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Role of Stem Cell Niche in Body Aging Processes

A. A. Moskalev

Institute of Biology, Komi Research Center, Ural Branch, Russian Academy of Sciences,
ul. Kommunisticheskaya 28, Syktyvkar, Komi, 167982 Russia
e-mail: amoskalev@list.ru

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Abstract—Replacement of damaged differentiated cells by new cells due to the asymmetric division of stem cells can provide unlimited tolerance to degeneration of human tissues, if multipotent cells themselves are "immortal." However, stem cells exist in a particular microenvironment (stem cell niche) and feel their negative impact with age, which attenuates the proliferate capacity of stem cells and leads to incorrect differentiation or, instead, uncontrolled division (promotion of tumor genesis). As a result, stem cell injection to elder persons will be not efficient, because "young" stem cell will engraft to the "old" niche. To sufficient increasing of lifespan, it is necessary to modify stem niche signals by injection of an additional quantity of required growth factors in well-defined proportions.

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Aging can be characterized as a multireason destructive process induced by a complex pf regulatory and stochastic factors and underlain by a genetically determined biological organization of a living system [1]. Thus, to understand the mechanisms of aging processes and develop technologies for its overcoming (existence beyond aging), one can find out the main reasons of aging and their share in the genetic deteminacy and also to estimate the relationship between regulatory and stochastic factors.

The thermal and oxidative stresses cause the genotoxic and proteotoxic stresses associated with a disorder in functioning the cellular genome and proteome (a set of body proteins). Due to the damage of macromolecules and inability of reparation systems (detoxifiction, DNA reparation, proteosomal degraation, autophagy) to cope with all mistakes, an aging cell gradually accumulates oxidized protein aggregates and lysosomal lipofuscine (insoluble pigment of the glycoprotein nature), point mutations and chromosome rearrangements, which distubs physiological process and induces a chronic stress response [2, 3].

There are also other age-related changes in cell nuclei, in particular telomere shortening [4]. True enough, the contribution of this phenomenon in an organism aging still remains questionable. At the same time, the length of telomeres in peripheral human blood lymphocytes is negatively related to enhanced risk of cardiovascular diseases [5], and telomerase overexpression at the background of stimulated oncosuppressor gene activity slows down the aging of mice [6]. It is known that to stop replication and induce cellular aging, the fraction of short telomeres may comprise as little as 10% of their total number [7]. Of great importance are also age-related epigenetic changes in a nucleus: demethylation of DNA [8–10] and histones [11], structural defects in the nuclear envelope lamina [12], and nuclear pore "leakage" [13]. These processes all affect gene expression (normally within 1–5% of the total gene number). Part of genes are pathologically overactivated and other genes are suppressed [14–19].

Apparently, molecular aging is a reason for cellular aging. Two forms of aging of differentiated cells are recognized: replicative and stress-induced. These are programmed cellular reactions on telomere shortening [4, 20] and chronic stress, oxidative in partucular [21]. Age-related oxidative stress is associated in part with antioxidant gene expression as a result of the repression of certain transcription factors over a time course of development [22], as well as with the generation of free radicals by defect mitochondria [23]. Depending on the depth and time of the oxidative stress, a cell can change its strategy: activate antioxidant, antiapoptosis, and reparative protein

expression (hormesis effect), effect temporary or permanent arrest of cellular cycle (cellular aging), or , if reparation is impossible, subject to apoptosis. The role of switchers between these programs is played by such regulatory proteins as the transcription factors p53 and FOXO, kinases p38, JNK, and MST-1, deacetylase SIRT, and adaptor protein p66, each of which is invoved in response to oxidative stress, cellular aging, and regulation of the lifespan of the whole organism [24–32].

Thus, age-related changes are likely not only a response to accidental molecular damages resulting from oxidative or thermal stresses or protein glycation (covanet boning between amino acids and sugars), but also a manifestation of side pleiotropic effects of genes controlling growth, development, and metabolism processes. In response to physicochemical changes in a cell, the mechanisms of stress response are activated, which, in the case of a short-term stress, operate to repare damages, but, in the case of unrepairable defects (formation of shortened telomeres or insoluble lipofuscine), can cause permanents arrest of cell division, chronic inflammation, or apoptosis. Such a dual role is characteristic of the above mentioned stress proteins p38 and p53, as well as their effectors p21 and p16 [33]. It is suggested that the dual role of these proteins is due to the evolutionary advantage during body growth and maturation, when they function to prevent cancer, but later cause accumulation of aging cells or apoptosis [34].

Many human body tussies, even in 100-year-old long-livers, contain only little aging cells [35]. Experiments on different organisms and tissues shows that the fraction of such cells varies from 1 to 15% [36]. However, the presence of even a few aging cells can affect the function of a normal somatic tissue [35]. This is primarily explained by the fact that aging cells actively damage their containing tissue due to vigorous secretion of cytokines which control inflammation processes, damage the intercellular metalloprotein kinase matrix, and promote oncogenesis growth factors [37, 38].

What is the weakest link in the multifactor aging process? How cellular and body aging processes are interrelated? Theoretically, replacement of a damaged differentiated cell by a new one due to asymmetrical division of a stem cell can provide an indefinite resistance to degenerative changes in any human body tissue under the condition that stem cells are in themselves immortal. However, this is not the case. Why with age stem cells tend to less frequently self-renew and differentiate or, vice versa, undergo uncontrollable division and transform into cancer cells?

As known, an individual starts to develop from embryonic stem cells. At early embryogenesis stages, these cells are totipotent, i.e.they have the capacity to form all body cells and tissues (more than 300 types). After a few first divisions the stem cells become plutipotent (i.e. they can form only certain, but not all cell lines) and then multipotent (i.e. ancestors of certain definite cell types). The latter group of stem cells is also inherent in an adult organism. Stem cells are present in small amount is any tissue of an ault organism. They are normally resting or divide symmetrically (self-reproduce), bur, if necessary, start to divide asymmetrically to form progenitor cells which further develop into differentiated cells.

Stem cells are suggested to be potentially immortal. One of the reasons for their enhanced vitality lies in the activity of ABC transport proteins which expel from cells xenobiotics and excess hormones [39]. Moreover, the immortality is provided by segregation of damages on the asymmetric stem cell division [40]. This phenomenon was observed in patiens with spinocerebellar ataxia type 3, in which toxic polyglutamine aggregates are present in differentiated cells in small intestine crypts but are lacking in the stem cells of the same organ (only microaggregates are detectable). It was shown in model experiments on drosophiles, oxidized and denaturated protein aggregates (aggresomes) are linked to one of the two centrosomes which are the main microtubule-organizang centers and regulator of the eukaryotic cell cycle, as a result of which aggresomes on division segregate into only one of the two daughter cells [40]. Mitosis of a stem cell leads to nonrandom distribution of not only damaged proteins, but also the DNA template in itself [41]. One of the consequences of this process is the observation of a decreased rate of spontaneous mutations in stem cells compared with differentiating somatic cells [42], as well as of a relatively constant telomere length. Telomer shortening can also occur under the action of oxidative stress [43], and, therefore, stem cells contain an active telomerase [44] which, if necessary, adds on chromosome ends. Thus stem cells make use of progenitor cells to get rid of the intracelllular “rubbish” and damages acquired via DNA replication, which is a less energy-consuming and more

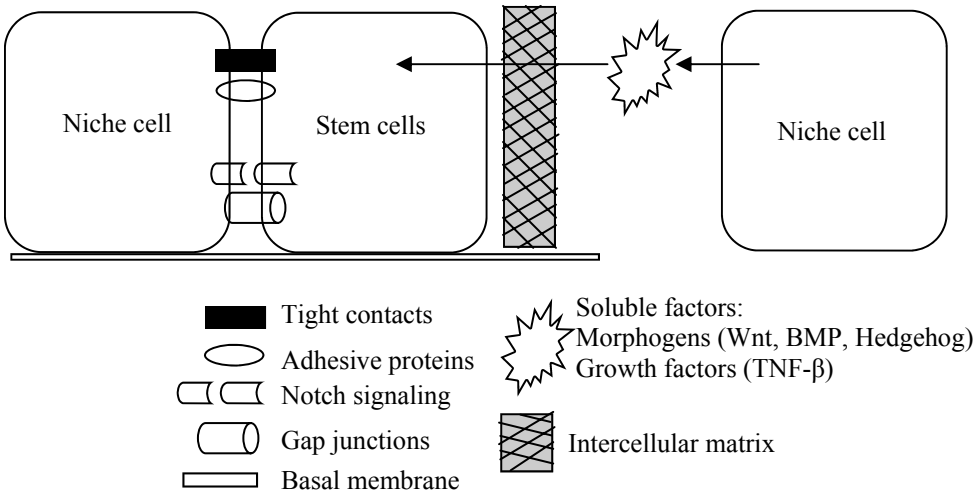

Fig. 1. Model of a Stem Cell of an Adult Human. Adapted from [52].

reliable mechanism of damage control than reparation, but entails faster aging of differentiated cells.

However, the proliferative activity of stem cells declines with age (as a result of gene bmi-1 inhibition and subsequent p16 activation), which favors development of degenerative processes in tissues. For example, hair graying is caused by a decrease of melanocyte stem cells in hair follicles [45]. Evidence for a gradual decline of the replicative ability of blood-making, intestinal, and muscular stem cells was reported [46].

Thus, the fact that stem cells undergo age-related functional changes can be considered established. A question arises: Whether the mechanism triggering this phenomenon is inherent in stem cells or associated with extrinsic factors?

Compared with the powerful systems protecting stem cells from mistakes, internal factors can be of secondary importance. Evidence for the defining role of extrinsic factors was obtained fairly recently, when spermatogonial stem cells from oil mice were successively transplanted to young mice over three years. Therewith, no appreciable functional decline was observed, providing indirect evidence for an incosiderable contribution of intrinsic factors into the aging of this type of stem cells [47]. Furthermore, satellite stem cells of aging mice continued to fulfill their function without changes in the presence of systemic factors obtained from a young mouse via heterochronic parabiosis (methodical approach that involves joining the circulation systems of two animals of different age) [48].

The suggestion that stem cells are controlled by the microenvironment stimulating their self-renewal and protecting them from differentiating effects was first advanced in 1978 and related to hematopoetic stem cells [49]. Experimental evidence for thos suggestion was obtained much later by Taichman and Emerson, who showed that osteoblasts affect the development of stem cells by secreting cytokines [50]. The stable microenvironment of a stem cell was given the name stem niche. Apart from fulfilling the nutritive function, the stem niche serves as a protective and information medium for a stem cell. The stem niche plays an important role in providing rest of stem cells and controls the tendency of a multipotent cell for differentiation [51].

Structurally, the stem niche is a combination of factors which provide the vitality and self-reproduction of stem cells and differentiation of daughter progenitor cells. These factors include the basal membrane, extracellular matrix molecules which tightly fix the stem cell in the niche by means of adhesive molecules means, (integrins, cadherins, and selectins), as well as certain-type neighboring cells producing growth factors and various regulator molecules (Table 1, Fig. 1) [52].

Unlike stem cells, stem niche cells are normal differentiated cells subject to aging. As mentioned above, aging cells affect the spectrum of secreted growth factors, secret inflammatory cytokines and metalloproteinases which destroy the extracellular matrix [38]. Thus, aging and carcinogenesis probably result from the age-related pathology of stem niches (Fig. 2).

Table 1. Examples of mammalian stem niches

Stem cells	Stem niches	References
Neutral	Vascular cells and nerve endings	[56]
Hematopoetic	Osteoblasts, sinusoidal endothelial cells, stromal marrow cells (fibroblasts, monocytes, adipocytes)	[57]
Intestinal crypt	Subepithelial fibroblasts and myoblasts, surrounding crypts	[58]
Hair cells	Hair follicle bottom at the point of attachment of the hair muscle	[45]
Satellite myocells	Muscle fibers, basal lamina, immune cells	[59]

Table 2. Age-related decay of niche signal

Niche signal[a]	Tissue	Animal	Reference
Unpaired (JAK/STAT pathway activator)	Spermary	Drosophila	[60]
GDNF (TGF-β pathway activator)	Spermary	Mouse	[47]
gbb, dpp (TGF-β pathway activators)	Ovaries	Drosophila	[61, 62]
E-Cadregin	Ovaries	Drosophila	[61]

[a] Cytokine proteins secreted by stem niche cells for controlling stem cell function.

If this scheme is valid, then two practical conclusions follow from it: (1) injection of stem cells to an old individual will be of low productivity, since a young stem cell with implant into an old niche; and (2) one should learn to modify niche signals, by introducing into it additional quantities of required growth factors in a required proportion.

Indirect evidence for the presented scheme of aging is provided by the age-related changes in niche signals, revealed in drosophiles in mice (Table 2). Furthermore, essential age-related changes were revealed in the stem niche of satellite cells [53]. In particular, changes in atrophying muscle fiber signals were observed, as well as thickening of the basal lamina, which disturbed functioning of satellite cells and changed the composition of the local medium due to increasing fraction of the conjunctive tissue (fibroblasts and lipid cells). Finctional changes or apoptosis in endothelial or immine cells occurred, entailing chemotaxis disorder. From the side of systemic surrounding, negative regulators of satellite cells gain in importance and positive regulators lose in importance [53]. Finally, the role of stem niche was confirmed by a direct experiment, when the suggested niche signal gene (magu) was expressed in adult drosophiles to observe a longer lifespan in both sexes and an increased female fecundity in late ages [54]. By constrast, over-expression in adult flies of wingless-activated niche cytokine transgenes (Wnt family gene) was found to reduce the lifespan [55].

Thus, to differentiate the contribution of different stem niche signals into body aging and to find out the possibility of their artificially controlling with the aim to prolong life are the tasks of future research.

Summarizing the views on the reasons of aging, we can conclude that the key role here belongs to age-related changes at the four principal life-supporting levels (Fig. 3).

(1) Metabolome which includes all intermediate exchange processes in an organism:protein glycation, free-radical molecular damage, intermolecular cross links, damage of bases and DNA strand breakage,

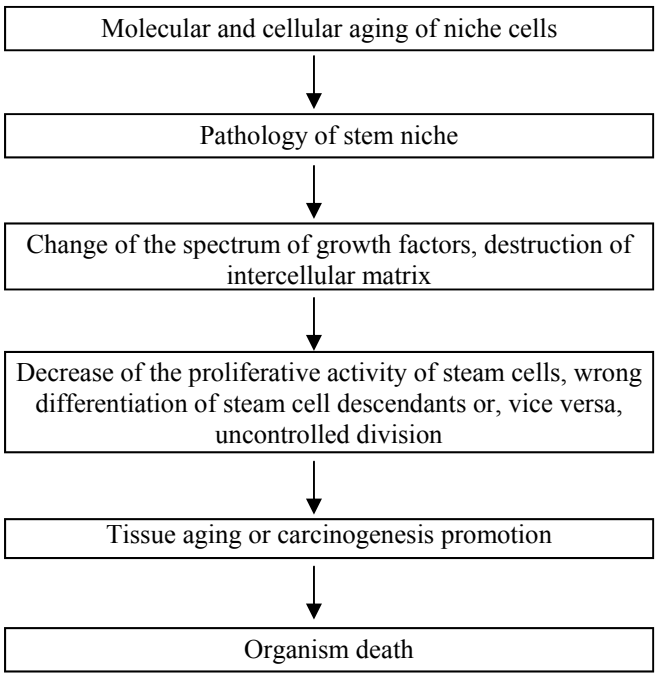

Fig. 2. Model of the involvement of stem niche in organism aging and oncogenesis.

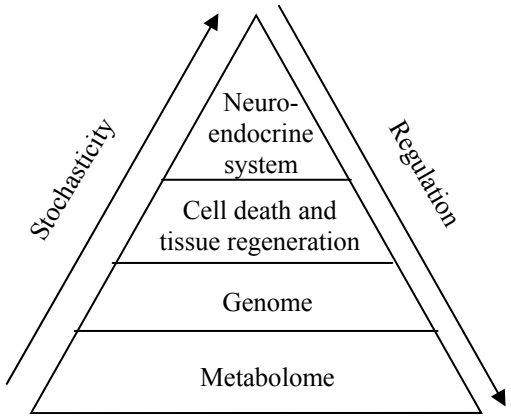

Fig. 3. Aging regulation levels.

protein denaturation, Accumulation of insoluble molecular aggregates, changes in the rigidity and permeability of biological membranes, and suppression of enzymatic processes and cellular energetics.

(2) Genome: impairing of gene expression due to mutational and epigenetic disorders, compensatory activation of stress-response genes, exhausting the energy resourses of cells and inducing inflammation processes in tissues.

(3) Cell death and tissue regeneration: chronic loss of functional cells by the apoptosis or cellular aging mechanisms, impairing of the capacity of stem cells for self-renewal and differentiation as a result of aging and death of niche cells.

(4) Neuroendocrine system: change in the homeostatic levels of hormones and neuromediators, decreasing their secretion (sex steroids, progesteron, dehyroepiandrosteron, somatotropin, IGF-1, melatonin, tireod hormones, dopamine, acetyl choline, norepinephrine, serotonine, GABA) or enhancing hormine secretion (vasopressine, glucocorticoids, TGF-β).

In this hierarchic system, the main source of stochastic disorders for the other levels is metabolism, and the main source of disorders in the regulation of physiological fucntions is the neuroendocrine system. Therewith, each level has a stochastic and regulatory impact on any other level, but the weakest link, in our opinion, is the aging of stem niche cells, impairing the regulation of multipotent cells and decreasing the regenerative potential of tissues.

Thus, aging is a systemic disease. According to the prominent gerontologist S. Rattan, it is impossible to rejuvenate, not changing the whole system.

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