# On the Physiology and Medicine of Aging

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**ABSTRACT:** World-over the population of aged is steadily increasing and physiology and medicine of aging constitute major biomedical concern. Evolutionary understanding of biology has given rise to multiple diverse causal theories of aging, with different extents of scientific validation. Genetic coding of life span has not been tenable, although the gene-environment interactions seem to heavily bear upon the phenomenon. Visibly, aging involves structural and functional erosion undermining efficient bodily readjustments to the demands of changing life environments. Age associated diseases indicate imbalance in energy intake and expenditure. Healthy process of ageing must be impacted by the same to acquire undesirable forms and rate of progression. Aberrations in lifestyle and nutrition prominently link to pathogenesis of age associated diseases, and provide objects for preventive and corrective interventions. Treading on such very frame, the physiologic and medical understanding of the ageing process, is herein, developed with a degree of over-simplification. The current understanding on biological factors of aging is reviewed emphasizing the interrelation among them, to contemplate personalized preventive and mitigative interventions.

**Author Keywords:** Biology of ageing; Physiology of ageing; Mechanisms of ageing; Ageing prevention; Medical management of ageing.

PII: S225199391600018-6

REVIEW

## INTRODUCTION

Aging is inevitable phenomenon of biology, driven by multiple factors at varied rates and fashion in different species and even among members of same species. As per the Darwinian principle, successful attainment of reproductive age is minimum essential life span for species [1]. Extended living beyond essential life span results in accumulating damages in biochemical architecture of body comprised of nucleic acids, proteins and lipids. A progressive failure of homeostasis and homeodynamics manifests at different levels of functional organization, worsening in to disease forms and may cause eventual death. The failures of repair and maintenance mechanisms are central to mechanistic principle of aging [2].

### Genes and Aging

Finite genetic basis for aging is unconceivable. Consensus is evolving over crucial contribution of threshold changes in epigenetic mechanisms to aging process and absence of any evolving superior repair mechanisms to avert aging. Aging studies in the centenarians, suggest role of human leukocyte antigen (HLA), alleles on specific chromosome loci and also of varied alleles of APOA and APOB genes coding for apolipoproteins A and B, and angiotensin converting enzyme genotype in conferring longevity [3]. Discovery of Klotho (KL) gene encoding α-klotho protein, has helped advancing understanding of ageing process. α- klotho protein is multifunctional and regulates metabolism of phosphates, calcium and vitamin D. Mutation of KL gene are associated with hypertension and kidney disease suggesting renal function as their prime target. In mice, klotho gene functions as ageing suppressor gene, extending life span upon over-expression and to cause accelerated ageing phenotype, when disrupted [4]. α klotho protein antagonizes a bone derived hormone that inhibits renal vitamin D3 biosynthesis, also suppress insulin and Wnt signaling pathways, inhibits oxidative stress and regulates phosphate and calcium absorption [5]. These proteins locate on renal tubule cell membrane and shed fragments in

circulation. The later interact with signaling pathways of multiple growth viz.insulin/ insulin like growth factor 1(IGF1), Wnt etc. and activity of several ion channels. The protein appears to also protect cells from oxidative stress [6]. Humanin is a mitochondria associated peptide that plays role in cell metabolism, survival, response to stress, inflammation and apoptosis. Humanin analogues favourably influence age related diseases. Association between human in levels and growth hormone/IGF1 axis and life span has also been demonstrated in mice [7].

Developmental ontogeny of organisms is programmed and co-ordinated by genes. No genes have been attributed deterministic role in survival span and genes never evolve to cause disadvantage to the organism [8]. Gene repair capacity is under both genetic as well as epigenetic control which does influence rate of aging. When genes encoding for molecules toward sustaining homeodynamics and homeostasis, cumulate damage and dysfunction, they become "virtual gerontogenes". Accumulating damages in form of mutations, epimutations, oxidation and aggregation of macromolecules are detrimental to longevity. Certain mutations accelerate aging changes, e.g. through altering insulin sensitivity and metabolism or dynamics of kinases, transcription factors and variety of biological pathways. Altered gene regulation, accumulation of somatic mutations, protein errors and modifications, imbalance of reactive oxygen species and free radicals, immune system deregulation and neuroendocrine dysfunction are involved in systemic homeodynamic failure. At the cellular level shortening of telomeres (the repeat neucliotide containing noncoding DNA at chromosomal ends that protect loss of important DNA), progressive demethylation in the DNA and consequent progressive compromise of renewal and repair system of cells are appealing mechanisms of aging.

Telomeres are DNA protein structures that form protective caps at ends of chromosomes providing safeguard from degradation and maintain genomic integrity. Telomerase enzyme adds DNA sequence repeats in telomere region at the end of chromosomes. Telomeres shorten with each cell division as process of aging. Accelerated loss of telomeres associates chronic age related diseases. Oxidative stress increases erosion of telomere length by oxidative modification of guanine in DNA at each cell division cycle in exposed cells. Shorter telomere length associates increase of body mass index and adiposity and age related pathologies [9]. While adiponectin correlates to longevity [10], disruptive leptin function results in metabolic decline and abnormal body fat distribution [11]. Fat plays important role in regulation of energy metabolism and immune responses. These effects are implemented through adipose tissue derived cytokines [12]. Gradual erosion of telomere length proportionately increase genetic instability over the life course. When critically short length is reached, cell stops dividing making no regenerative contribution to systemic maintenance [13].

### Pathophysiologic understanding of the aging process

Ongoing biomedical research suggests disturbed rhythm of lifestyle eg., night shifts and stressors, improper and excess eating, physical inactivity as provocative to multifaceted molecular mechanisms hastening the process of ageing. The cellular senescence displays arrested division and threatened survival. Aging organism displays progressive compromise in physiological functions and inability for homeostasis in face of stress, with increased risk of age related diseases. Many aspects of physiology and behavior are driven by intrinsic circadian rhythm which keeps synchrony among varied biological processes of the organism and co-ordinates them with the environment. Components of the biological clock are also crucially involved in modulating physiological response to genotoxic stress (specially, the oxidative stress), regulation of cell cycle, other proageing mechanisms, carcinogenesis etc. Components of energy homeostasis, notably in the adipocytes, exhibit circadian rhythm in energy balance, feeding behavior and regulation of body weight [14]. Dysegulation of glucose and lipid metabolism, insulin sensitivity, detoxification of xenobiotics, and such other activities in varied permutations and combination, aggravating ageing changes [15]. Psychological stress denotes overwhelming demand for constant adjustments to changing environment and its molecular consequences (e.g. stress hormones, insulin sensitivity, oxidative stress, inflammation, etc.). It links to unhealthy aging process [16, 17].

Negative effects of major stress on health are well documented. The aspects of stress-resistance however, have potential to guide strategies for delaying ageing, especially at cellular level. Exposure to short term stress may strengthen cellular adaptive response to stress (hormetic stress) with enhanced activity of molecular chaperones and other defensive mechanisms. Prolonged exposure to stress, on the contrary, may overwhelm compensatory responses [18].

### Ageing process: as mTOR driven

Among the earliest theories of ageing being driven by oxidative stress , presupposes intracellular nutrient and energy status as under constant scrutiny including, functional state of mitochondria and concentration of reactive oxygen species produced in them and co-ordinated flow of such information along diverse multiple

To cite this paper: Pandit A, Pandey Bahuguna D, Kumar Pandey A, Pandey BL. 2016. On the Physiology and Medicine of Aging. *J. Life Sci. Biomed.* 6(5): 106-114; www.jlsb.science-line.com

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signaling pathways subserves regulation of life span. The concept now prevalent is that ageing is not simple result of molecular damage (nor by free radicals), but results from a purposeless quasi programme (programme like but not a programme), partly driven by TOR (target of rapamycin). TOR in eukaryotic cells is a conserved member of phosphatidylinositol kinase-related kinases family. In the mammals rapamycin sensitive is the mTOR Complex 1mTORC1. mTOR signaling pathway is master regulator of cell growth and metabolism [19]. The quasi-programmed phenomenon of ageing is driven by the over reaction of the crucial nutrient sensing mTOR (mammalian target of rapamycin) gero-gene. mTOR driven ageing may be triggered or accelerated by decline or loss of responsiveness to activation of another energy sensing protein AMPK (AMP Kinase). AMPK is a critical gero-suppressor of mTOR. The age related infirmity, therefore reflects synergistic interaction with our evolutionary path to sedentarism. Physical inactivity chronically increases a number of mTOR activating gero-promoters (e.g. Food, growth factors, cytokines, insulin). These lead to defective design of central metabolic integrators such as mTOR and AMPK [20]. mTOR kinase integrates signals from nutrients, energy status, growth factors and a variety of stressors. It then affects rate of protein synthesis and degradation via autophagy, through number of downstream effects [21]. mTOR mediates the switch between growth and somatic stability to extend lifespan.

Nutrients (glucose, amino acids, especially leucine) and fatty acids directly activate the mTOR pathway and also increase insulin levels, which can additionally activate mTOR [22]. Modulation of mTOR signaling network affects mRNA translation, transcription, autophagy, ribosomal biogenesis, metabolism and cell survival, proliferation, cell size and growth, endoplasmic reticulum stress signaling and other stress responses [23]. Constitutively active TORC1 augments overall protein synthesis by increasing the speed of ribosomal elongation along transcripts. Such elongation induces different extents of translational errors with wrong incorporation of amino acids and defective folding of polypeptides, resulting in failure of protein quality control [24]. Rapamycin can inhibit TORC1 and inhibit translational activity. This will reduce waste-full formation of rough proteins during cell division that can impair lifespan of non-dividing cells. Rapamycin inhibitory effect is mediated via ribosomal S6Kinases.

Hyperfunction theory of ageing postulates that proximal cause of ageing is not the accumulation of random molecular damage, but overactive cellular functions (25). The nutrient sensing TORC1 signalling pathway seems to be a key contributor. Its inhibition by drugs or dietary restriction reduces translation, apparently allowing for better protein quality control. Accumulation of protein misfolding is thus reduced, which would otherwise cause age related pathologies. Reduced protein translation has been linked to increased life span [26].

Inhibition of mTOR is major way to maintain proteome and manage energy through the aging process. When cell energy content falls, that activates AMPK.AMPK directly phosphorylates TSC2 (Tuberous Sclerosis Complex 2), a negative regulator of mTORC1 and Raptor, an essential binding partner for induction of translation by mTORC1, resulting in inhibition of laters activity. The mTORCI1, S6K and AMPK constitute a complex feedback loop that is sensitive to dietary restriction and can redirect growth, metabolism and lifespan. Besides nutrients and growth factors, inputs about environmental stressors also influence control of growth. Osmotic stress, hypoxia, endoplasmic reticulum(ER), stress, genotoxic stress, mechanical forces and contraction (muscle movement) may all regulate mTORC1 activity. The growth hormone/insulin like growth factor 1(GH/IGF1), axis is strongly implicated in diet restriction effect. Reduced GH and IGF1 signaling associates with longer lifespan. Dietary Restriction (DR) reduces GH/IGF1 pathway signaling. There is key role of energy efficiency in determining health and longevity. Equally importantly, modulation of mTOR activity mediates proteostasis [27].

**Role of GCN2**: General Control Non depressible Kinase 2(GCN2 kinase) is another nutrient sensing pathway. It phosphorylates elF2-alfa transcription factor following nutrient and other stress.GCN2 has central role in stress management by activating key transcription factors such as ATF4 and NFkB in mammals. This stress induced reprogramming also determines life span [28]. For resource conservation and homeostasis under stress, the typical response is inhibition of protein synthesis with reprogramming of gene expression [29]. Inhibition of protein synthesis is attained through phosphorylation of elF2- α, the translation initiator factor 2.GCN2 is the only elF2-alfa kinase conserved through evolution that responds to nutrient depletion by regulating amino acid transport and metabolism. Other stressors also activate GCN2. The kinase also regulates lipid metabolism, oxidative stress resistance, feeding behavior, NFkB signaling, synaptic plasticity and memory.

**AMPK: The anti-ageing crusader:**
Adenosine mono phosphate activated protein kinase AMPK has emerged as key nutrient-sensor, with ability to regulate whole body metabolism. AMPK is activated by fall in cellular ATP or energy status, indicated by

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increased AMP/ATP ratio. Upon activation AMPK turns on, catabolic pathways to restore ATP levels. For the short time frame, glycolysis and fatty acid oxidation is promoted. For long time frame mitochondria content of cell and use of mitochondrial substrates as energy source are increased. Mitochondrial fitness is of great interest in ageing, as effective control of mitochondrial biogenesis, metabolism and turnover is crucial for healthy ageing [30].

AMPK activation is generally linked to the stimulation of metabolic responses in order to prevent metabolic and energy crisis, in situations where ATP synthesis is compromised. Such situations can be low nutrient availability and accelerated ATP consumption states, as exercise and fasting. Activated AMPK stimulates catabolic processes to generate ATP and inhibits ATP consuming anabolic processes that are not essential to immediate cell survival. The later include biosynthesis of fatty acids and sterols, cell growth and division. AMPK is final sensor for glucose and lipid metabolism and integrates nutritional and hormonal signals in peripheral tissue and the hypothalamus. It mediates regulation of food intake, body weight and glucose and lipid homeostasis [31].

### mTOR/ ULK 1 Regulation

AMPK signaling is major inducer of autophagy associated with the reduction of energy metabolism, autophagy can be activated by several stressors and seems to be associated with stress resistance. AMPK can regulate initiation of autophagosome formation via different signaling mechanisms. mTOR, the conserved serine/threonine protein kinase is potent inhibitor of autophagy. mTOR is involved in the signaling pathways induced by growth factors, abundant nutrients and sufficient energy states. AMPK can inhibit activity of mTOR complex (mTORC1) via two different mechanisms. It may directly phosphorylate a regulatory component of TORC1, Raptor. It may phosphorylate also TSC2 protein which also suppresses mTOR activity [32, 33]. AMPK dissociates mTORC1 from ULK1 complex to positively regulate autophagy indirectly. Directly, AMPK may bind ULK1 complex and phosphorylate it to stimulate autophagy [34].

### AMPK opposing effect of Insulin/IGF1 pathway, in respect to longevity

Insulin/IGF1 pathway also activates mTOR kinase and its downstream targets that regulate protein and ribosome synthesis. mTOR is detrimental as it accelerates ageing process by potent inhibition of autophagy. It is yet unsettled, if lifespan extension is conferred through activation of autophagy or by inhibition of other downstream targets of mTOR. A downstream target of insulin/IGF1-mTOR pathway, S6K1 kinase, can repress AMPK signaling. Deletion of S6K1 stimulates AMPK signaling allowing longevity promotion [35]. Insulin /IGF1 signalling associated with growth hormone regulation represents crucial somatotrophic axis in mammals. Kurosu et al. [36] demonstrated that over expression of klotho protein inhibited insulin/IGF1 signaling and increased life span. Functional deficiency of klotho enhanced premature ageing.

Insulin/IGF1 and AMPK signaling pathways are mutually inhibitory. Insulin/IGF1 pathway may inhibit many networking antiageing pathways of AMPK also. AMPK phosphorylates insulin receptor substrate 1 to inhibit insulin/IGF1 signalling [37]. AMPK however seems to enhance insulin/IGF1 signalling if that supports its metabolic function, e.g. glucose uptake, but represses energy consuming pathways.

AMPK activity is key for mitochondrial biogenesis, but declines with age. Another theory of ageing as consequent to decline in mitochondrial biogenesis is thus, promulgated. Multiple endogenous and exogenous factors regulate mitochondrial biogenesis through PPAR-gamma co-activator- 1alpha (PGC 1alpha). Activators of PGC-1alpha include nitric oxide, CREB (AMP response element binding protein) and AMPK. Activation of the AMPK pathway results in inhibition of the mTOR pathway, conferring possible longevity benefit.

Calorie restriction stimulates, while nutritional overload impairs AMPK activity and concurrently induces insulin resistance. New roles of AMPK beyond maintenance of energy metabolism during state of increased consumption have become known [20]. The rate of living theory of ageing emphasized that energy metabolism maintains homeostasis in the organism, whereas excessive energy consumption enhances ageing process. AMPK may co-ordinate preserving mechanisms as autophagy and increased stress resistance of tissue. AMPK upregulates thioredoxin expression to beat oxidative stress, and represses endoplasmic reticulum stress and inflammation. All these are antiageing in effect. AMPK responsiveness declines during ageing process leading to emergence of age related disorders. Age related changes in protein phosphatases may be basis for suppressed AMPK activation in ageing. Low grade inflammation of ageing also prominently impairs AMPK function.

### Multiple networking pathways of lifespan regulation

Ageing research reveals several signaling pathways simultaneously engaging for regulating aging and affecting lifespan. They are organized in integrated network, which has positive feedback effect on AMPK activity.

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CTRCs (CREB-regulated transcription co-activator 1), are coactivators of CREB mediated gene transcription and are targets of AMPK action. Inhibition of CRTC induced CREB activation is crucial regulator of ageing and longevity.

AMPK and SIRT1 (silent information regulators) signaling pathways are evolutionarily conserved energy sensors in cells responding to the increase in cellular AMP and NAD+ concentrations respectively(38). SIRT1 is major regulator of cellular energy metabolism and many components of cell survival, e.g. apoptosis, cell proliferation and inflammation. SIRT1 regulates stress resistance by directly modulating function of FaxO, p53 and NFkB signaling. The activation of AMPK stimulates functional activity of SIRT1 by increasing intracellular NAD+ concentration [39].

FaxO axis: the fork head transcription factors are involved in regulation of apoptosis, cell cycle, stress resistance, glucose and lipid metabolism and inflammation. The target genes of AMPK-FaxO3 pathway associated with longevity include those involved in defense against oxidative stress and DNA repair. The FaxO factors are integral to other longevity mechanisms as, inhibition of NFkB and age related inflammation. Stimulation of autophagy occurs both through FaxO andULK1/mTOR pathways.

FaxO factors and p53 exhist in complex interaction networks.p53 is one target protein of AMPK for control of expression as well as transactivation. Arf/p53 pathway activation promotes longevity via increased expression of antioxidant genes and autophagy. Mitochondria are major targets of several p53 actions which foster their integrity.

AMPK activation can inhibit signaling of master regulator transcription factors of inflammation [40]. AMPK-SIRT1-NFkB signaling pathway has major implication in controlling immune function. AMPK can stimulate Nrf2/SKN 1 signalling which acts in concert with the function of AMPK-FaxO3a axis in the generation of oxidation stress resistant phenotype of long lived animals.

**Biomedical contemplation on interventions for control of Life span:**

Autophagy is process of lysosome dependant intracellular recycling amino acids and energy resource particularly important in stress. Autophagy, insulin/IGF1 signaling, dietary restriction and reduced mitochondrial function, can modulate the proteostatic machinery to maintain stability of proteome. These mechanisms provide targets for therapeutic intervention [41]. Reducing insulin/IGF1 signaling is prime aging regulatory pathway, effected by protection against toxic protein aggregates in models of Alzheimers disease.

Pharmacologically upregulated autophagy increases clearance of toxic intracellular waste and enhanced lifespan. An understanding on regulatory signals of autophagy however bears serious gaps [42]. Deregulation of mTOR pathway is implicated in age associated disorders and mTOR inhibitor rapamycin treatment offers some curb, with scope for developments in multimodal combination regimens [19].

Pathways sensitive to dietary nutrients can be targeted to alter lifespan include, mTOR pathway, AMPK pathway, oxidative stress response through SRN1/Nrf2. Protein quality control through increased autophagy and general (hermetic) stress response.

**Benefit of Weight Reduction:** Under calorie restriction more body fat is lost influencing factors at interface of metabolism and inflammation [43]. Calorie restriction in aging rat improves carbohydrate metabolism by decreasing visceral fat and increasing insulin sensitivity [44]. Interventions that stimulate metabolism and/or activate white adipose tissue signaling mimick calorie restriction. Rapamycin is approved classical TOR-inhibitory agent with diverse potentials of imparting longevity. mTORC1 plays central role via S6K and 4E BP [45], that leads to decreasing over all translation allowing better fidelity of autophagy and mechanisms degrading misfolded and damaged proteins. Anti-inflammatory effect of rapamycin and role in depletion of small molecules such as endocannabinoids may also be relevant. Many clinically employed compounds, e.g. aspirin, reduce MTORC1 activity and also activate AMPK. Perhexiline, niclosamide, rottlerin and amiodarone also inhibit mTORC1, as does natural product phenylethyl isothiocynate (in brassicaceae vegetables).Many mTOR inhibitory drugs may target insulin/IGF1 signaling, pathway to increase lifespan.

**AMPK Activation:**

Mitochondrial dysfunction is an important component of age related diseases, e.g. type 2 diabetes, Alzheimers etc. AMPK acts as an energy sensor of cell and works as key regulator of mitochondrial biogenesis. Number of drugs and hormones directly or indirectly activate AMPK. Therapeutic exploration is however limited to only metformin that activates AMPK and suppresses mTOR, both life extending actions [46]. Many longevity genes are clustered in to nutrient sensing and metabolic adaptation pathways.

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### Hormetic stress response induction/preconditioning (47)

Adaptation and survival of cells and organism requires ability to sense proteotoxic insults and to co-ordinate protective cellular stress response pathways and chaperone networks related to protein quality control and stability. The toxic effects that stem from the misassembly or aggregation of peptides/proteins in cell are collectively termed proteotoxicity and result in metabolic, degenerative and neoplastic pathologies.

Strong interest lies in discovery of agents capable of inducing beneficial cytoprotective heat shock response and resistance against major stress. Low dose "HORMETIC" stress pathways include signaling mechanisms by which the carnitine system, mitochondrial energetics and activation of critical vitagenes, modulate signal transduction cascades conferring cytoprotection.

Modest free radical stress and lipid peroxidation products induce hermetic stimulation of energy metabolism pathways, mitochondrial biogenesis and upregulation of protein chaperones and antioxidant systems [48].

Protein thiols regulating cellular redox state are crucial mediator of multiple metabolic signaling and transcriptional processes. Pro-survival pathways are activated by vitagenes producing Hsps, glutathione, bilirubin with antioxidant and antiapoptotic property. Drugs capable of inducing Hsp response are of great interest, therefore.

SIRT1 deacetylates and activates transcription regulator PGC1-alfa that directs adaptive response to caloric restriction and exercise, promoting production of antioxidant and detoxifying enzymes. Heat Shock transcription factor 1(HSF1) is central regulator of gene expression of Hsps and other vitagenes in electrophile counterattack response (against reactive oxygen species and radicals). The vitagenes expression of this group is regulated by Keilch-like ECH-associated protein 1 Keap1/Nrf2 /ARE (antioxidant response element) pathway [49].

Variety of natural chemicals are inducers of Keap1/Nrf2/ARE pathway. Their common shared property is reactivity with sulfhydryl groups.

Hormetic mechanisms account for health benefits of phytochemicals. They generally activate adaptive cellular response pathways including kinases, and transcription factors that induce the expression of genes encoding antioxidant enzymes, protein chaperones, phase-2 enzymes, neurotrophic factors and other cytoprotective proteins. Sulforaphane (Brassicaceae), curcumin and resveratrol are inducers of Keap1/Nrf2/ARE pathway. Resveratrol also activates Sirtuin/FOXO pathway with increased antioxidant enzymes and survival protein buildup [50]. Other phytochemicals may activate hermetic transcription factors CREB (cyclic AMP response Element Binding protein) leading to induction of genes coding growth factors and antiapoptotic proteins [51].

**Carnitine and Acetyl Carnitine:** Mitochondrial content of endogenous acetyl carnitine is indicator of mitochondrial metabolism of acetyl CoA. Acetyl CoA acts on the acetylation status of mitochondrial proteins that increase mitochondrial transcription and protein synthesis. As a result, cytochrome B content increases with consequent increase in electron transport chain activity and stimulation of oxidative phosphorylation. Supplement should potentially restore aging related mitochondrial defect, therefore [52]. Acetyl carnitine (ALC) upregulated Hsps and expression of redox sensitive transcription factor Nrf2 following the hormetic low dose effect [53]. The evidence for modulation of mitochondrial biogenesis via transcriptional control of nuclear-respiratory factor NRF1 [54], highlight role of carnitine system in mitochondrial metabolism.

Carnitine system functions as vitagene prototype for processes of cell survival that require energy for cellular stress response and redox homeostasis [55].

### Redox Biology Paradigm

As per redox biology paradigm, antioxidants primarily serve to modulate complex networks controlling cell signaling and metabolism. Central idea is that redox active mediators,eg nitric oxide, hydrogen peroxide and lipid radicals act as site specific mediators of cell signaling, protein cystein residues are the sensors or receptors of these different redox mediators AND the" traditional" antioxidants, e.g. glutathione, α-tocopherol serve the essential functions of insulating distinct redox signaling domains in the cell from cross-talk.

Dysregulation of these pathways would influence metabolism, autophagy, cell growth and repair. Most successful translational use of these pathways is of course, the selective activation of Keap1/Nrf2 system, sure to yield new drugs. Lifespan enhancing metformin effect is also dependant on oxidative stress transcription factor Nrf2 [56]. Mechanisms of hormetic triggering of endogenous cellular defense pathways include, sirtuins and Nrf2 and related pathways that integrate adaptive stress. Emerging role of nitric oxide, carbon monoxide and Hydrogen sulphide gases in hormesis based neuroprotection and their relation to radical dynamics in membrane and redox signaling is drawing perticular research attention [57].

## CONCLUSION AND PROSPECTS

Modern technical advances applied in aging research span across, nanotechnology, bioinformatics, single cell analysis, molecular heterogeneity analysis, analyses of epigenetic regulators of stress, analysis of post synthetic modification of biomolecules etc. Scientific gerontology, envisages rational steps to slow down aging process and rejuvenate physiological function. Redesigning of structural and functional units of body by manipulations at level of genes, gene products, macromolecular interactions, interaction with the milieu etc. are being worked upon. Their practical application in checking or reversing aging changes, is currently, far too distant.

Biochemical interactions and tradeoffs between stressor and biologic cellular responses, including pleotropic effects require thorough learning. A range of usable physical, chemical or biological stressor options with feasible technology for application must become available and must also conform to safety and efficacy standards like drugs. The task of advancing hormesis principle for practical use requires competent calibration and monitoring of magnitudes appropriate for different stressor interventions and ways to monitor them, including need for defining optimal stressor dose for given stage of aging process. Bioactive constituents from plant food have shown novel modulatory potential for transcription phenomena [58]. Since redox regulation and transcription factor cystein modification are central to both Keap1/Nrf2/ARE pathway and the Heat shock response, such multi target agents, all of which are reactive with sulfhydryl groups, are ideal for simultaneously manipulating ageing pathways to achieve synergistic benefits. Exploiting the ability of small molecules, many of them from diet and safe, to stimulate defensive stress response is highly aspired, and the ultimate objective ought be adding life to years rather than years to life [59].

### Conflict of interest statement
There is no conflict of interest among the authors.

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To cite this paper: Pandit A, Pandey Bahuguna D, Kumar Pandey A, Pandey BL. 2016. On the Physiology and Medicine of Aging. *J. Life Sci. Biomed.* 6(5): 106-114; www.jlsb.science-line.com

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