

Brief View on Future and Current Ageing Science and beyond: Going Simple is the New Exciting

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Abstract

Focus on future and current ageing research; here we briefly discussed frontiers of ageing science, such as current ageing theories, exploring new health beneficial windows in mTOR - regulated cellular processes, synthetic and systems biology, nanotechnology, etc. In addition, *ex laboratorio* emphasizes two points for JASC.

Ageing is among the most critical risk factors for human diseases prevalent in the elderly such as Neurodegenerative Diseases (ND), different forms of cancer, Osteoarthritis (OA) to metabolic disease. An increasing elderly population in our society promotes future and current research of longevity, ageing and Ageing-related Diseases (ARD) as one attractive topic.

Acrossing the evolutionary spectrum, ageing appears universal but complex. Research of ageing is aim to unerstand, slow, stop and/ or reverse its process. Going simple is the new exciting. For instance, whether single gene may control ageing? Around twenty years ago, “many, not single gene”, probably most answers you may heard. However, for the first time, surprisingly biochemist genius Dr. Cynthia Kenyon [1] was able to prove that a simple genetic mutation Daf-2/IGF-1 caused a simple worm, *Caenorhabditis elegans* (*C. elegans*) to double the lifespan. Moreover, ten years ago, Vellai et al. [2] in lab described that deficiency of single protein kinase termed “the target of rapamycin” (TOR) may double its life span in *C. elegans* too. Interestingly, long-lived mutants are resistant to many ageing-related diseases and bacterial infection [3]. One latest study agrees that there might be some universal mechanisms for activating anti-ageing pathway, i.e., single molecule that treats multiple age-related diseases, for example, SIRT1, yet controversy is not completely resolved [4]. Thus some “drivers” for ageing may exist; even it need eventually dictate a defined group of genes via its cascade [5]. Lifespan in model organisms appears plastic and subjected to modulation of genetic, nutritional or pharmacological intervention [5,6]. Thus we might significantly extend youthful human life through understanding of the influence that genetics have on age-related diseases (from cancer, ND [7], OA [8], diabetes to heart failure) in living things. Remarkably, if we can extrapolate from the adult lifespan in age-1(mg44) (i.e.AGEing alteration) animals relative to its control wild type nematode *C. elegans*, we may live extremely long lives, and up to 1000 years [9]. It is always tantalizing to discover the “fountain of youth”. Indeed, countless men tried this or that way to avoid ageing, from Babylonian epic of Gilgamesh, to Poncede Leon, as well as Emperor Chin in chin Dynasty in China sending out 300 young boys sailing to Pacific sea to seek for “the elixir pill”. Of certain, a long distance remains to translate from insights gained in animal models to human beings! A better understanding of the targets of such interventions, as well as the proximate causes of ageing-related degeneration and disease, is critical for the evaluation in abrogation of human senescence [5,10]. However, one study from one German group reported that the mortality rate for 70 years-old population at present is similar to that for 30 years-old during 1800s. This indicates health care have dramatically contributed to extension of our life span together with many other factors [10].

Current Ageing Theories

A great ageing theory may foster ideas that push the bounaries and leads to original breakthroughs. Among many is the aforementioned Dr. Kenyon’s theory of “universal hormonal control for ageing”:

carbohydrate intake, which can have a dramatic effect on how daf-2/ IGF-1 and daf-16/Foxo genes behave, boosting repair and renovation activities [1]. So far, her theory has proved true for worms, mice, rats, and monkeys [2,5,6] and she suspects it applies to humans, too. New, controversy or shaking are for other ageing -or ARD-related theories, such as ROS [11], Damage dilution [12] and many more. Basically, Dr.Kenyon’s theory may revolutionize our understanding of ageing and ageing-related diseases and suggest combating many ARDs all at once; namely, by focus on targeting their greatest risk factor: ageing itself.

Exploring new health -beneficial windows in mTOR -regulated cellular processes

It is essential to better understand the molecular pathways underpinning the ageing process, with this knowledge to obtain novel therapeutic strategies to treat ARDs. In general, some interventions could be two-sided swords. However, we may hypothesize, by modulating the natural machinery; there is a huge room to explore new health beneficial windows in cellular processes. With a cost, the modulation or reversal of ageing and ARD emerge through modulation of mTOR and beyond, such as telomere [13], adult stem cell regeneration [14], reprogramming [15,16], etc. Focus here is on modulation of the processes [16] which TOR regulates, i.e., synthesis of protein and of nucleotides [17], and autophagy [18,19], which have some potentially beneficial windows. Autophagy functions in cellular and tissue homeostasis and protection against disease. Thus, strategies that augment autophagy may provide some prevention or treatment for some human diseases. Shoji-Kawata et al. [20] developed a specific autophagy-inducing agent (7 AA Becn1 peptide) with a potentially wide range of therapeutic effects [20] and they also established that several health benefits from autophagy correspond closely to the effects of exercise [18,19], namely activation of autophagy may contribute to other health benefits of exercise, including

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Received March 04, 2013; Accepted March 25, 2013; Published March 30, 2013

Citation: Li Y, Zhang Y (2013) Brief View on Future and Current Ageing Science and beyond: Going Simple is the New Exciting. Aging Sci 1: e101. doi: [10.4172/2329-8847.1000e101](https://doi.org/10.4172/2329-8847.1000e101)

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protection against cancer, ND, ageing and diabetes. Besides, we and other group [8] observed that augmentation of autophagy can alleviate the OA symptom in model and however treatment of pancreatic cancer needs the inhibition of autophagy [21]. Further, many animals can slow ageing when energy availability is low and thus gain protections from many age-related diseases. Future and current efforts need recapitulate the positive effects of dietary restriction on lifespan and healthspan but minimize its side-effects.

Synthetic and systems biology

Synthetic biology uses designed genetic devices to reprogram cellular activities in mammalian cells, so it may benefit ageing science too. A synthetic optogenetic transcription implant enhances blood-glucose homeostasis in mice, and light-controlled expression of the Glucagon-like Peptide 1 (GLP-1) may manage the glucose level in type II diabetic mice [22]. So far, little is known about systems biology and its potential for changing how we diagnose and treat ARD. However it is clear that systems biology may provide us one opportunity of comprehensive rather than isolated view on omics data through some intuitive web-based tools for quickly analyzing and accurately interpreting the biological meaning with simple visualization computation program, such as Gene Expression Dynamic Inspector (GEDI) for cell attractors [23] of progenitor cells and cancer cell type [24,25], Ingenuity Program Analysis (IPA) for genomic data (<http://www.ingenuity.com>) [24-26], Affymetrix TAS software (Affymetrix) for identification of all genes positive in transgenic Chromatin IP-chip (e.g. for DAF-12/Liver X receptor regulating a genetic regulatory network to ensure robust developmental and longevity decisions) [27], and many more for other application [28].

Nanotechnology

For early diagnosis, nanotechnology made for Mars, known as "ARTIDIS", holds promise for detecting breast cancer and OA in that it owns the exquisite nanomechanical sensitivity to detect and differentiate between the various stages of disease in soft human tissues—in minutes, while conventional breast cancer diagnostics needs much longer times. Moreover, the atomic force microscope may determine the onset of disease. The possibility of diagnosis with ARTIDIS in the early stages is promising for better treatment options and better chances of cure. Further, a simply added gold nanoparticle detection reagent can be easily used for sorting of cells based on gene expression live cell tracking of RNAs, and detection of multiple types of biomolecules (such as protein+RNA) in the same sample [29]. This holds promise for many researches in ageing and ARD. Finally, it is not unexpected that the nano-material could become feasible as an in vivo delivery therapeutic tool kit.

Others

Epigenetics is critical for ageing and accelerated ageing, for instance, LMNA and its related Mi-2/NuRD [30-32]. It is thus essential to determine not only abovementioned genetic but also epigenetic causal underlying deterioration of tissue, cellular and molecular processes with age as well as increased disease susceptibility and frailty. Currently researchers started to reprogramme cells to fight diabetes through epigenetic modulation with compounds [33]. Other key regulators of ageing and ARD are telomere and telomerase [13,34] and telomerase reactivation may reverse tissue degeneration in aged telomerase-deficient mice [13].

Together we are invincible: International collaborations may accelerate new discoveries of future and current ageing sciences.

Lastly, one simple question: If one longevity or ageing -delay pill was available, could you like to buy and take it? If no free-lunch available, what kind of cost you will accept? At another hand, keep in mind, there will likely be the growing healthcare needs of growing ageing human populations in the near future, so now investigate our money into army (and war) or ageing sciences?

Ex laboratorio: 1st, now information explosion generated by omics and systems biology makes data-mining more and more important. Traditionally, the data-miner (and literature-miner) is probably the supervisor, which may generate the hypothesis based on their rich experience and broad view, thus naturally credits went to them. However, now some research might enter "data-first" era. Sometimes one postdoc new comer could be able to master well some new knowledge and some types of unique techniques as well. For some unexpected reasons, maybe rarely, in worse contexts, the whole project could be shifted to another lab member after its initial design and exploring, which has been accomplished by such postdoc newcomer at the beginning. Finally, such initial design and progress could be credited defaultly to that supervisor by the successor of project, ex lab and other members. "The rich-get-richer" dynamics is consistent with the power-law distribution in lab-credit distribution. Sometimes some cases could end up a better credit-sharing among the initiator, new successor and their PIs. Importantly, several labs in Boston started to credit their part-time or full-time data-miner and literature-miner, which may initiate the fantastic but feasible conception and design. In one case, one data-miner and literature-miner was finally credited as the 2nd co-first author in one important publication. We won't go deeper here, but point to that there is unmet need / gap between raw data (e.g. generated from omics) together with literature "mountains" and any meaningful biological project proposals. For this point, one of grant adminster in National Institute of Health (NIH) did also note such gap during our discussion in one table in one Keystone symposium and agreed that it need bridge up with some efforts. Future efforts will encourage more original (e.g. smart designs) contribution to research along with right crediting systems, therefore it will eventually benefit our research (e.g. ageing sciences). We could encourage authors to detail their contributions, including an emphasis of their original design. 2nd, we need to escape from editor and reviewer's subconscious meta-ignorance and help to correct a deficit of the peer-review process that stifles the diversity of ideas, innovation and paradigm shifts in traditional journals since some compensatory use of "reacharound knowledge" prevents any recognition of paradigm-shifting novelty that emerges in unfamiliar territories because of the failure to understand the novel usage of an existing term and concept as discussed in [35]. This issue may have not happened to us but need the attention from editors of JASC. It will be more than great for JASC while both reviewers and editors may extensively share their expertises with authors and contribute many efforts [36] to welcome paradigm-shifting novelty that even emerges in unfamiliar territories.

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Citation: Li Y, Zhang Y (2013) Brief View on Future and Current Ageing Science and beyond: Going Simple is the New Exciting. *Aging Sci* 1: e101. doi: [10.4172/2329-8847.1000e101](https://doi.org/10.4172/2329-8847.1000e101)

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