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Ian James Martins
Edith Cowan University, i.martins@ecu.edu.au

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Research & Reviews: Neuroscience

Inactivation of Endoplasmic Reticulum Stress and the Prevention of Neurodegenerative Diseases

Ian James Martins[1,2,3*]

[1]Centre of Excellence in Alzheimer's Disease Research and Care, Sarich Neuroscience Research Institute, Edith Cowan University, Australia

[2]School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Australia

[3]McCusker Alzheimer's Research Foundation, Hollywood Medical Centre, Australia

Mini Review

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*For Correspondence:

Dr. Ian Martins, School of Medical and Health Sciences, Edith Cowan University, Western Australia, Australia, Tel: +61863042574

E-mail: i.martins@ecu.edu.au

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ABSTRACT

Biotherapeutics and nutritional therapy are essential for the treatment of endoplasmic reticulum (ER) stress in diabetes and neurodegenerative diseases. Oxidative stress and nutrient excess may induce ER stress associated with activation of the unfolded protein response and connected to cell death. The heat shock gene Sirtuin 1 (Sirt 1) is important to the heat shock response with amyloid beta aggregation associated with the induction of mitophagy and ER stress in neuron cells. Genomic medicine that activates nuclear Sirt 1 is essential for the prevention of mitochondrial apoptosis and ER stress. Inhibitors such as drugs, alcohol, excess caffeine and palmitic acid may override the therapeutic effects of Sirt 1 activators with relevance to ER stress associated cell life and death decisions.

TEXT

Biotherapeutics have become of importance to global chronic diseases to prevent accelerated aging associated with uncontrolled toxic cellular reactions that determine accelerated cell death. In the global burden of disease connections between nutritional therapy is now critical to stabilize obesity, diabetes and neurodegenerative diseases. Nutritional diets are essential to maintain or stabilize neurodegenerative diseases with dietary interventions such as glucose and fat consumption critical to determine biotherapeutics important to the treatment of metabolic disease and neurodegenerative diseases. Genomic medicine for the treatment of neurodegenerative disease has become of major interest to the scientific and medical community with nuclear alterations important to mitochondrial and endoplasmic reticulum (ER) connections with genomic medicine associated with the treatment of ER stress in neurons associated with unfolded protein response (UPR) and calcium dyshomeostasis [1-3].

Major interests in amyloid beta aggregation [4-6] and trigger of ER stress and UPR is now relevant to various neurodegenerative diseases. The ER as an organelle is involved in protein folding, quality-control system and protein secretion in association with calcium and lipid homeostasis [7]. Stimuli such as oxidative stress, nutrient excess (glucose, fatty acid) may lead to accumulation of unfolded /misfolded proteins with the induction of ER stress. The accumulation of misfolded proteins in the ER activates the UPR sensors such as activating transcription factor 6 (ATF6), double-stranded-RNA-dependent protein kinase-like ER kinase, and inositol-requiring protein 1 (IRE1α) associated regulation of transcription factor X-box binding protein 1 (XBP-1) an important player in UPR signalling and ER stress [7].

Genomic medicine in biotherapeutics and nutritional therapy [8] is essential in the treatment of ER stress in neurodegenerative disease and diabetes [1-3,9] with excess glucose and fatty acids associated with UPR activation and connected to ER stress and cell death. The calorie sensitive gene Sirtuin 1 (Sirt 1) is a nicotinamide adenine dinucleotide (NAD^+) dependent class III histone deacetylase (HDAC) and as a heat shock gene is involved in the deacetylation of heat shock factor 1 and regulation of heat shock protein (HSP) amyloid beta aggregation [10]. Sirt 1 targets the deacetylation of transcription factors to nuclear receptors with its critical involvement in insulin resistance [11], heat shock response [10] and ER stress [12,13]. Sirt 1 is involved with the deacetylation of XBP-1 and ATF 4 regulation of ER stress in various mammalian cells and human diseases [14-16]. Sirt 1 is a regulator of PGC1 alpha and mitochondrial biogenesis [17] with PGC-1alpha connected to ATF4 and XBP-1 in glucose and cellular metabolism [18,19]. The heat shock response and Sirt 1[10] play an important role in the induction of ER stress with core body temperature important in the regulation of ER stress and programmed cell death.

The connections between the mitochondria and ER stress **Figure 1** is determined by Sirt 1/p53 transcriptional regulation of the nuclear-mitochondria interaction [17] with relevance to mitochondria-ER interactions [20] in calcium homeostasis and induction of programmed cell death [21]. Sirt 1 may primarily involve p53 regulation [14] of ER stress by deacetylation of IRE alpha/XBP1 or deacetylation of p53/XBP1 in neurodegenerative diseases [22,23]. Sirt 1 may be regulated by the UPR sensors ATF4/ATF6 with relevance to ER stress induced cell damage [13-16]. Genomic medicine to stabilize the heat shock gene Sirt 1 with the prevention of mitochondia-ER stress may be associated with the consumption of specific Sirt 1 activators and inhibitors [10]. These activators are essential to maintain the peripheral sink amyloid beta clearance pathway [6] to prevent accelerated HSP-amyloid beta aggregation associated with ER stress in the periphery and brain [10]. Sirt 1 activators such as zinc, resveratrol, leucine, alpha lipoic acid, taurine and rutin [10,24,25] are critical for the prevention of ER stress **Figure 1** with these Sirt 1 activators important as intracellular nutrients for the endoplasmic reticulum [26-31].

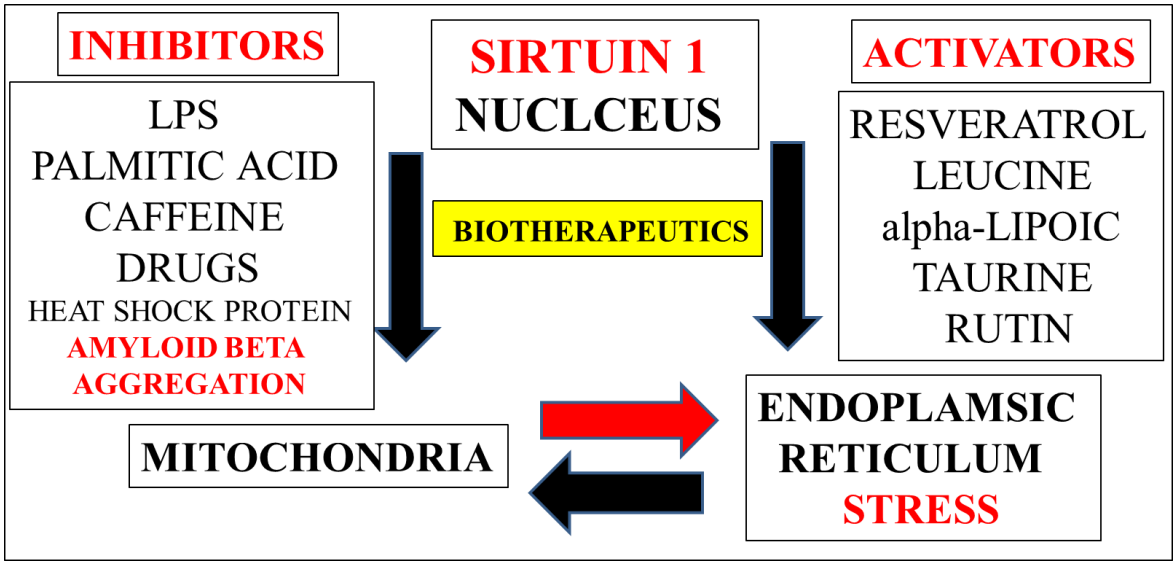

Figure 1. The interconnections between the nuclear-mitochondria interaction

It is important to prevent ER stress in neurodegenerative diseases. Sirt 1 activators are critical to prevent mitophagy induced ER stress (Red Arrow) relevant to global chronic diseases and neurodegenerative diseases. Excess caffeine, food quality safety, specific drugs and core body temperature disturbances should be assessed to prevent accelerated ER stress (Black Arrows) and decisions associated with cell death in neurodegenerative diseases.

Sirt 1 inhibitors [10] such as bacterial lipopolysaccharides (LPS), excess caffeine, palmitic acid [32] and various drugs [33,34] are associated with ER stress with Sirt 1 inactivation **Figure 1** relevant to defective caffeine, drug metabolism and neurodegenerative disease [35]. Nutritional biotherapy such as excess glucose, fatty acid consumption (palmitic acid) and food quality [36] are critical to genomic medicine and control of the mitochondria-ER interaction in neuron cells. The dose and therapeutic use of Sirt 1 activators may be effective ER nutrients but not effective nuclear Sirt 1 activators associated with control of the nuclear-mitochondria-ER stress pathway **Figure 1**. Excess caffeine consumption may inactivate biotherapeutics for the mitochondria-ER stress pathway with caffeine interference with calcium dyshomeostasis [37] relevant to global chronic and neurodegenerative diseases. Biotherapeuctics that involve mitochondrial nutrients [38] to prevent mitochondrial-ER stress programmed cell death may be ineffective in the presence of Sirt 1 inhibitors such as excess caffeine, LPS, drugs and palmitic acid.

The role of Sirt 1 in chronic diseases has become of major concern with Sirt 1 repression involved in non alcoholic fatty liver disease, obesity, diabetes and neurodegenerative diseases [17,38-40]. The plasma measurement of Sirt 1 [35] is critical to delay ER stress and the induction of various chronic diseases connected to neurodegenerative diseases. Inactivation of Sirt 1 may lead to mitophagy and multiple organ diseases [41] with irreversible programmed cell death. Core body temperature is critical to prevent Sirt 1 inactivation [10] and autoimmune disease in chronic diseases. Consumption of Sirt 1 activators are essential to prevent ER stress and the induction of acute cardiovascular disease, stroke and neurodegenerative disease [38,42].

CONCLUSION

Biotherapeutics in neurodegenerative disease have become important to prevent mitophagy and ER stress that leads to neuron apoptosis. The role of Sirt 1 activators are essential to maintain the nuclear and mitochondria interaction and the prevention of ER stress. Genomic medicine for the treatment of ER stress is critical to global chronic disease and connected to neurodegenerative disease. Nutritional therapy with low glucose/fatty acid diets are required to prevent ER stress with critical identification of specific Sirt 1 inhibitors such as palmitic acid and toxic drugs involved in the induction of ER stress and neurodegenerative disease.

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