., 2008; Laschober et al., 2009; Li et al., 2007; Moerman et al., 2004; Pignolo et al., 2008; Serakinci et al., 2008; Shockley et al., 2007; Stolzing et al., 2008; Zhou et al., 2008b). An increased risk of atherosclerosis and cardiovascular diseases with age has also been associated with an enhanced rate of senescence and apoptotic cell death of heart-resident cardiac stem/progenitor cells and BM-derived circulating endothelial progenitor cells (EPCs) (Fig. 3) (Anversa et al., 2006; Ballard and Edelberg, 2008; Gonzalez et al., 2008; Jie et al., 2008; Pu and Liu, 2008; Satoh et al., 2008; Tsirpanlis, 2008; Yang et al., 2008a). An up-regulation of p16^{INK4A} and p19^{ARF}/p53 pathways in aged cardiac stem/progenitor cells may notably promote their replicative senescence (Anversa et al., 2006).

In addition, a decline in the functions and number of adipose-derived stem cells (ADSCs) and/or pre-adipocytes leading to a reduced adipogenesis and a loss of fully functional mature adipocytes, also appears to occur during the aging process (Fig. 3) (Cartwright et al., 2007; Cederberg and Enerback, 2003; Schipper et al., 2008; Shi et al., 2005). These cellular changes may contribute to the adipose tissue defects, and thereby enhance the incidence of certain age-related metabolic disorders such as fat accumulation outside adipose tissues including in the muscles, liver and bone, atherosclerosis, dyslipidemia and type II diabetes mellitus in old individuals (Cederberg and Enerback, 2003; Schipper et al., 2008; Shi et al., 2005). In the same way, a gradual decline in the functional properties or number of muscle-derived stem cells (MDSCs) and satellite cells and the changes in their niche or external environment such as chronic inflammation during aging may also contribute to trigger distinct muscle disorders and fibrosis (Fig. 3) (Barani et al., 2003; Brack et al., 2007; Carlson and Conboy, 2007; Conboy et al., 2005; Deasy et al., 2005; Dhawan and Rando, 2005; Gopinath and Rando, 2008; Jejurikar et al., 2006; Machida and Booth, 2004; Rando, 2006; Shefer et al., 2006). For instance, muscle aging may lead to sarcopenia, a severe degenerative disorder characterized by a progressive loss of muscle cell mass and alterations in its contractile function (Barani et al., 2003). In this matter, it has also been noticed that an increase of cell-division cycle inhibitors including p53/p21^{CIP1/WAF1}- and FOXO1/p27^{KIP1}-dependent pathways might contribute to the age-associated decrease in satellite cell

proliferation in old rats as compared to young, growing animals (Machida and Booth, 2004). Importantly, dysfunctions of NSCs and/or their progenies as well as the changes in their local microenvironment, including increased oxidative stress and inflammation, leading to an altered neurogenesis, also appear to be prevalent in the mammalian brain with advancing age (Fig. 3) (Bachstetter et al., 2008; Droge and Schipper, 2007; Enwere et al., 2004; Galvan and Jin, 2007; Haughey et al., 2002; Ma et al., 2008a; Maslov et al., 2004; Mattson and Magnus, 2006; Molofsky et al., 2006; Parent, 2007; Pekcec et al., 2008; Schmidt and Duman, 2007; van Praag et al., 2005; Wong et al., 2003; Zhao et al., 2008). In regard with this, it has been shown that mild oxidative stress and inflammation, which are generally enhanced in the aged brain, may repress the proliferation of mouse NSCs and promote their differentiation toward an astroglial lineage by modulating activity of the anti-aging gene product, sirtuin 1 (Prozorovski et al., 2008). Thereby, these molecular events may contribute to impaired sensory or cognitive functions such as learning and memory and certain age related-neurological diseases as well as an enhanced prevalence of brain tumors of glial origin in aged individuals. Particularly, in rodents, a decline in the functions or number of NSCs in the forebrain subventricular zone and defects in olfactory bulb neurogenesis during aging has been associated with a reduced EGFR signaling, enhanced p16^{INK4A} expression and an occurrence of Parkinsonian disease development and/or an impairment of olfactory discrimination (Enwere et al., 2004; Maslov et al., 2004; Molofsky et al., 2006; Wong et al., 2003; Zhao et al., 2008). Moreover, an age-dependent impairment of hippocampal neurogenesis has also been observed in transgenic mouse models of Alzheimer's disease harboring the mutations in the β -amyloid precursor protein, presenilin-1 and tau as compared to their respective non-transgenic mice controls (Rodriguez et al., 2008). Additionally, the dysfunctions or a progressive loss of skin stem/progenitor cells including melanocyte stem/progenitor cells and their progenies, the melanin-producing melanocytes with aging may lead to skin disorders (Fig. 3) (Flores et al., 2008; Kwon et al., 2008; McCullough and Kelly, 2006; Moriyama et al., 2006; Nishimura et al., 2005; Roh and Lyle, 2006; Schouwey and Beermann, 2008; Youn et al., 2004). These disorders include a severe defect in hair pigmentation and an intensive hair graying, the prototypical signs of aging as well as an enhanced incidence of basal cell and squamous cell carcinomas and melanoma after chronic ultraviolet light exposure (Flores et al., 2008; Kwon et al., 2008; McCullough and Kelly, 2006; Moriyama et al., 2006; Nijhof et al., 2007; Nishimura et al., 2005; Pacifico et al., 2008; Pillai et al., 2005; Roh and Lyle, 2006; Schouwey and Beermann, 2008; Youn et al., 2004).

Collectively, these observations suggest a major implication of a deregulation or decreased number of tissue-resident adult stem/progenitor cells in the development of numerous age-related disorders and carcinogenesis. These studies support the therapeutic interest of targeting these immature dysfunctional cells to prevent or treat numerous human disorders and aggressive cancers that may be promoted with the passage of time. In this matter, we describe new therapeutic approaches consisting of cell-replacement, gene therapies and molecular targeting of aged and malignant adult stem/progenitor cells for treating diverse human age-related diseases, degenerative disorders, and aggressive and recurrent cancers in human.

6. New stem cell-based therapies

6.1. New anti-aging therapies

The fascinating discovery in recent years of endogenous sources of multipotent tissue-resident stem/progenitor cells able to give rise to all the differentiated cell lineages from their tissue of origin has led to an explosion of interest in the development of stem cell-based therapies aimed at promote the tissue repair mechanisms, and thereby prevent or counteract the development of numerous human disorders (Ballard and Edelberg, 2007,

2008; Bellantuono and Keith, 2007; Brazel and Rao, 2004; Carlson and Conboy, 2007; Gonzalez et al., 2008; Mantel and Broxmeyer, 2008; Mattson, 2000; McCullough and Kelly, 2006; Mimeault et al., 2007a; Mimeault and Batra, 2006, 2008b; Shay and Wright, 2005a). Since the age-associated decline in adult stem/progenitor cell functions or loss may contribute to a progressive deterioration of tissue and vascular regeneration, and thereby promote the age-related disease development, novel therapeutic approaches with multiple applications in humans, have been designed to reverse this chronological decline. These approaches include the modulation of endogenous adult stem/progenitor cell behavior by therapeutic agents, cell-replacement therapies by using functional adult stem/progenitor cells or their differentiated progenies expanded *ex vivo* and gene therapies (Fig. 3) (Bachstetter et al., 2008; Ballard and Edelberg, 2007, 2008; Bellantuono and Keith, 2007; Brazel and Rao, 2004; Carlson and Conboy, 2007; Gonzalez et al., 2008; Gopinath and Rando, 2008; Mantel and Broxmeyer, 2008; Mattson, 2000; Mimeault and Batra, 2008b). These therapeutic strategies offer great promise to regenerate damaged tissues and serve as cell-specific gene delivery vehicles for treating and even curing diverse human diseases including premature aging diseases, diabetes, atherosclerosis and hematopoietic, cardiovascular, musculoskeletal, gastrointestinal, pulmonary, urogenital, ocular, neurodegenerative and skin disorders. Particularly, the use of constructs to express and deliver a therapeutic gene product of interest in specific adult stem/progenitor cells represents a promising approach to treat the inherited diseases or age-related disorders. Since inherited or acquired altered expression levels and functions of TR, TERT and/or telomere-interacting proteins have been associated with the normal aging and etiopathogenesis of numerous premature aging diseases such as aplastic anemia and dyskeratosis congenita, several strategies have been designed for overcoming the telomere shortening (Calado and Young, 2008; Shay and Wright, 2005a, 2007; Tsakiri et al., 2007; Westin et al., 2007). The use of adenovirus (Ad)-based therapies by overexpressing TR and/or TERT have provided interesting results. It has been reported that an autosomal dominant form of dyskeratosis congenita, which is caused by mutations in the TERC component in cells, may be rescued from defects in telomere by co-expressing TR and TERT that contribute to elongate telomeres (Westin et al., 2007). Therefore, similar telomere-based therapies as well as bioengineered tissues expressing human TERT could also be used to prevent the detrimental effects including replicative senescence resulting from the telomere shortening caused by telomerase or telomere defects in adult stem/progenitor cells and their progenies occurring with chronological aging (Shay and Wright, 2005a).

Although a high telomerase activity is generally not sufficient to induce the malignant transformation of adult stem/progenitor cells, it will be important to prevent the possibility of occurrence of additional genomic alterations in the long-term, which may predispose an individual to cancer development (Maurelli et al., 2006; Shay and Keith, 2008; Shay and Wright, 2007; Siegl-Cachedenier et al., 2007). The use of inducible TR and/or TERT expression constructs could notably allow for regeneration of the telomere length at appropriate period of time (Jiang et al., 1999). Moreover, *in vivo* stimulation of telomerase activity by using the specific pharmacological agents able to induce the TR and/or TERT expression in adult stem/progenitor cells and their progenies may also constitute another alternative method. In the same way, the exercise, calorie restriction and use of dietary natural compounds or pharmacological agents provided with anti-inflammatory and antioxidant properties also may represent potential therapeutic strategies to modulate the expression and/or activity of signaling elements known to be involved in inflammation, oxidative stress, senescence or apoptotic death of adult stem/progenitor cells during aging (Gonzalez et al., 2008; Mantel and Broxmeyer, 2008; Mattson et al., 2007; Naka et al., 2008; Neugebauer et al., 2008; Pillai et al., 2005; Pu and Liu, 2008; Trapp and Jung, 2006; van Praag et al., 2005). For instance, the modulation of mitochondrial metabolism by using activators of sirtuins, which act as NAD⁺-dependent protein deacetylases, may lead to a

reduction of the ROS levels that cause severe cellular damage during aging, and thereby constitute a potential therapeutic strategy for improving cell survival and treating diverse metabolic disorders such as type II diabetes mellitus (Furumoto et al., 1998; Mantel and Broxmeyer, 2008; Neugebauer et al., 2008; Trapp and Jung, 2006). Of particular therapeutic interest, it has also been reported that the number of circulating EPCs may be increased by down-regulating oxidative stress-induced EPC senescence by using vitamin C or through plasma high-density lipoprotein (HDL)-induced nitride oxide (NO) production and telomerase activity *via* the stimulation of the PI₃K/Akt signaling pathway (Furumoto et al., 1998; Pu and Liu, 2008). Hence, these therapeutic strategies could be used to prevent or delay EPC senescence, and thereby promote the angiogenic process and decrease the incidence of atherosclerosis-related ischemic diseases.

On the other hand, based on the recent observations that the down-regulation of signaling cascades initiated through NOTCH-1 and 2 and its ligands in melanocyte stem cells may contribute to depigmentation and hair graying with aging, the use of selective activators of these pathways may also represent a cosmetic treatment of interest for preventing these detrimental effects in aged individuals (Moriyama et al., 2006; Nishimura et al., 2005; Schouwey and Beermann, 2008). It is noteworthy the anti-aging strategies aimed to improve the functions and survival of adult stem/progenitor cells may also promote the development of cancers. Thus, it will be necessary to establish the precise molecular mechanisms of action of anti-aging drugs in a long-term before their potential use in the clinical settings.

6.2. New cancer therapies targeting cancer-initiating cells and their microenvironment

The recent advances in cancer stem/progenitor cell biology have provided important knowledge on the signal transduction pathways that are often deregulated in aged and dysfunctional tissue-resident adult stem cells and their niches during their malignant transformation into leukemic or tumorigenic cancer-initiating cells. Therefore, the molecular targeting of these altered gene products in cancer-initiating cells and their local micro-environment during cancer etiology and progression may represent new strategies to develop more effective chemopreventive treatments and cancer therapies (Fig. 4) (Barker and Clevers, 2006; Bauerschmitz et al., 2008; Calabrese et al., 2007; Chumsri et al., 2007; Folkins et al., 2007; Hermann et al., 2007; Mantel and Broxmeyer, 2008; Mimeault et al., 2007b; Rubin and de Sauvage, 2006; Shih and Wang, 2007; Toole and Slomiany, 2008; Zhang et al., 2008c). In view of the fact that an enhanced expression of TERT appears to contribute to the survival of most human cancer cells including cancer-initiating cells, the down-regulating of telomerase activity may constitute a potential attractive chemopreventive or therapeutic approach to prevent or counteract cancer development. In support with this, numerous anti-telomerase strategies have been designed, including the specific inhibitors of TERT or TR expression and telomerase assembly or activity. Among them, there are antisense oligonucleotides/ribozymes targeting TERT or TR, G-quadruplex interacting agents interfering with telomerase accessibility (RHPS4) as well as oligonucleotide substrates targeting the template region of TR (GRN163) and specific inhibitors of TERT (nucleoside analogs and isothiazolone derivatives) (Deng and Chang, 2007; Harley, 2008; Jackson et al., 2007; Mimeault and Batra, 2008a; Phatak and Burger, 2007; Shay and Keith, 2008; Shay and Wright, 2006). Other promising strategies also implicate using delivery systems consisting of a dominant-negative mutant of human TERT or TR and telomerase promoter-dependent gene therapy expressing the pro-apoptotic gene products such as Bax, constitutive active caspase-6 and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or tumor-specific replication competent Ad vector generating oncolytic virus and telomerase specific-immunotherapy (Fig. 4) (Bauerschmitz et al., 2008; Cortez-Gonzalez and Zanetti, 2007; Harley, 2008; Murofushi et al., 2006; Phatak and Burger, 2007; Shay and Keith, 2008; Zhang et al., 2008c). Of particular interest, the

telomerase-specific oncolytic Ad expressing apoptotic TRAIL resulted in a preferential eradication of the radioresistant stem-like esophageal cancer cell fraction, significant tumor growth suppression and an enhanced survival of mice with no significant toxicity *in vivo* (Zhang et al., 2008c). In the same way, the results from a recent study carried out with oncolytic Ad constructs engineered with the specific promoters such as telomerase (Ad5/3-TERT-d24), cyclooxygenase-2 (COX-2) (Ad5/3-COX-2L-d24) or multidrug resistance (MDR) (Ad5/3-MDR-d24) have also revealed that this strategy was able to completely eradicate CD44⁺CD24^{-/low} breast cancer stem/progenitor cells *in vitro* and *in vivo* without major toxicity (Bauerschmitz et al., 2008). Human TERT-directed immunotherapies have also given promising results in clinical trials for the treatment of the patients with lung, breast, prostate and pancreatic cancers without major secondary effects (Brunsvig et al., 2006; Shay and Wright, 2006; Su et al., 2005; Vonderheide et al., 2004). In fact, since the normal cells, including the adult stem/progenitor cells, generally possess longer telomeres than cancer cells including cancer-initiating cells, the normal stem/progenitor cells could be more resistant to these treatment types, and thereby persist after the treatment ends.

In addition, the molecular targeting of deregulated oncogenic signaling elements that may contribute to a sustained growth, survival, invasion and metastasis and/or treatment resistance of highly leukemic or tumorigenic cancer-initiating cells during cancer progression is also of great therapeutic interest to eradicate these immature cells, and thereby counteract the disease relapse (Altaba et al., 2007; Chumsri et al., 2007; Feldmann et al., 2007; Mimeault et al., 2007b, 2008a; Schmidt, 2008; Shih and Wang, 2007; Todaro et al., 2007; Toole and Slomiany, 2008). Among the potential molecular therapeutic targets in cancer-initiating cells, there are hedgehog, EGFR, Wnt/ β -catenin, NOTCH, SCF/KIT, hyaluronan (HA)/CD44 receptor, interleukin-4 (IL-4)/IL-4R, SDF-1/CXCR4 axes, oncogenic fusion proteins such as BCL-ABL and ABC multidrug transporters as well as diverse oncogenic signaling elements [Ras/MAPK, PI₃K/Akt, NF- κ B, Bcl-2, Bcl-xL, survivin, snail, slug and twist] (Fig. 4). Numerous studies have revealed the benefit of targeting these signaling elements, alone or in combination therapies, to eliminate the total cancer cell mass including highly leukemic or tumorigenic cancer stem/progenitor cells and their progenies, and thereby improve the efficacy of current clinical therapies and prevent disease relapse (Altaba et al., 2007; Chumsri et al., 2007; Feldmann et al., 2007; Mimeault and Batra, 2008c; Mimeault et al., 2007a,b; Misra et al., 2006; Schmidt, 2008; Shih and Wang, 2007; Todaro et al., 2007; Toole and Slomiany, 2008; Yang et al., 2008b). For instance, it has been reported that the interaction of the pericellular matrix glycosaminoglycan, hyaluronan (HA), also called hyaluronic acid or hyaluronate, with its surface cell receptor CD44, whose signaling elements are often overexpressed on cancer cells including cancer-initiating cells may contribute to their survival, invasion, multidrug resistance and/or protection against DNA oxidative damage (Ahrens et al., 2001; Bourguignon et al., 2008; Ghatak et al., 2002; Gilg et al., 2008; Misra et al., 2006; Toole and Slomiany, 2008). Interestingly, it has been shown that the blockade of the HA-CD44 signaling cascade by using specific anti-CD44 antibody, soluble CD44 form, CD44 small interference RNA (siRNA), HA antagonists such as HA oligosaccharides or hyaluronan synthase (HAS) siRNA may inhibit the survival, growth, mobility, invasion and/or metastases of diverse cancer cells *in vitro* and/or *in vivo* and enhance their chemosensitivity (Ahrens et al., 2001; Bourguignon et al., 2008; Ghatak et al., 2002; Gilg et al., 2008; Misra et al., 2006; Yang et al., 2008b). The anti-carcinogenic effects of these agents may be mediated, in part, *via* the inhibition of multidrug resistance mechanisms as well as several receptor tyrosine kinases such as EGFR, ErbB2, insulin growth factor 1 receptor- (IGF1R-), platelet-derived growth factor- (PDGFR-) and/or the c-MET receptor of hepatocyte growth factor (HGF) in cancer cells (Gilg et al., 2008; Misra et al., 2006; Toole and Slomiany, 2008). Moreover, the administration of an anti-CD44 antibody to non-obese diabetic-severe combined immune-deficient mice transplanted with human AML also

reduced the leukemic repopulation (Jin et al., 2006). Of particular therapeutic interest, the inhibition of hedgehog pathway by using smoothened (SMO) inhibitor, cyclopamine also eliminated the cancer-initiating cells and improved the cytotoxic and anti-metastatic effects of current therapeutic drugs such as temozolomide (TMZ) and gemcitabine on glioma and pancreatic cancer cell lines *in vitro* and/or *in vivo* (Clement et al., 2007; Feldmann et al., 2007). Moreover, the combined use of differentiating agents such as retinoic acid and histone deacetylase inhibitors with other cytotoxic drug types may also represent another potential strategy to eliminate cancer-initiating cells (Neugebauer et al., 2008; Sano et al., 2005; Sell, 2004; Yokoyama et al., 2008).

On the other hand, the molecular targeting of a local microenvironment of cancer-initiating cells and their progenies also constitutes a promising approach as adjuvant cancer therapy. Among the potential strategies, there are the use of the specific inhibitors of angiogenic process and anti-inflammatory compounds such as the inhibitors of vascular growth factor (VEGF) and its receptors VEGFR-1 and -2, metalloproteinase (MMPs), urokinase type-plasminogen activator (uPA) and COX-2 (Calabrese et al., 2007; Folkins et al., 2007; Mimeault et al., 2007b). In support with this, recent studies have revealed the potential benefit of targeting the supporting cells including endothelial cells within the niche to eradicate the glioma-initiating cells and their progenies (Calabrese et al., 2007; Folkins et al., 2007). The use of a monoclonal anti-SDF-1 or -CXCR4 antibody or competitive antagonist of CXCR4 such as 14-mer peptide (TN14003) and AMD3100, which inhibit SDF-1/CXCR4-induced signaling cascade, also constitutes a promising adjuvant anticancer therapy to counteract the migration and metastatic spread of cancer-initiating cells to distant sites (Billadeau et al., 2006; Kucia et al., 2005; Liang et al., 2004; Rubin et al., 2003). Additionally, the combination of a stem cell transplant with the current therapeutic regimens, including the use of genetically modified stem cells such as EPCs and MSCs expressing anti-angiogenic factor or cytotoxic product specifically in cancer cells, may also represent an alternative treatment against the advanced, metastatic and recurrent cancers (Mimeault et al., 2007a,b).

7. Conclusions and future directions

Substantial progress has been made toward the establishment of molecular mechanisms that may contribute to dysfunctions, senescence and/or apoptotic death as well as malignant transformation of tissue-resident adult stem/progenitor cells during chronological aging in the last few years. Particularly, it appears that a decline in the functions or number of these immature and regenerative cells and changes in their specialized microenvironment, niche may occur with chronological aging and have detrimental consequences on the tissue regeneration in homeostatic conditions or after severe stress or injuries. Therefore, the development of new stem cell-based therapies and pharmacological agents that are able to block the deregulated signaling cascades involved in the age-related decline of physiological functions, senescence or programmed cell death of adult stem/progenitor cells offers great promise to treat age-related disorders, and thereby lengthen the lifespan of individuals. Future investigations carried out with human adult stem/progenitor cell models are however necessary to corroborate the mechanisms of the aging process established from animal models to humans. Moreover, since the bypassing of senescence and apoptotic death programs and an accumulation of distinct genetic and/or epigenetic alterations in tissue-resident adult stem/progenitor cells during the chronological aging may also promote the development of aggressive and recurrent cancers, it will be important to further characterize these new anti-aging agents before the potential applications in clinical settings. Although there is immense interest in using the anti-cancer agents acting on cancer-initiating cells, further characterization of their effects in a long-term is necessary to estimate their potential

detrimental effects on normal tissue-resident adult stem/progenitor cell behavior including the acceleration of aging process.

Taken together, these recent studies in the field of adult stem/progenitor cell biology and their malignant counterpart, cancer stem/progenitor cells, have provided important information on the genetic and/or epigenetic alterations that may contribute to the pathogenesis of numerous human diseases and aggressive and recurrent cancers during chronological aging. This new information should help to develop new effective anti-aging and cancer treatments in the near future.

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Abbreviations

ABC	ATP-binding cassette
Ad	adenovirus
ATM	ataxia-telangiectasia mutated
BM	bone marrow
CDK	cyclin-dependent kinase
CK	cytokeratine
COX-2	cytochrome oxidase 2
CXCR4	CXC chemokine receptor 4
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EPCs	endothelial progenitor cells
ESCs	epithelial stem cells
FOXOs	forkhead box O transcription factors
Fzd	Frizzled receptor
ICN	intracellular domain of NOTCH
KIT	stem cell factor receptor
KSCs	keratinocyte stem cells
HA	hyaluronan
HSCs	hematopoietic stem cells
MMPs	matrix metalloproteinases
MSCs	mesenchymal stem cells
NF-κB	nuclear factor-kappa B
NK	natural killer
PI₃K	phosphoinositide 3-kinase
PTCH	hedgehog patched receptor

PTEN	phosphatase and tensin homolog deleted on chromosome 10
Rb	retinoblastoma
SDF-1	stromal cell-derived factor-1
SHH	sonic hedgehog ligand
SMO	smoothened
TA	transit-amplifying
TERT	telomerase reverse transcriptase
TK	tyrosine kinase
TR	telomere RNA component
uPA	urokinase-type plasminogen activator
UV	ultraviolet
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
Wnt	Wingless ligand

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Fig. 1.

Proposed model of the potential cellular events associated with the loss of functions, senescence, apoptosis and malignant transformation of tissue-resident adult stem/progenitor cells into cancer-initiating cells during chronological aging. The scheme shows that the telomere shortening at the chromosome ends, oxidative stress and UV radiations may induce an accumulation of DNA damages and chromosome instability in tissue-resident adult stem/progenitor cells during chronological aging. Moreover, a down-regulation of growth factor signaling cascades involved in the self-renewal ability of adult stem/progenitor cells as well as an activation of tumor suppressor gene products such as p16^{INK4A}, p19^{ARF}, ATM and/or p53 may contribute to inducing their dysfunctions, a viable and senescent state (permanent growth arrest) and/or programmed cell death (apoptosis). These cellular events may culminate in a loss of self-renewal and regenerative capacities and/or the number of tissue-resident adult stem/progenitor cells with the passage of time, and thereby lead to age-related disorders. The mutations in oncogenic products such as Ras and Myc in these immature cells may also trigger the activation of tumor suppressor pathways (p16/pRb and/or p53) leading to their senescence or apoptotic cell death, and thereby counteract cancer initiation. Alternatively, a persistent re-activation of the telomerase activity and an accumulation of distinct genetic and/or epigenetic alterations leading to an activation of diverse growth factor cascades and inactivation of tumor-suppressor genes in the precancerous stem/progenitor cells may culminate in their immortalization and malignant transformation and cancer development during chronological aging.

Fig. 2.

Potential molecular events associated with tumor suppressor gene product-induced senescence or apoptotic cell death of tissue-resident stem/progenitor cells during chronological aging. The up-regulated expression of p16^{INK4A} tumor suppressor protein may lead to an inhibition of the activities of cyclin-dependent kinase CDK4/6-cyclin D complex, whose event in turn may impair the phosphorylation of pRb. The maintenance of the pRb tumor suppressor protein under its hypophosphorylated state and its interaction with the E2F transcription factor may prevent the release of E2F and repress the free E2F-induced gene products resulting in blocking G₁/S cell cycle progression, a growth arrest and senescence of aged adult stem/progenitor cells. Additionally, the activation of p53 tumor suppressor protein-dependent pathways induced in response to genotoxic stress and DNA damages, which may be mediated *via* the stimulation of the p19^{ARF} protein or ATM serine/threonine kinase, may also promote a cell cycle arrest, growth inhibition and acquisition of a senescent state by up-regulating CDK inhibitor, p21^{CIP1/WAF1} and down-regulating pRb/E2F axis. Particularly, an enhanced expression of the p19^{ARF} protein may inhibit an ubiquitin ligase (E3), human double minute 2 (HDM2), and thereby prevent the formation of HDM2-p53 complex, p53 ubiquitination, nucleo-cytoplasmic shuttling of HDM2-p53 complex and proteasome-induced p53 degradation. Moreover, an inhibition of the growth factor-induced PI₃K/Akt or PKB signaling pathway by PTEN may also lead to an inhibition of the nuclear export of FOXO transcription factors. Hence, nuclear FOXOs may induce an enhanced expression of p19^{ARF} and cycle cycle inhibitors such as p27^{KIP1} and p57^{KIP2} and growth inhibition. Alternatively, p53 transcription factor may also stimulate the expression of pro-apoptotic factors such as mitochondrial Bax protein, whose molecular event in turn may result in the caspase activation and apoptotic death of aged stem/progenitor cells.

Fig. 3.

Potential age-related disorders associated with dysfunctions and loss of tissue-resident adult stem/progenitor cells during chronological aging and stem cell-based therapies. The anatomic localization of diverse adult stem/progenitor cells and the potential age-related disorders that may be associated with their dysfunctions or loss during chronological aging are indicated. Particularly, a decline of functions or number of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), may result in an enhanced commitment of HSCs into myeloid cell lineages and decreased B and T lymphoid cells in the bloodstream. These events may culminate in a bone marrow (BM) failure, hematological and immune disorders and myeloblastic leukemogenesis in old individual. A loss of BM-resident endothelial progenitor cells (EPCs) with advancing age may also reduce the number of circulating EPCs, and thereby increase the incidence of vascular disorders. Moreover, the dereglements of neural stem/progenitor cells (NSCs) with advancing age may be associated with an altered neurogenesis and brain disorders. Additionally, this scheme also shows that the age-related dysfunctions and/or loss of melanocyte stem cells in the bulge niche in skin hair follicles leading to a decreased number of functional melanocytes in hair matrix at bulb areas may result in a reduced pigmentation and hair graying, the prototype signs of aging. A decline in the number of functional adipose-derive stem cells (ADSCs) and/or pre-adipocytes, may also result in a reduced adipogenesis and fat depot accumulation in other tissues such as muscles, liver and bone and enhanced atherosclerosis and lipidemia in elderly individuals. The potential stem cell-based therapies by autologous or allogeneic transplantation of stem cells or genetically modified stem cells is also indicated.

Fig. 4.

Potential oncogenic events involved in the malignant behavior of tissue-resident stem cells and the molecular targeting and telomere-based cancer therapies. The signaling elements induced *via* the sustained activation of distinct tumorigenic cascades including tyrosine kinase (TK) receptor, sonic hedgehog, NOTCH, Wnt/ β -catenin and hyaluronan (HA)/CD44 are indicated. Moreover, the inhibitory effects induced by diverse pharmacological agents such as the selective inhibitors of TK activity (gefitinib, erlotinib or CL1033), smoothened (SMO) hedgehog signaling element (cyclopamine) and γ -secretase or monoclonal antibody (mAb) on growth, survival, invasion and metastasis of cancer-initiating cells are shown. The telomere-based therapies including the use of the TERT or TR inhibitor of telomerase complex as well as adenovirus (Ad)-produced oncolytic virus in cancer-initiating cells are illustrated. In addition, the potent inhibitory effect mediated by a specific inhibitor of the ABC multidrug transporter, which may result in an intracellular drug accumulation, is also indicated.