Decoding Complexity of Aging

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Introduction

Aging, the process of growing old, is characterized by the gradual deterioration of normal cellular functions, leading to a steady decline in the biological, physical and psychological abilities. It is a phenomenon which is genetically determined and environmentally modulated [1]. It also increases the susceptibility for a number of complex diseases, regardless of whether or not they are ultimately responsible for the death of the individual developing them. Aging activates some irreversible series of biological changes that inevitably result in death of the organism. Although, the causes of these changes may be entirely different in different cases implying no common mechanism, yet they often imply a mutual element of descent. Therefore, aging is a most common yet mysterious aspect of biological studies, even after being a subject of interest to humans since the beginning of recorded history.

Finding Suitable Model System for Aging Research

Years of research on aging have found several genes and many biological processes that are associated with; however, many fundamental questions continue to be intensely debated [2,3]. Some of the fundamental questions which are still unanswered are: (i) How many biological processes contribute to aging? What are they? (ii) Is it possible to reverse the phenomenon of aging? (iii) Can a single gene mutation recapitulate all the aging induced consequences? Moreover, the molecular basis of aging remains poorly understood, in part, because we lack a large number of molecular markers of aging that can be used to measure the aging process in specific tissues. Thus, unravelling the mysteries of aging is still on the frontier of biomedical research.

The last two decades have witnessed a tremendous upsurge in the genetic analyses of aging, with a greater emphasis towards the elucidation of the molecular mechanisms, pathways, and physiological processes implicated in longevity. Since the limitations of human genetic studies make it difficult to identify or analyse a candidate gene and pathways in greater detail, and with the fact that the basic biological processes remain conserved throughout phylogeny, model organisms from bacteria to mammals have been utilized to resolve different aspects of aging [4]. However, classical model systems such as Caenorhabditis elegans and Drosophila melanogaster have emerged as excellent systems to elucidate essential genetic/cellular pathways of human aging. Some of the major advantages of using Drosophila for aging related studies include its short life span, ease of maintenance, availability of powerful genetic tools, accessibility of stocks with many different alterations, knowledge of the complete genomic sequence and large homogeneous populations. Moreover, two major attractions for choosing Drosophila for aging related studies include its precise identification of sexually mature state, which starts within 24 h of eclosion. It is during this “adult” phase of its life when aging is usually thought to take place, which is otherwise little difficult to determine with other model systems [5]. Successively, D. melanogaster is almost exclusively a post-mitotic organism, i.e. an adult fruit fly almost consists of post-mitotic cells, and therefore, they are considered to harbour a set of synchronously aging cells, which simplifies recording of observations and provides conclusive results [6].

Complexity of Aging

Aging is complex. Diverse molecular and cellular damages accumulate over time, causing functional failures in different tissues. Aging is associated with the accumulation of a large variety of post-translational modifications in stable proteins, which include deamidation of asparaginyl and glutaminyl residues and the subsequent formation of isopeptide bonds, protein glycation, methionine oxidation, etc. [7]. Furthermore, the disturbed cellular homeostasis leads to an increased rate of protein modification: in an 80-year old human, half of all proteins may become oxidized [8]. In prokaryotes, translational errors result in folding defects and subsequent protein oxidation [9], which predominantly takes place in growth arrested cells [10]. Additionally, damaged signalling networks induced by aged proteins tend to lose their original stringency and induce irregular protein phosphorylation [11].

Heat Shock Proteins and Aging

Age-related post-translational modifications induce conformational changes and impaired protein function. Although in normal conditions intracellular protein turnover is rather fast, increased carbonyl content of aging proteins (an indicator of oxidative damage) significantly reduces the turnover rate in several tissues, e.g. brain [12]. Subsequently, all of these “old age” induced events cause a substantial accumulation of post-translationally modified, mis-folded proteins, which pose a great danger to the aging individual. Since the folding anomaly in aged organism/cell is mostly due to posttranslational modifications, the changes become irreversible and cannot be reversed by conventional protein folding machinery. Thus, the only solution to protect the aging cells from these mis-folded proteins is their elimination, and not their repair. The changes in protein levels and their folding states in aged organisms are sensed by Heat shock proteins (Hsps), which selectively recognize and bind to the exposed hydrophobic surfaces of non-native proteins in a non-covalent interaction, in order to inhibit irreversible aggregation, and to mark them for further degradation [13].

As it is increasingly clear now that aging arises due to reduced capacity of cells to protect, maintain, and repair tissues over time and these occur at multiple levels; from the physiological system, through organs, to cells and individual biomolecules; Hsps appear to be a major group of proteins involved in modulation of aging related phenomenon. Hsps or stress proteins are also known as molecular chaperones, because they are synthesized in increased amounts after heat shock phenomenon. Hsps are very important for preventing the protein aggregation, and to mark them for further degradation [13].

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other stresses such as irradiation, viral infection, oxidative stress, etc. [14]. They represent groups of ubiquitous and highly conserved protein families which utilize ATPs to stabilize unfolded proteins, or unfold them for translocation through membranes, or mark them for degradation [14]. Conventionally, principal Hsps range in molecular mass from 15 to 110 kDa, and are grouped into 5 major families, viz. Hsp100 (100-104 kDa), Hsp90 (82-90 kDa), Hsp70 (68-75 kDa), Hsp60 (58-65 kDa), and the small Hsp (15-30 kDa) families. In addition to stress response and protein folding, Hsps have also been demonstrated to be involved in various aspects of development, apoptosis, fertility, maintenance of cellular homeostasis, evolution, modulation of signals for immune/inflammatory responses, etc. [14].

In D. melanogaster, mild stress in the form of heat shock has been found to result in an increase in life span. This response has been credited partly to the activation of protective and/or repair systems, especially the induction of the heat shock chaperone system with Hsp70 being in the centre [15]. Hsp70 is one of the major components of the chaperone system of the cell, which exhibit increased level with age. It was also reported that presence of additional copies of the Hsp70 resulted in decreased mortality rates in Drosophila following a heat stress, which was otherwise too brief to extend life span in normal flies [16].

Subsequently, several other Hsps such as Hsp90, Hsc70, Hsp60, Hsp40, and small Hsps (αHsps) have been found to be involved in aging related phenomenon [17]. Interestingly, it has been demonstrated that age induced damaged proteins compete with the Heat shock factors (Hsf) in binding to the Hsp90-based cytosolic complexes, which contributes to the generally observed constitutively elevated chaperone levels in aged organisms [18]. Furthermore, since the protein degradation is mostly accomplished by the proteasome and mediated by various Hsps, accumulation of abnormal proteins in aged organisms requires an increased amount of Hsps to prevent protein aggregation and to assist in refolding, or degradation. It has been suggested that in aged animals or human subjects, Hsp90 protects the age-related decline of proteasome activity. However, the association of Hsp90 with the proteasome decreases with age, which may lead to an enhanced vulnerability of the proteasome for stress, induced damage in aged organisms. It appears that the decline in Hsp induction and the increase in denatured proteins, including damage to chaperones, all contribute to the overall decline in chaperone capacity with age, and these may lead to an increase in cellular senescence, apoptosis or necrosis, depending on the degree of damage and the balance between damaged proteins and available free functional chaperones [19].

**Insulin Pathway and Aging**

Parallel to Hsps, dietary restriction (DR) has also emerged as one of the major factors involved in aging and longevity. Dietary restriction is the condition of reduced nutrient intake that extends an organism’s life span by altering the pattern of energy utilization in the body, and allowing organisms to survive under stress. Insulin signalling pathway is one of the key nutrient sensors in the body, which plays critical role in mediating longevity in dietary restriction stress condition [20,21].

Insulin/Insulin-like growth factor-1 (IGF-1) signalling pathway is conserved across the phyla in worms, flies, mice and humans [22]. This is one of the most prominent and best characterized regulatory pathways that influence life span of organisms. The discovery that mutations in thedaf-2gene, which encodes an insulin/IGF-1 receptor homologue, dramatically increase the life span inC. elegansled to the investigation of similar genes in the Drosophila [23,24]. It was also demonstrated that Insulin/IGF-1 receptor negatively regulates downstream transcription factors, FOXO/DAF-16, SKN-1/NRF and HSF-1 [22]. Insulin receptor/DAF-2 activates AKT kinase and phosphorylates DAF-16 and SKN-1, and prevents its nuclear localization, which in turn inhibits the expression of downstream target genes, such as sHsps [25]. In contrast, reduced insulin signal hyper-activates DAF-16/FOXO and HSF-1, therefore altering the transcriptome of downstream target genes, resulting in degradation of toxic protein aggregates and refolding of denatured proteins, finally helping in developing increased stress tolerance and delayed aging [26]. Similarly, mutations in the genes encoding the insulin-like receptor (InR) in Drosophila also resulted in life span extension, corroborating the role of insulin or insulin-like signalling pathway in regulating longevity [27].

**Oxidative Stress/Mitochondrial Dysfunction and Aging**

The process of aging that is brought about due to the accumulation of oxygen-free radicals with time falls under the class of damage-induced aging. Oxidative stress hypothesis of aging accounts for one of the most primitive, but prominent theories of aging [28]. Mitochondrial dysfunction or oxidative stress is common in both aging and neurodegenerative diseases [29]. During aging, mitochondrial dysfunction results in increased reactive oxygen species (ROS) and reduced antioxidants causing cellular oxidative damage, which is also believed to function as a key factor for triggering pathogenesis in neurodegenerative diseases [29]. Studies have showed that manipulating the mitochondrial electron transport chain (ETC) can extend longevity in organisms [28].

**Finding Link Between Aging and Neurodegenerative Diseases**

Neurodegenerative diseases are types of protein conformational disorders characterized by late onset, accumulation of mis-folded proteins at the intracellular and extracellular levels [30]. Similarly, aging is a universal phenomenon again characterized by accumulation of damaged macromolecules at the molecular, cellular and organismal level exponentially. Scientific advance in aging research and the development of molecular tools enable us to address the question, whether aging related changes allow protein aggregation in toxic condition, and become susceptible to initiate diseases late in life. It also appears that many of the aging related changes are sufficiently fatal to trigger early onset of complex diseases [30]. Several studies suggested a mechanistic link between aging, toxic protein aggregation and onset of neurodegenerative disorders, and therefore, it raises the prospects to prevent accumulation of toxic protein aggregates by slow aging process, to postpone onset of neurodegenerative diseases and alleviate their disease symptoms that once have emerged [31].

Since prevention of protein aggregation holds the key for the cure of neurodegenerative disorders, subsequent in-depth functional catherization of chaperones seems to explain the mysterious link between neurodegeneration and aging, which in turn could be helpful in the management of this fatal illness. Amelioration of Poly (Q) induced neurodegenerative phenotypes by modulating the expression of various Hsps in human disease models strongly supports the above hypothesis [32].

**Concluding Remarks and Future Perspectives**

Growing evidences suggest that endocrine/ neuroendocrine signalling may play a major role in influencing the life span in humans, which is not surprising because many other age-specific developmental programs, such as puberty and menopause are hormonally controlled.
Moreover, several recent findings indicate a direct influence of neuroendocrine pathways upon longevity and aging in vertebrates and invertebrates [33]. Although it is increasingly clear now that aging is regulated by explicit signaling pathways, however, whether the influence of these signaling pathways is applicable to an organism “as whole” or regulates the aging phenomenon by targeting specific tissues, which then affect aging systemically remains to be determined. Taken together, exactly how these various pathways/factors control life span and influence aging is still a “great scientific mystery”. The dramatic progress made in recent years utilizing various model organisms has demonstrated the feasibility of decoding this mystery, and further studies are expected to reveal insights of the biological aging and longevity.

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