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Review

# Cellular stress responses, hormetic phytochemicals and vitagenes in aging and longevity ☆

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ABSTRACT

Modulation of endogenous cellular defense mechanisms represents an innovative approach to therapeutic intervention in diseases causing chronic tissue damage, such as in neurodegeneration. This paper introduces the emerging role of exogenous molecules in hormetic-based neuroprotection and the mitochondrial redox signaling concept of hormesis and its applications to the field of neuroprotection and longevity. Maintenance of optimal long-term health conditions is accomplished by a complex network of longevity assurance processes that are controlled by vitagenes, a group of genes involved in preserving cellular homeostasis during stressful conditions. Vitagenes encode for heat shock proteins (Hsp) Hsp32, Hsp70, the thioredoxin and the sirtuin protein systems. Dietary antioxidants, such as polyphenols and L-carnitine/acetyl-L-carnitine, have recently been demonstrated to be neuroprotective through the activation of hormetic pathways, including vitagenes. Hormesis provides the central underpinning of neuroprotective responses, providing a framework for explaining the common quantitative features of their dose response relationships, their mechanistic foundations, their relationship to the concept of biological plasticity as well as providing a key insight for improving the accuracy of the therapeutic dose of pharmaceutical agents within the highly heterogeneous human population. This paper describes in mechanistic detail how hormetic dose responses are mediated for endogenous cellular defense pathways including sirtuin, Nrfs and related pathways that integrate adaptive stress responses in the prevention of neurodegenerative diseases. This article is part of a Special Issue entitled: Antioxidants and Antioxidant Treatment in Disease.

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## 1. Introduction

In recent years, studies have shown that aging (more correctly defined as longevity) is due to a complex genetic and cellular process that seems to be partly regulated by sirtuins [1,2] the human and murine homologs of the *Saccharomyces cerevisiae* Sir2 that control both replicative and overall lifespan [3,4]. Findings have also shown that this gene family regulates longevity in *Caenorhabditis elegans* and *Drosophila melanogaster* [1,2], suggesting that there is an evolutionary need in many different complex species to preserve these proteins in the cells. Sirtuins, which are classified as class III histone deacetylases, differ from traditional class I and II histone deacetylases [5,6]. They differ from conventional HDACs in that their substrates range from metabolic enzymes to structural proteins and histones [7–9].

The activity, stability and intracellular location of nearly all proteins depend on post-translational modifications (PTMs) that include phosphor-ylations, acetylations, sumoylations, ubiquitinations, ADP-ribosylations and nitrations [10]. Most of these highly dynamic processes occur as a result of opposing enzyme activity (e.g. kinases vs. phosphatases, acetylases vs. deacetylases, etc.). Numerous studies have demonstrated that PTM signaling pathways play a significant role in crosstalk between the cell and its environment and in enabling cells to become flexible towards change [10]. For this reason, nicotinamide adeninedinucleotide (NAD) has aroused new interest as it is an

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important substrate for a number of enzymes that catalyze a set of post-translational modifications, such as deacetylationorADP- ribosylation. The role of NAD in these regulatory processes differs from its involvement in energy metabolism since it is based on the ability to act as an ADP-ribose donor, thus requiring NAD re-synthesis to avoid depletion of the intracellular NAD pool [11]. The fundamental role of NAD in energy metabolism and protein modification has an important physiological influence on the control of cell metabolism, cell death and longevity [12,13].

Since transient post-translational modifications such as acetylation, phosphorylation and ubiquitination determine a rapid and efficient cell response to intra- and extracellular stimuli, they play a central role in cell signaling cascades. Recent research has identified a PTM involving the attachment of a SUMO peptide, a process frequently referred to as SUMOylation that occurs in signaling pathways both within the nucleus and other parts of the cell. SUMO attachment is thought to be involved in a number of cell processes, e.g. transcription, nuclear transport, DNA repair, mitochondrial activity, plasma membrane ion channels, cell cycle and chromatin structure. Although its function is as diverse as its substrates, modification of a protein substrate by SUMO generally alters its interactions with other protein and DNA molecules [14].

A prediction of oxidative stress theory of aging is that, among species, differential rates of aging may be apparent on the basis of intrinsic differences in oxidative damage accrual. Although widely accepted, exceptions to this theory, mostly related to the specificity of species, strain and even tissues of investigation, are occurring more frequently. Proteins are a principal target for oxidative damage and cysteine residues are highly sensitive to reversible and irreversible oxidation. To adapt and survive, cells and organisms need to sense proteotoxic insults and to protect themselves by coordinating cellular stress response pathways and chaperone networks related to protein quality control and stability. The mis-assembly or aggregation of proteins or peptides, in any cell type leads to toxic effects or proteotoxicity. Despite the abundance and apparent capacity of chaperones and other components of homeostasis to re-establish folding equilibrium, cells do not appear to adapt well to chronic proteotoxic stress which increases in cancer, metabolic and neurodegenerative diseases. The use of drugs to modulate cellular stress response pathways is emerging as a treatment for human diseases such as neurodegenerative disorders, cardiovascular disease and cancer. For medical intervention to be successful, the dose must be right, but it can be extremely difficult to achieve this goal on account of human inter-individual variation in age, gender, diet, exercise, genetic factors and health status. The past decade has witnessed considerable progress in the nature of the dose response in and adjacent to the therapeutic zones. Long-standing ideas about the nature of the dose–response in a low dose zone, have been challenged by the hormetic dose–response which could significantly influence the design of pre-clinical studies, clinical trials and optimal patient dosing strategies in the treatment of numerous diseases. The broad cytoprotective properties of the heat shock response have aroused strong interest in discovering and developing pharmacological agents that can induce stress responses, including carnitines. This paper illustrates the mechanisms by which hormetic dose responses are mediated for endogenous cellular defense pathways. These include the possible signaling mechanisms through which, by interplaying metabolism, mitochondrial energetics and activation of critical vitagenes, the carnitine system modulates signal transduction cascades that provide cytoprotection against chronic degenerative damage associated with aging and neurodegenerative disorders.

## 2. The mitochondrial theory of aging

Mitochondria are membrane-enclosed organelles found in eukaryotic cells where they generate ATP as a source of chemical energy. ATP synthesis occurs through the respiratory or electron transport chain (ETC) located at the inner mitochondrial membrane, and consists of five protein complexes (Complexes I–V) [15–18].

Besides supplying ATP, mitochondria are involved in many other cell functions including the biosynthesis of heme, cholesterol and phospholipids [16] and initiation of the apoptotic process [18]. According to the endosymbiosis theory, mitochondria are organelles that evolved from purpurbacteria approximately 1.5 billion years ago. Mitochondria have their own genome [17,19] and can replicate and transcribe their DNA semi-autonomously. Mitochondrial DNA (mtDNA), like nuclear DNA, is constantly exposed to DNA damaging agents. For many years it was thought, in mtDNA repair, that excessively damaged mtDNA molecules were simply degraded and replaced by newly-generated successors copied from undamaged genomes. However, findings now indicate that mitochondria possess the machinery needed to repair genome damage caused by endogenous or exogenous harmful agents. Harman [20,21] suggested that free radicals are involved in the aging process and that mitochondria-derived ROS may influence cellular aging [21]. The treatment of IMR-90 fibroblasts with N-tertbutyl hydroxylamine (an antioxidant recycled by the mitochondrial electron-transport chain), initially gave support to the theory of mitochondrial involvement in cellular senescence. N-tert-butyl hydroxylamine extends fibroblast replicative capacity and delays changes in mitochondrial function due to age by reducing ROS production, preservation of mitochondrial membrane potential and by increasing the cellular GSH/GSSG ratio [16]. A more recent study has demonstrated that mitochondria derived ROS play an important and direct role in the shortening of telomeres and the onset of senescence [16]. Other findings have proposed that mitochondrial dysfunction leads to mitochondrial biogenesis, thereby increasing the number of cell sites for the production of ROS that causes telomere shortening [15,18].

On account of its elevated mutagenic propensity, accumulation of mtDNA during life is thought to be a major cause of age-related disease. The lack of introns and protective histones, limited nucleotide excision and recombination DNA repair mechanisms, location in proximity of the inner mitochondrial membrane with exposure to an enriched free radical milieu are all factors contributing to a mutation rate that is 10-fold higher in the mtDNA than in the nuclear DNA (nDNA) [22]. Furthermore, considerable evidence suggests that mtDNA mutations increase as a function of age, reaching the highest levels in brain and muscle. It has been reported that more than twenty different types of deletions accumulate in aging human tissues. The first report on an age-related increase in a mtDNA deletion was found in elderly brain and in Parkinson's disease [22]. This deletion, called the “common deletion”, was observed between 13-bp sequence repeats beginning at nucleotides 8470 and 13447, removing almost a 5-kb region of mtDNA between ATPase 8 and the ND5 genes. The deletion takes place during replication of the mtDNA, the missing sequence encodes for six essential polypeptides of the respiratory chain and 5 tRNAs, and has been associated with several clinical diseases, such as chronic progressive external ophthalmoplegia and Kearns Sayre syndrome. In a comparison with age-matched controls, an association was found between numerous age-related disorders and higher levels of mtDNA mutations. In the central nervous system (CNS), patients with Parkinson's disease were found to have a 17 times higher level of the common deletion in the striatum, compared to age-matched controls. There is also evidence of higher levels of this deletion in patients with Alzheimer's disease, parallelling increased levels in the oxidized nucleotide 8-OH-dG [15]. More than 100 mutations of mtDNA have been associated with human diseas [23]. Phenotypic manifestation of mtDNA mutations is extremely broad ranging from oligosymptomatic patients with isolated deafness, diabetes, ophthalmoplegia, etc., to complex encephalomyopathic disorders that may include dementia, seizures, ataxia, stroke-like episode and so on. There is also a wide range of genotype variants, with

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