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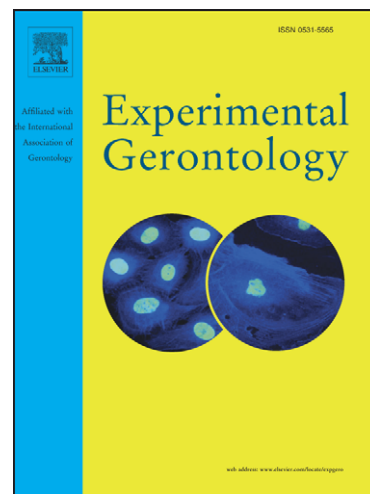
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# Rejuvenation in distinct cell populations – what does it mean?

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**Abstract**

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3 Rejuvenation represents a well organized and tightly regulated cellular process *in vitro*  
4 and *in vivo*, whereby senescent and/or certain differentiated cells revert specific  
5 properties acquired during previous steps of maturation to restore again a younger  
6 phenotype. Effects of the microenvironment and cellular mechanisms including  
7 asymmetric mitosis or retrodifferentiation can contribute to rejuvenation during a dynamic  
8 cellular development in contrast to terminally differentiated cells like unicellular  
9 organisms, which appear unable to retrodifferentiate and to rejuvenate. The process of  
10 rejuvenation is observed in distinct cell populations and includes a coordinated multistep  
11 network of transduction cascades with extracellular signalling and cell-to-cell  
12 communication to relay intracellular pathways. This provides a certain tissue homeostasis  
13 by a regenerative potential and renewal upon tissue-specific repair requirements in  
14 addition to residual stem cells, which can vary among different organs and species to  
15 extend their life span. However, dysfunctions within a rejuvenation program may also  
16 include the risk of neoplastic growth during such a retrograde development. In contrast to  
17 rejuvenation in certain cell types, a life span extension – also termed longevity – does not  
18 represent a retrograde development but an overall prolonged function of tissues, organs  
19 and/or whole organisms. Thus, rejuvenation of a distinct cell population could contribute  
20 to longevity of the corresponding organism but may not necessarily be required since  
21 longevity could also be achieved mechanistically by inhibition of the mTOR-mediated  
22 signalling pathway or by sufficient supply of anti-oxidative defence compounds,  
23 physiologically by nutrient restrictions, genetically by the induction of longevity genes or  
24 environmentally by the inhibition of aging.  
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### Cell models of rejuvenation *in vivo* and *in vitro*

1 Rejuvenation *in vitro* and *in vivo* has been observed and characterized in a variety of  
2 different cell types and can be triggered by different mechanisms, including asymmetric  
3 cell division or retrodifferentiation as a retrograde development to a more juvenile  
4 phenotype (Fig. 1). Thus, rejuvenation has been described in a regained pluripotency of  
5 unmobilised adult human peripheral blood mononuclear cells in response to a CR3/43  
6 monoclonal antibody directed against the human monomorphic region of the beta chain of  
7 HLA-DP, DQ and DR. These mononuclear cells rejuvenated into pluripotent progenitors  
8 cells and displayed again certain properties associated with stem cells [Abuljadayel,  
9 2003]. Moreover, *in vitro* rejuvenation has been detected in an accompanying  
10 retrodifferentiation system with human myeloid cell lines, involving signaling of poly(ADP-  
11 ribose)polymerase-1 (PARP-1) [Selle et al., 2007]. Further rejuvenation studies using an  
12 *in vivo* approach in a drosophila model demonstrated a reversion of spermatogonia back  
13 to the stem cell phenotype. This effect was dependent on a functional Jak-STAT  
14 signalling pathway [Brawley and Matunis, 2004]. A retrograde development from  
15 unipotent testicular cells to form pluripotent stem cells with a germline-derived phenotype  
16 has been recently observed without further stimulation *in vitro* and *in vivo* [Ko et al.,  
17 2009]. This process was determined by clonal analysis and suggested effects of the  
18 cellular microenvironment and intercellular communication for establishing a  
19 retrodifferentiation/rejuvenation program which restores a stem cell phenotype (Fig. 1). In  
20 this context, Conboy et al. designed a system of parabiotic pairings, whereby young and  
21 old animals share a circulatory environment to induce effects of rejuvenation *in vivo*. In  
22 this heterochronic parabiosis model, satellite cells from old mice were exposed to serum  
23 factors present in young mice which rejuvenated by restoring Notch signalling as well as  
24 the proliferative and regenerative capacity in aged satellite tissues [Conboy et al., 2005].  
25 Together, distinct molecular pathways and predominantly the cellular microenvironment  
26 coupled with intercellular communication appear to be associated with phenotypes of  
27 rejuvenation in a variety of different cell types (Fig. 1).  
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### Damage-induced aging, repair-mediated longevity, rejuvenation and tumor promotion

51 Aging, longevity as a prolonged life span, and a possible rejuvenation program could be  
52 affected very early in life with long-lasting consequences. For example, aging and  
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1 rejuvenation can reflect a response to environmental changes such as accumulation of  
2 somatic damage accompanied by an insufficient cellular repair [Kirkwood, 2008] and  
3 interference with a proper repair or damage elimination may uncouple this sensitive  
4 network. Thus, certain environmental factors and damaging compounds can induce  
5 epigenetic effects during early developments to influence a variety of stable gene  
6 expression patterns, which sustain even following disappearance of the initial signal and  
7 may thus persistently determine a distinct phenotype [Vaiserman, 2009]. Multiple damage  
8 products, including chemical damage to macromolecules (e.g. proteins, lipids,  
9 carbohydrates) are formed throughout the cellular metabolism and need to be sufficiently  
10 neutralized to avoid persistent dysfunctions. Moreover, reactive oxygen species (ROS)  
11 generated either from exogenous sources such as radiation (UV, X-ray) and  
12 pharmacological compounds or ROS exposure from endogenous metabolites (e.g. by  
13 mitochondria), can promote oxidative stress in proteins and lipids and eventually cause DNA  
14 damage, whereby insufficient cellular repair efforts may contribute to premature aging and  
15 apoptosis [von Zglinicki et al., 2001; Bertram and Hass, 2008].

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29 To cope with oxidative stress and accelerated aging, a variety of anti-oxidative defence  
30 systems are available including superoxide dismutase, glutathione peroxidase and  
31 catalase together with the cofactors glutaredoxin and thioredoxin [Jones, 2006]. To  
32 minimize the generation of oxidative stress products, previous work has shown in a  
33 variety of mammalian species that caloric restriction significantly contributes to an overall  
34 extension in life span [Barzilai and Bartke, 2009]. Although these effects are not  
35 necessarily associated with rejuvenation, longevity is also observed in certain animals  
36 even after starvation [Egger, 2008] and may imply the risk to develop neoplastic  
37 properties. Conversely, a certain threshold of oxidative stress or nutrient restriction can  
38 also trigger rejuvenation in certain cell types, whereby the activation of poly(ADP-  
39 ribose)polymerase (PARP) enzymes confers signals during the stress response via  
40 associated factors such as the proteasome complex [Harnacke et al., 2006; Selle et al.  
41 2007]. A molecular involvement of PARP in aging, longevity and tumor development is  
42 widely acknowledged [Bürkle, 2006; Beneke and Bürkle, 2007]. Thus, insufficient  
43 activities by the cellular repair machinery due to a significant threshold of damaged DNA  
44 and damaged protein components may simultaneously dysfunction telomeres and result in  
45 chromosomal instability to favorize neoplastic growth [Hande, 2004].

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However, effects of ROS may vary among certain cell types and particularly among tissues and whole organisms with respect to the induction of aging and rejuvenation. For example, the long-lived naked mole-rat can cope with high levels of oxidative damage without the promotion of aging [Andziak et al., 2006]. In contrast, increased oxidative stress in mice with a deficiency of the anti-oxidative enzyme manganese superoxide dismutase express higher incidents of cancer instead of premature aging [Van Remmen et al., 2003]. Thus, a sufficient multi-component response to ROS including a variety of different signalling pathways may limit the induction of aging in certain species or tissues to favor longevity (Fig. 1). This is also addressed by the hypothesis, that aging is variable and may significantly alter even within individuals of the same stem [Campisi and Vijg, 2009]. Further observations in mutant worms of *Caenorhabditis elegans* revealed an extended life span following resistance to thermal injury and to oxidative stress and to heavy metal poisoning, which evoked the theory of a so-called “multiplex stress resistance” and postulates an association between stress resistance and longevity [Johnson et al., 1996; Miller, 2009]. Extension of the life span may also be achieved by exogenous compounds which stimulate growth activities in certain cells and tissues irrespective of a persisting aged phenotype. Thus, *in vivo* studies in 65 healthy older adults (men and women) at 60 to 81 years of age describe clinical evidence of rejuvenation after daily oral administration of a mimetic of the growth-hormone-releasing acylated peptide ghrelin for more than 1 year [Nass et al., 2008]. Despite the relatively low sample number and the short duration of this study, multi-systemic alterations were observed similar to a younger phenotype which contributes to the discussion of a life span extension upon endocrine interventions (Fig. 1).

### **Aging-related dysfunctional protein aggregates and rejuvenation by asymmetric cell division**

A variety of aging-related diseases including neurodegenerative disorders (e.g. Parkinson's disease, Alzheimer's disease, Huntington's disease) are associated with the formation of protein aggregates [Dobson, 2001]. These protein components can be generated by transcription and translation errors, by misfolding of functional tertiary structures or by oxidative stress-induced formation of protein carbonyls. Moreover, accumulation of advanced glycation end products (AGEs) can relay signals via the appropriate receptor (RAGE) for the continuous production of pro-inflammatory cytokines

1 and are also implicated in multiple detrimental human illnesses (including diabetes,  
2 atherosclerosis, arthritis) and aging-associated diseases [Lin et al., 2009]. When these  
3 compounds are insufficiently metabolised by appropriate control mechanisms such as the  
4 proteasome system, they can form insoluble inclusion bodies that accumulate within the  
5 cells [Kopito, 2000]. Defects in the immune response, which develop with advanced age,  
6 also contribute to a less effective clearance from aberrant functioning cells with damaging  
7 compounds, although the loss of immune function with aging and the concomitant age-  
8 associated increase in circulating pro-inflammatory cytokines is poorly understood [Swain  
9 and Nikolich-Zugich, 2009].

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18 Further examples of dysfunctional aggresome appearance *in vivo* are represented by the  
19 polyglutamin aggregation in epithelial crypts of ataxia type 3 patients or by lens cataracts.  
20 The aggresomes can interfere with the normal metabolism by trapping and depleting  
21 freely diffused key proteins to paralyse distinct signalling pathways and to damage DNA.  
22 Thus, an accumulation of protein aggregates may be associated with increasing  
23 impairment of cellular functions and the promotion of aging [Lindner et al., 2008]. In  
24 addition, a significant and persistent increase of damaging compounds in aged cells  
25 contributes to the deterioration of cellular homeostasis and DNA damage-induced cell cycle  
26 arrest, eventually resulting in cell death, which are hallmarks of STASIS (stress or aberrant  
27 signaling-inducing senescence). Whereas this process appears to be irreversible, certain  
28 organisms can cope with these insoluble inclusion bodies by an asymmetric segregation  
29 during cell division suggesting rejuvenation by the production of an aggresome-free  
30 daughter cell as compared to the corresponding parental cell (Fig. 1). Indeed, studies in  
31 *Escherichia coli* have demonstrated an asymmetric distribution of damaging protein  
32 aggregates during mitosis resulting in a loss of reproductive activity in those cells  
33 eventually carrying the insoluble protein aggregates at the older poles. In contrast,  
34 daughter cells without damaging inclusion bodies continue proliferation and thus appear  
35 rejuvenated as compared to the corresponding parental cells [Lindner et al., 2008].  
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#### 54 **Differentiation-associated rejuvenation by retrodifferentiation**

55 Retrodifferentiation characterizes a biological phenomenon of completely reversible  
56 differentiation events, whereby all morphological and functional properties of  
57 retrodifferentiated and previously more undifferentiated cells are indistinguishable.  
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Moreover, retrodifferentiation as a retrograde development includes a process of rejuvenation to a previous younger state of development [Hass, 2009]. Consequently, retrodifferentiation-associated rejuvenation could provide enormous potential to maintain tissue homeostasis by cell renewal and repair mechanisms (Fig. 1), however, regulatory dysfunctions within these reversible developments may also involve the risk of tumor promotion.

A variety of cellular phenomena *in vitro* have been characterised as retrodifferentiation, including the reversion of nerve growth factor-induced PC12 cells, a regained pluripotency in unmobilised adult human peripheral blood mononuclear cells in response to a certain monoclonal antibody or the retrograde development and reversion of phorbol ester-differentiated human myeloid leukemia cells [Hass, 2009]. The molecular events for the induction of a retrodifferentiation and rejuvenation program in these cell systems, however, develop their own sequence and kinetic upon a distinct trigger. Consequently, retrodifferentiation and rejuvenation does not necessarily follow the previous maturation process in opposite direction since the eventual reversion to the original cellular phenotype involves different signalling cascades [Hass, 2009].

The simultaneous association of retrodifferentiation with the reversibility of an aged phenotype and thus rejuvenation, has been observed *in vitro* in a differentiated monoblastoid human cell line model [Selle et al., 2007]. Retrodifferentiation of differentiated and aged monocyte-like cells by involving signaling cascades of poly(ADP-ribose)polymerase-1 (PARP-1) lost markers such as expression of senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -gal) and reverted to more undifferentiated and juvenile myeloid precursor phenotype with a restored proliferative capacity [Selle et al., 2007].

Since retrodifferentiation-associated rejuvenation requires a highly organized and timely coordinated network of a retrograde development in combination with an escape from aging, dysfunctional control mechanisms may result in aberrant cell cycle progression and thus, tumor growth. For example, proliferation of retrodifferentiated cells supported by factors such as Bmi-1 which can also promote self-renewal of diverse adult stem cells or growth of cancer cells, needs to be balanced with tumor suppressor and growth inhibitory activities such as the cell cycle inhibitor p16<sup>ink4a</sup> to avoid neoplastic growth [Pardal et al., 2005]. Consequently, certain imbalances in the cell and tissue homeostasis and across

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the dynamic equilibrium between retrodifferentiation steps and the velocity of cell cycle progression may favour either rejuvenation, contribute to tumorigenesis or result in cell death (e.g. apoptosis) (Fig. 1).

### Rejuvenation by regeneration

One property of aging is supposed to be a decline in regenerative capacity and conversely, increasing regenerative potential should represent a characteristic of rejuvenation. Whereas the regeneration of tissues and organs is performed by proliferating and differentiating precursor cells and/or appropriate stem cells, it seems plausible to postulate that stem cell aging may trigger organismal aging. However, several elegant studies successfully question such a correlation, since the self-renewal of stem cells with sustained proliferative capacity (for example in the hematopoietic system, the intestinal epithelium or skin) exceeds the 'normal' life time and it thus appears unlikely, that the 'normal' life span would be determined by a limitation of available stem cell populations or their functionality [Rubin, 2002; Conboy et al., 2005; Rando, 2006]. This is also supported by the fact, that different tissues exhibit different regenerative potential including those with the ability for high tissue turnover combined with high regenerative potential (e.g. blood, gut, skin), low tissue turnover combined with high regenerative potential (e.g. skeletal muscle, liver) and low tissue turnover combined with low regenerative potential (e.g. heart, brain).

Therefore, the reduced regenerative potential with increasing age may also be associated with secondary effects. Indeed, regeneration e.g. of adult skeletal muscle by myoblasts and/or appropriate resident stem cells is controlled by the Notch signaling pathway, which is altered during aging [Brack et al., 2007]. Moreover, experiments of heterochronic parabiotic pairings demonstrated, that the exposure of resident stem cells from aged tissue to serum from young animals restores the ability of the stem cells again to participate in tissue maintenance, repair and regeneration [Conboy et al., 2005; Conboy and Rando, 2005]. Thus, stem cells would function permanently to restore tissues and organs after providing an appropriate microenvironment, however, in an aged microenvironment, their function of self-renewal is limited or abolished. Despite correlative data with no clear evidence available to date, these findings may suggest that declining options for cell renewal and a reduced regenerative potential of certain tissues in

1 combination with environmental factors influence the life span of a corresponding  
2 organism, although these effects may be limited in those organisms carrying  
3 predominantly postmitotic tissues. Conversely, rejuvenation of distinct cells which  
4 enhance the regenerative potential and maintenance of tissue homeostasis contribute to  
5 a life span extension.  
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10 Previous work has demonstrated that certain fishes and amphibians, e.g. salamanders  
11 can continuously regenerate most organs and body parts, such as limbs, eyes, jaw, brain  
12 (and spinal cord), heart by reprogramming differentiated cells to retrodifferentiate and  
13 rejuvenate. Thus, lost or damaged tissues are reconstituted in a subsequent proliferation  
14 and differentiation program [Tsonis, 2008]. Similar types of rejuvenation to preserve the  
15 regenerative potential are also observed in some annelids, whereby repeated  
16 regeneration in animals following consecutive amputations contributed to a substantially  
17 increased life span as compared to untreated animals [Egger, 2008]. However, the  
18 mechanisms which regulate cellular rejuvenation and simultaneously limit this process to  
19 restore and maintain the previous tissue size and homeostasis remain obscure.  
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30 Indeed, although rejuvenation of somatic cells may preserve a certain pluripotency to  
31 balance biological requirements and developmental flexibility for the maintenance of a  
32 regenerative potential, these processes are tightly controlled and limited by the  
33 appropriate size of the reconstituted organ or tissue. However, why can certain species  
34 reconstitute distinct organs or tissues while others cannot? A seemingly plausible  
35 explanation implies, that the induction of regenerative capacities in growth-arrested  
36 differentiated tissues would require a retrodifferentiation-associated rejuvenation to obtain  
37 precursor cells with proliferative capacity, whereby for example, a large accumulation of  
38 undifferentiated proliferating blastema involves the risk to develop uncontrolled growth  
39 and thus, a subsequent tumorigenic development. Another possible explanation regards  
40 the rejuvenation processes to provide a required prerequisite for enabling a distinct tissue  
41 homeostasis to ensure the survival in certain species, whereas a similar regenerative  
42 effort in other species may not even be economically beneficial for nature without  
43 changing important parts of the physiology. Together, this would suggest a strictly limited  
44 rejuvenation ability to fulfill certain requirements (Fig. 1). However, the regenerative ability  
45 e.g. of cartilage or ear hole scars at significantly elevated levels in middle-aged mice as  
46 compared to young mice [Reines et al., 2009] questions this hypothesis, since the  
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1 regeneration of ear hole scars does not represent an absolute requirement for the survival  
2 of the mice. More interestingly, the reconstitution of ear hole scars by local  
3 retrodifferentiation-associated rejuvenation, followed by subsequent proliferation and  
4 differentiation processes increases with age, suggesting that aging can be paralleled by  
5 enhanced regenerative ability to a certain extend [Reines et al., 2009]. At the cellular  
6 level, these findings may appear counterintuitive and contradictory to the theory of an  
7 age-dependent reduction in regenerative potential. Regarding the entire organism and  
8 thus, the sum of the simultaneous biological interplay of all cells, tissues and organs,  
9 however, this apparent controversy could make sense, whereby the potential of a  
10 regeneration program in certain cell types may not fully be established at the time when  
11 many other cell populations already age. Consequently, the whole functionality of these  
12 mice would be developed to maximal extension in middle-age whereby differentiated  
13 somatic cells are optimized for their appropriate requirements including regenerative  
14 pathways. This hypothesis suggests a progressively-increasing rejuvenation ability of  
15 distinct cells or cell types in parallel to aging to provide a maximal regenerative potential  
16 and tissue homeostasis during middle age.  
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### 30 **Concluding remarks**

31 Rejuvenation is determined by distinct molecular effects in certain cell populations  
32 causing a retrograde development to restore a more juvenile phenotype. This needs to be  
33 distinguished from longevity, which represents an extension of the life span at the level of  
34 tissues or whole organisms displaying the sum of various kinds of development from  
35 different cell populations (rejuvenation versus aging, proliferation versus apoptosis).  
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43 Although a variety of different and cell type-specific effects may trigger a rejuvenation  
44 program, a certain homeostatic balance, distinct stem cell interaction with their neighbors  
45 (the niche) and a coordinated interplay of transcription factors may be required to relay  
46 sufficient signals for a stable induction of this machinery. Moreover, while specific types of  
47 damage may promote aging not in general, but in distinct tissues or cells, these effects  
48 indicate furthermore, that only a limited cell number or just a single individual cell within a  
49 certain population may retain the capability to rejuvenate for re-establishing pluripotent  
50 precursors. However, since most studies in support of this hypothesis represent only  
51 correlative data, more efforts are required which causally address a relationship between  
52 damage and aging and vice versa, between rejuvenation and repair. This would also  
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1 address the suggestion of an increasing regenerative potential during middle age followed  
2 by a reduced regenerative ability in the older organism.  
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5 Together, rejuvenation can be linked to different phenotypes: In the case of cellular  
6 regeneration or an accompanying retrodifferentiation process, rejuvenation is linked to the  
7 restoration of previous younger cell functions, whereas in the case of ROS-induced cell  
8 damage and asymmetric aggresom distribution during mitosis, rejuvenation is associated  
9 with a loss of dysfunction displayed during aging (Fig. 1). Finally, as concentration  
10 gradients and threshold effects in the microenvironment combined with a corresponding  
11 metabolic balance in certain individual cells can contribute to rejuvenation, this  
12 interference with the normal biological clock and the apparently infinite life span of stem  
13 cells and cells with a capability to rejuvenate may eventually be terminated by multi-  
14 metabolic breakdown of the systemic interdependent and intrinsic entity of all cells and  
15 tissues combined in the corresponding organism during the mystery of death.  
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## Figure Legend

### Figure 1:

Undifferentiated and juvenile stem or precursor cells are induced to develop along a pathway to form a certain differentiated cell phenotype (e.g. differentiated cell A). This differentiated cell population contributes to specific tissue functions and provides structural maintenance within the appropriate tissues and organs. During the steps of differentiation, the cells can also acquire properties of aging including the accumulation of damage products, a reduction in telomerase activity or the induction of senescence-associated  $\beta$ -galactosidase activity. Upon distinct microenvironmental conditions such as exogenous growth factor/chemokine stimulation and contact communication between neighboring cells at a certain cell density, however, some cells could be triggered to rejuvenate to a younger phenotype by losing properties of aging. Further contributors to the microenvironmental conditions include pH, osmolarity, temperature, air pressure, O<sub>2</sub> concentration, biomechanical or electromagnetic influence, etc. Examples of rejuvenation upon microenvironmental conditions are represented by the system of heterochronic parabiosis which underscores the importance of the cellular microenvironment to decide on cell fate [Conboy and Rando, 2005; Brack et al., 2007]. Recent studies substantiate this hypothesis demonstrating a rejuvenation of a unipotent population back to pluripotent stem cells depending on the maintenance of a certain cell density over time [Ko et al., 2009]. Other effects of rejuvenation can be accompanied by disproportional mitosis [Lindner et al., 2008] or by a retrodifferentiation process, whereby the cells revert back to a previous stable state of development to restore again a younger phenotype [Hass, 2009].

Processes which can interfere with the normal biological clock including rejuvenation could contribute to an organismal life span extension as compared to the average life span of the appropriate species, also termed longevity. Besides rejuvenation, longevity can also be achieved pharmacologically by the inhibition of distinct pathways, including the mTOR signalling [Harrison et al., 2009], or genetically, e.g. by an induction of anti-oxidative defence products. Longevity could furthermore be displayed by a more general resistance mechanism involving an adaptation to environmental stress [Johnson et al., 1996]. However, aberrant signaling and impaired cell cycle regulation of either stem/precursor cell development into mature phenotypes or vice versa the rejuvenation back to a more juvenile state may include the risk of neoplastic growth and tumor progression.

1 According to several different expressions characterizing certain phenomena associated with rejuvenation,  
2 it appears worthwhile trying to summarize some definitions used in the literature:

3 retrodifferentiation: characterizes a biological phenomenon of completely reversible differentiation events,  
4 whereby all morphological and functional properties of retrodifferentiated and previously more  
5 undifferentiated cells are indistinguishable. Retrodifferentiation-associated rejuvenation requires a highly  
6 organized and timely coordinated network of a retrograde development in combination with an escape from  
7 aging [Hass et al., 2009].  
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10 longevity: denotes the length or duration of the life span of living organisms and is often used to indicate an  
11 unusually long life. It can be determined by statistical analysis based on mortality rates of various population  
12 groups [Guarente et al., 2008].  
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14 rejuvenation: restores cells to a more youthful condition and increases regenerative potential. It is distinct  
15 from life extension. Life extension strategies often study the causes of aging and try to oppose those  
16 causes in order to slow aging. Rejuvenation is the reversal of aging and thus requires a different strategy,  
17 namely repair of the damage that is associated with aging or replacement of damaged tissue with new  
18 tissue. Rejuvenation can be a means of life extension, but most life extension strategies do not involve  
19 rejuvenation. The reverse of the damage is also termed "SENS" (Strategies for Engineered Negligible  
20 Senescence) [de Grey and Rae, 2007].  
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