Advancements in Genetic Engineering
ISSN: 2169-0111

Zhang, Adv Genet Eng 2012, 1:1
DOI: 10.4172/2169-0111.1000e101

Editorial Open Access

# New Frontiers of Aging Reversal and Aging-Related Diseases Reprogramming

**Yue Zhang***

[1]*Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA*

**Keywords:** Aging;StemCell;mTOR;Osteoarthritis;Reprogramming

How would you like to stay 25 forever?To some extent, it might be not a dream in the future to reverse the aging and aging- related diseases. Certainly, aging was thus far programmed by natural selection during evolution so eventually inevitable [1-2]. However, performance can come from a cost. Through systematical modifications of the Genome Regulatory Network (GRN) and/or proteome, human cell and tissue engineering could couple with such inevitability by means of cellular reprogramming, genome editing [3] and tissue regenerative engineering. Many reviews previously speculated that the exhaustion of adult stem cell promotes the ageing and degenerative diseases, shortening the longevity [4]. Indeed, one of latest exciting investigations shows us the case of age reversal: implanting young stem cells to rejuvenate aging stem cells. Interestingly, the research team injected the stem like /progenitor cells into the abdomens of 17-day-old progeria mice, which generally have a lifespan of 21 to 28 days, some of them have a robust health and a life span up to 66 days [5]. Progeria is a disease that causes abnormally accelerated aging, such as loss of muscle mass,mesodermal/mesenchymal defects, accelerated atherosclerosis, neurodegeneration, osteoporosis, and trembling. It has been genetically shown that the deficiency of Lamina A (also the components of its embedded Mi-2/Nucelosome Remodeling and histone Deacetylation, i.e. NuRD complex) causes the chromatin old and leads thus to ageing [4,6]. After receiving the injection of stem cells, the mice recipients showed new blood vessel growth in the brain and muscle, improvement of health and increase of longevity. The injections of stem cells also delayed the onset of the majority of aging-related symptomsin a less acute model of accelerated aging. Intriguingly, the "labelled" injected cells went all over the place rather than home in on muscle or one kind of tissue.It raised the suspicion that the cells were secreting something that was kick-start regenerative capacity in whole organisms but effectively staving off aging [5]. This somehow mimics the kick-start of OSKM reprogramming of the cell pluripotency in cellular engineering [3,7], namely, to hit one node in the network, then spread to the whole system. We can view it with system biology: as on one balloon, to touch one starting point, the pressure reshapes the whole balloon.

Caner is certainly the leading ageing –related lethal disease. Through Mi-2/NuRD chromatin remodeling –related cancer attractors theory, we could understand better the carcinogenesis, especially for germline gene - reactivated cancers [1-2,8], and hence develop strategy to reprogram the cancerous diseased cells to normal-like cells[9]. Hereby we focus on another ageing -related disease. It is well-known that cartilage makes the movement of joints smooth and the fading- away and breakdown of articular cartilage by injury or age-related "wear and tear" causes osteoarthritis (OA), the most common degenerative chronic disease, which is further characterized by synovial inflammation, pain, subchondral bone alterations, loss of tissue cellularity and extracellular matrix (ECM) damages, a major cause of decreased quality of life in adults in the world. Yet therapy remains a challenge because cartilage has minimal ability to repair and renew itself. Alongside studies for decades, in clinical trials in patients with established or advanced OA, candidate disease-modifying drugs have failed to show efficacy, as the case in cancer research [1-2].

Recent laboratory studies and clinic trials emergently include stem cell osteoarthritis therapy [12-15]. Mesenchymal Stem Cells (MSC) derived from human umbilical cord blood (CBMSCs) have been characterized by their multipotency to differentiate into mesenchyme-lineage cell types, including chondrocytes, osteoblasts, and adipocytes. Mesenchymal Stem Cells (MSCs) in a polymeric carrier implanted into a cartilage and/or bone defect could differentiate to form cartilage and/or bone, as appropriate. Although ethical barriers could be resolved, some laboratory investigations and clinic trials could be probably undergoing.

In addition to stem cell tissue engineering, there will be highly promising upfront for therapy of cellular engineering in near future. The disorder of multi-cellularity could likely leads to ageing and ageing -related diseases. Previously, it was speculated that the ageing-related diseases in multi-cellular organisms like human beings could be due to a system failure (Figure 1), namely going awry to somehow retrograde to unicellular state or disordered mixture, typically such as aforementioned germ -line gene ectopically- expressed brain cancer[1-2], and also likely OA (this study); subsequently, its therapy

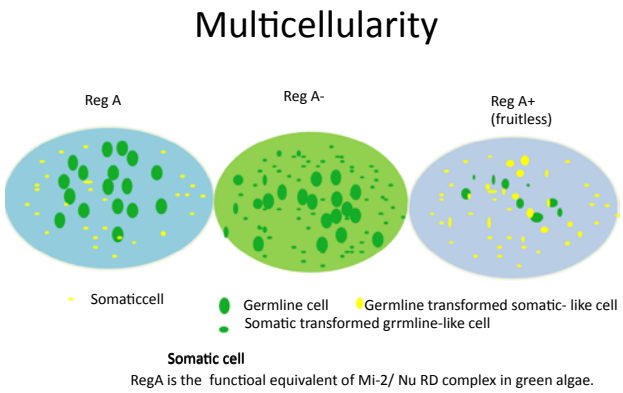



**Figure 1:** The RegA orchestrates the distinct of soma-germline in the green algae (*Volvoxcarteri*).

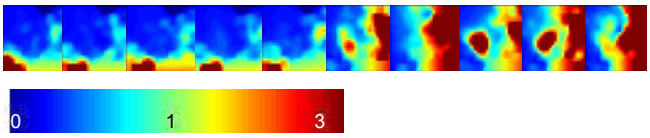
***Corresponding author:** Yue Zhang, Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, 99 Brookline Ave, Boston 02215, USA, E-mail: zy101@yahoo.com or yzhang1@bdimc.harvard.edu

**Received** January 12, 2012; **Accepted** January 13, 2012; **Published** January 16, 2012

**Citation:** Zhang Y (2012) New Frontiers of Aging Reversal and Aging-Related Diseases Reprogramming. Adv Genet Eng. 1:e101. doi:10.4172/2169-0111.1000e101

requires one tradeoff to systematically reprogram diseased states to the buffering range of natural robustness of these systems.

The deficiency of RegA, the functional equivalent of Mi-2/NuRD enables the relatively "differentiated" somatic cells (i.e. more multi-cellularity state) to the somewhat rogue but pluripotent "stem –like" germline cell (i.e. more or less uni-cellularity state). Some new traits are essential for the multi-cellularity state, such as the new level of self-organization, the extracellular matrix for cell –cell communications, programmed cell death, more complex protein syntheses and degradation, advanced pre mRNA and mRNA processing, new chromatin remodelling systems, and ATP -productions with mitochondrial OXPHOS rather than relying on archaic hypoxia glycolysis mechanisms alone, *etc*. (for the details, please refer to [1-2, 16] and its references therein)




An holistic view on genome-wide gene expression profile (GEP) of OA as system level GRN 's surrogate. In red, represents the high gene expression levels; in blue, the low expression levels. GEDI: gene expression dynamic inspector, one program characterized with self- organization [17].

**Figure 2:** The GEDI "cloud"s of normal (left 1-5 ) or mice ( right 6-10) with OA induction.

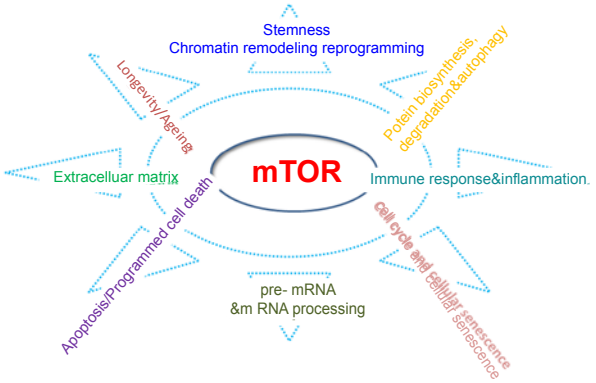
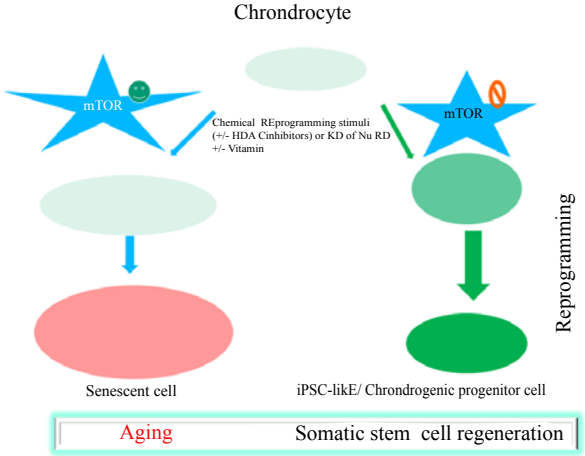



**Figure3:** mTOR and its orchestrated system biology.




Some new studies examining the specific effects of mTOR signalling may provide crucial clues to their potential use in delaying the aging process and preventing the onset of aging-related diseases, such as OA, cancer and neurodegenerative diseases[27,32].

**Figure 4:** Inducing autophagy with mTOR inhibitors will maximize the efficiency of reprogramming to pluripotency.

One surrogate for "absolute" bona-fide system of multi-cellular organisms would be dynamics global Gene Regulatory Network (GRN), which inherently bears characterization of self- organization and it is critical for functionality of organism level systems. More recent efforts are directed at defining early changes that predispose or lead to the onset of OA. As the majority patients develop OA as a function of increasing age, it is essential to understand aging-related changes in cell function. The genome-wide Gene Expression Profiles (GEP) would be expected to assess the early prediction, diagnosis, and prognosis for OA [1-2,17-18] (Figure 2). The matter of fact is that researchers could hence identify the unique patterns of each stage in the evolution of disease, which are suitable for its corresponding stage-specific interventions with drug against biomarkers. Similarly, the fractural analysis, which have been applied on cancer research for a while [19], could be another elegant independent surrogate for laboratory investigation and /or clinic on OA. So they could mutually benefit.

In addition to chromatin remodeling complexes, like Mi-2/NuRD, it was ascertained that the telomere and mitochondria could also contribute to ageing [reviewed in 11]. One prior study on deficiency in TOR kinase has revealed one tradeoff of fertility and longevity in *C.elegans* (unpublished). One recent study has further confirmed that there will be one balance between health ageing and reproduction [20]. It is important to look at GRN's derivatives or representative, i.e. key driver pathways of ageing -related diseases include (but likely not limited to): the longevity, Extracellular Matrix (ECM), apoptosis, immune response and inflammation, pre-mRNA and mRNA processing, chromatin remodeling and cellular reprogramming, protein biosynthesis, degradation and autophagy, cell cycle and cellular senescence, all of which mTOR takes the control to some extent (Figure 3). Briefly, mTOR inhibition by rapamycin significantly decreases extracellular matrix deposition in a rat model [21]. One study in *C. elegans* revealed that TOR deficiency doubles its natural lifespan [22]. This function for TOR signalling in ageing control may represent a link between nutrition, metabolism and longevity, so putting TOR as a key mediator of lifespan regulation by insulin signaling and nutrient sensing. Ma et al.[23] observed that the nutrient-, stress-, and energy-sensing checkpoint kinase, mTOR, contributes to the observed enhanced translation efficiency of spliced over nonspliced mRNAs. Autophagy is compromised in OA cartilage and this is in part related to reduced expression of autophagy regulators. The telomere-p53-PGC1 pathway contribute to mitochondrial dysfunction, which affects the ageing [24], as abovementioned, impaired mTOR -directed autophagy. The mTOR inhibition by rapamycin induces autophagy. As one kind of confirmation in TOR deficiency in *C.elegans*, the rapamycin extends median and maximal lifespan of both male and female mice [25], providing further support for the importance of autophagy in aging. In an *in vitro* model, rapamycin treatment of cartilage explants alongside high levels of mechanical load reduced cell death and extracellular matrix damage. Rapamycin also suppressed biochemically induced cell death and nitric oxide production in response to proinflammatory cytokines [11].

The Lotz lab [26] firstly studied the potential therapeutic benefits of rapamycin in vivo used a knee instability induced OA model in mice. Rapamycin treatment reprogrammed the OA through

autophagy and reduced the severity of OA and this was associated with preservation of cartilage cellularity. These findings are the first to suggest that rapamycin is a promising new approach towards chondroprotection. However, there might be another possibility of interpretation from alternative potential cellular reprogramming. In cartilage, chondrocytes are the only resident cells found in cartilage and are in charge of both synthesis and turnover of the abundant ECM. Therefore maintaining the chondrocytes in a healthy condition may be important to maintain the entire cartilage and preventing degeneration of cartilage. Recent findings that well-characterized mTOR inhibitors and autophagy activators (e.g., PP242, rapamycin and resveratrol) notably improve the speed and efficiency of induced pluripotent stem cells (iPSC) generation [27]. A landmark study by Cao et al. [28] has recently confirmed that by stimulating autophagy, the mTOR inhibitor rapamycin can efficiently prevent the accelerated geroconversion of human cells that is induced by progerin accumulation as we discussed at the beginning [5]. Therefore rapamycin could possibly increase the number of chondrogenic progenitor cell [12-13] or mesenchyml progenitor-like cells [29], so resulting in effects of MSC stem cell therapy as aforementioned [3, 12-13].

Additional studies are required to evaluate the combinatory effects of rapamycin , vitamin C and HDAC inhibitors (i.e. inhibition ofMi-2/NuRD) to reprogram the cellular pluripotency to analyze its efficacy in models of aging-related OA(Figure 4). Inhibitions of Mi-2/NuRD for HDAC or knock-down of RBBPP48/46 facilitate the direct conversion, for instance, the direct conversion of *C. elegans* germ cells into specific neuron types [30].The histone demethylases Jhdm1a/1b are key effectors of somatic cell reprogramming downstream of vitamin C [31]. Therefore, we need keep looking for "the fountains of youth".

## References

1. Zhang Y (2011) New concepts of germline gene-reactivated cancer. Human Genet Embryol 1: e101.
2. Zhang Y, Moriguchi H (2011) Chromatin remodeling system, cancer stem-like attractors, and cellular reprogramming. Cell Mol Life Sci 68: 3557-3571.
3. Mali P, Cheng L (2012) Concise review: human cell engineering: cellular reprogramming and genome editing. Stem Cells 30: 75-81.
4. Zhang Y (2011) Biology of the Mi-2/NuRD Complex in SLAC (Stemness, Longevity/Ageing, and Cancer). Gene RegulSyst Bio 5: 1-26.
5. Lavasani M, Robinson AR, Lu A, Song M, Feduska JM, et al. (2012) Muscle-derived stem/progenitor cell dysfunction limits healthspan and lifespan in a murine progeria model. Nat Commun 3: 608.
6. Pegoraro G, Kubben N, Wickert U, Göhler H, Hoffmann K, et al. (2009) Ageing-related chromatin defects through loss of the NURD complex. Nat Cell Biol 11: 1261-1267.
7. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663-676.
8. Zhang Y, Calderwood SK, Moriguchi H (2011) Visualization of Archaic Cancer Attractors and Chromatin Regulators Connecting to Ageing, Robustness and Cellular Reprogramming. Advances in Medicine and Biology. Volume 44, Nova Scientific Inc.
9. Moriguchi H, Zhang Y, Mihara M, Sato C (2012) A therapeutic method for the direct reprogramming of human liver cancer cells with only chemicals. Nature Scientific Reports (*in press*).
10. van den Berg WB (2011) Osteoarthritis year 2010 in review: pathomechanisms. Osteoarthritis Cartilage 19: 338-341.
11. Lotz M (2011) Osteoarthritis year 2011 in review: biology. Osteoarthritis Cartilage.
12. Koelling S, Miosge N (2009) Stem cell therapy for cartilage regeneration in osteoarthritis. Expert OpinBiolTher 9: 1399-1405.
13. Koelling S, Kruegel J, Irmer M, Path JR, Sadowski B, et al. (2009) Migratory chondrogenic progenitor cells from repair tissue during the later stages of human osteoarthritis. Cell Stem Cell 4: 324-335.
14. Nelson L, Fairclough J, Archer CW (2010) Use of stem cells in the biological repair of articular cartilage. Expert OpinBiolTher 10: 43-55.
15. Myers TJ, Granero-Molto F, Longobardi L, Li T, Yan Y, et al. (2010) Mesenchymal stem cells at the intersection of cell and gene therapy. Expert OpinBiolTher 10: 1663-1679.
16. Miller SM (2010) Volvox, Chlamydomonas, and the evolution of multicellularity. Nature Education 3: 65.
17. Eichler GS, Huang S, Ingber DE (2003) Gene Expression Dynamics Inspector (GEDI): for integrative analysis of expression profiles. Bioinformatics 19: 2321-2322.
18. Karlsson C, Dehne T, Lindahl A, Brittberg M, Pruss A, et al. (2010) Genome-wide expression profiling reveals new candidate genes associated with osteoarthritis. Osteoarthritis Cartilage 18: 581-592.
19. Metze K (2010) Fractal dimension of chromatin and cancer prognosis. Epigenomics 2: 601-604.
20. Hughes SE, Evason K, Xiong C, Kornfeld K (2007) Genetic and pharmacological factors that influence reproductive aging in nematodes. PLoS Genet 3: e25.
21. Zhu J, Wu J, Frizell E, Liu SL, Bashey R, et al. (1999) Rapamycin inhibits hepatic stellate cell proliferation in vitro and limits fibrogenesis in an in vivo model of liver fibrosis. Gastroenterology 117: 1198-1204.
22. Vellai T, Takacs-Vellai K, Zhang Y, Kovacs AL, Orosz L, et al. (2003) Genetics: influence of TOR kinase on lifespan in C. elegans. Nature 426: 620.
23. Ma XM, Yoon SO, Richardson CJ, Jülich K, Blenis J (2008) SKAR links pre-mRNA splicing to mTOR/S6K1-mediated enhanced translation efficiency of spliced mRNAs. Cell 133: 303-313.
24. Sahin E, Colla S, Liesa M, Moslehi J, Müller FL, et al. (2011) Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 470: 359-365.
25. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, et al. (2009) Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460: 392-395.
26. Caramés B, Hasegawa A, Taniguchi N, Miyaki S, Blanco FJ, et al. (2011) Autophagy activation by rapamycin reduces severity of experimental osteoarthritis. Ann Rheum Dis.
27. Menendez JA, Vellon L, Oliveras-Ferraros C, Cufí S, Vazquez-Martin A (2011) mTOR-regulated senescence and autophagy during reprogramming of somatic cells to pluripotency: A roadmap from energy metabolism to stem cell renewal and aging. Cell Cycle 10: 3658-3677.
28. Cao K, Graziotto JJ, Blair CD, Mazzulli JR, Erdos MR, et al. (2011) Rapamycin reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson-Gilford progeria syndrome cells. SciTransl Med.
29. Grogan SP, Miyaki S, Asahara H, D'Lima DD, Lotz MK (2009) Mesenchymal progenitor cell markers in human articular cartilage: normal distribution and changes in osteoarthritis. Arthritis Res Ther 11: R85.
30. Wang T, Chen K, Zeng X, Yang J, Wu Y, et al. (2011) The histone demethylases Jhdm1a/1b enhance somatic cell reprogramming in a vitamin-C-dependent manner. Cell Stem Cell 9: 575-587.
31. Tursun B, Patel T, Kratsios P, Hobert O (2011) Direct conversion of C. elegans germ cells into specific neuron types. Science 331: 304-308.
32. Graziotto JJ, Cao K, Collins FS, Krainc D (2012) Rapamycin activates autophagy in Hutchinson-Gilford progeria syndrome: Implications for normal aging and age-dependent neurodegenerative disorders. Autophagy.