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Heat Shock Gene Sirtuin 1 Regulates Post-Prandial Lipid Metabolism with Relevance to Nutrition and Appetite Regulation in Diabetes

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New discoveries in medicine are required to understand the importance of appetite regulation that is associated with the overconsumption of foodin Type 2 and Type 3 diabetes. Food restriction in diabetes is essential to maintain the hepatic metabolism of dietary fat with relevance to defective post-prandial lipid metabolism and to the global non alcoholic fatty liver disease (NAFLD) epidemic [1,2]. Premature brain aging has become important with the development of Type 3 diabetesand Alzheimer's disease [3] that is associated with repression of the anti-aging gene Sirtuin 1 (Sirt 1) relevant topost-prandial lipid metabolism, amyloid beta metabolism (peptide involved in amyloid beta plaques)and circadian rhythm abnormalities in the brain biological clock associated with the development of NAFLD.Nutritional interventions such as very low carbohydrate diets have become important to diabetes (Figure 1) to reverse defective post-prandial lipid and amyloid beta metabolism without atherogenic lipoprotein formation [4,5] with the prevention of accelerated atherosclerosis in various communities. Western diets that are high in fat and glucose are linked to diabetes and NAFLD with anti-aging geneSirt 1 transcriptional dysregulation [6] in cell and tissues associated with, hyperglycemia, mitochondrial apoptosis and delayed hepatic fat and amyloid beta metabolism (Figure 1).

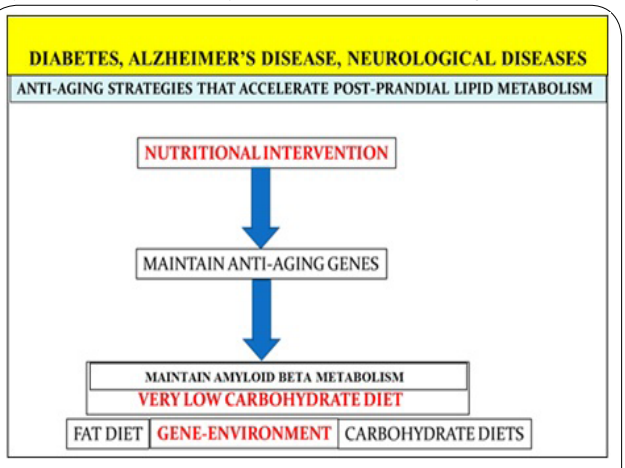

Figure 1: In diabetes and neurodegenerative diseases nutritional interventions are required to activate the anti-aging gene Sirt 1 and prevent defective liver lipid metabolism (NAFLD) and amyloid beta metabolism. Diets that are low in fat such as very low carbohydrate diets activate the calorie sensitive gene Sirt 1 with glucose metabolism connected to accelerated hepatic lipid/amyloid beta metabolism in diabetes and neurodegenerative diseases.

Accelerated aging that disturbs the brain to liver crosstalk [6,7] involves the calorie sensitive gene Sirtuin 1 (Sirt 1) that is a nicotinamide adenine dependent dinucleotide class III histone deacetylase involved in the prevention of defective post-prandial metabolism and NAFLD [8-10]. The intake of fat is sensitive to the regulation of the heat shock gene Sirt 1 that is responsible for the metabolism of heat shock proteins(HSP) [3] that are produced by living cells in response to temperature regulation above physiological levels [11, 12]. Heat shock proteins facilitate the rapid metabolism by the liver of amyloid beta by preventing its misfolding and aggregation in the brain [3,13,14]. Sirt 1 is also sensitive to α-synuclein metabolism [15] and relevant to temperature alterations in α-synuclein oligomer and amyloid beta formation [16, 17].

Down regulation of Sirt 1 expression and activity disturbs the nuclear and mitochondria interactions with effects on the metabolism of fatty acids, glucose and amyloid beta metabolism in diabetes [16, 17]. Heat shock protein (HSP) induces endoplasmic reticulum stress (ER) stress with delayed metabolism of amyloid beta/ α-synuclein oligomers associated with liver disease linked to NAFLD and neurodegenerative diseases. ER stress is associated with programmed cell death with relevance to mitochondrial apoptosis, defective post-prandial lipid metabolism and NAFLD [18-22] with Sirt 1 regulation of PGC1 associated with mitochondrial biogenesis after ingestion of various fat diets. Sirt 1 regulates HSP by deacetylation of heat shock factor (HSF) via peroxisome proliferator-activated receptor gamma co activator 1-alpha(PGC1α) as a critical repressor of HSF1-mediated transcriptional programs [23,24]. Sirt 1 is involved in body temperature regulation of the mammalian target of rapamycin(mTOR) signaling through the tumor suppressor tuberous sclerosis complex 1 with relevance to the expression of hepatic PGC-1α and fibroblast growth factor 21 (FGF21) [25-29].

Sirt 1 regulation of cell senescence in diabetes involves cell ontogeny with transcriptional ontogeny defective via the transcriptional factor p53 involved in the regulation of various other anti-aging genes [30-35] such as klotho, p66shc, FOXO3a, micro RNA 34a [18] and transcription factors involve post-prandial lipid metabolism, metabolic activity, insulin resistance, cellular ontogeny, inflammation

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and xenobiotic metabolism[18,36] (Figure 2). In the developing and developed world diabetic treatment has become important with defective Sirt 1 gene expression determined by miR-34a [18, 36] related to defective cell proliferation in the brain and the liver (Figure 2). Defective thermoregulation may be relevant to ingestion of food (Sirt 1 defective)with inappropriate post-prandial lipid and amyloid beta metabolism that inactivate magnesium therapy that may now be relevant to HSP and amyloid beta metabolism with relevance to myocardial infarction [3,37].

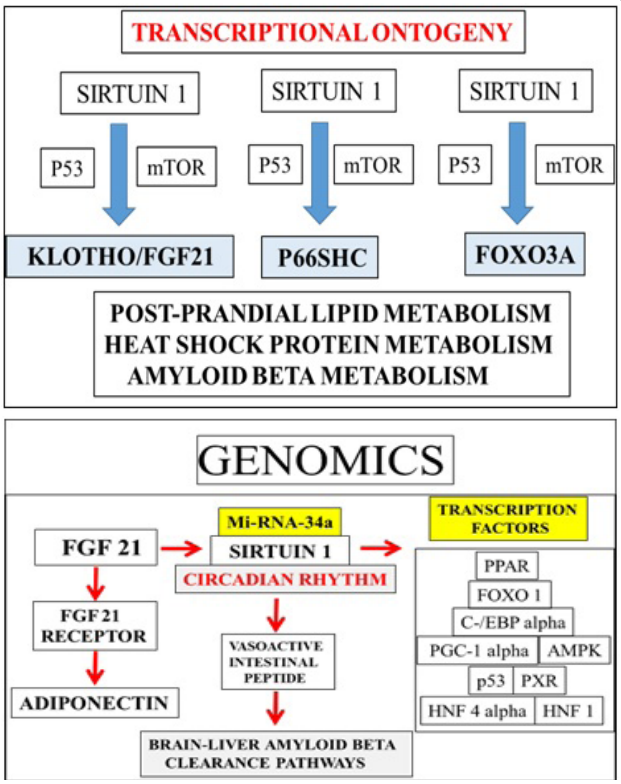

Figure 2: Appetite regulation in diabetes involve the maintenance of the heat shock gene Sirtuin 1 that is essential for thermo regulation function and hepatic lipid metabolism. The repression of the anti-aging gene Sirt 1 involves p53/mTOR dysregulation of the other anti-aging genes (klotho, p66shc, FOXO3a) associated with hepatic lipid, heat shock protein and amyloid beta metabolism. FGF 21 treatment in diabetes has become important to NAFLD [38] and myocardial infarction treatment [39, 40] but defective cell transcriptional ontogeny in the liver and brain related to mi-34a inhibition of Sirtuin 1/transcription factors interactions inactivates hepatic lipid metabolism with the induction of NAFLD, defective amyloid beta metabolism and neurodegenerative disease.

Food restriction and fasting regulate Sirt 1 and FGF21 involved in the prevention of the metabolic syndrome and maintenance of high density lipoprotein levels [39-41]. FGF21 therapy [42, 43] in Type 2 and Type 3 diabetes may be ineffective with the development of cardiac ageing with relevance to core body temperature regulation that is determined by mi-34a/Sirt 1 gene expression with low adiponectin levels [36,44] (Figure 2). Healthy diets that maintain Sirt 1 activity in the brain and liver have become important to many diabetics in the developing and developed world with relevance to food technology that involve the hepatic metabolism of bacterial lipopolysaccharides (LPS) that has become important to the reversal of Type 2 diabetes and Type 3 diabetes [45, 46]. Plasma LPS and xenobiotic levels [47] have risen in various developed countries and consumption of activators such as leucine, pyruvic acid and magnesium may supersede LPS inhibition of Sirt 1 [18, 37] with prevention of defective cell transcriptional ontogeny and membrane transformations in the brain and liver [45, 46]. Appetite dysregulation in diabetes may require these activators of Sirt 1 with relevance to the maintenance of neurons and the treatment of Type 3 diabetes with defective apelinergic system that involves thermo dysregulation.

Conclusion

Dyslipidemia is one of the key risk factors for cardiovascular disease in diabetes. The management of dyslipidemia in diabetes continues to remain controversial and improvements in the characteristic diabetic dyslipidemia of high triglyceride and low HDL may not indicate that defective cell ontogeny is underway early in life. Diabetes and defective hepatic cell transcriptional programs induce delayed post-prandial lipid metabolism associated with Western diets rich in fat and glucose. The clinical management of diabetes in the young and elderly now not only involves appetite regulation with calorie restricted diets that maintain the heat shock gene Sirt 1 expression but also careful core body temperature (37°C) to activate hepatic and brain Sirt 1. The biological active release of FGF21 is connected to Sirt 1 activation and glucose homeostasis with relevance to treatment of dyslipidemia, NAFLD, cardiovascular disease and neurodegenerative diseases. Consumption of Sirt 1 inhibitors such as alcohol, suramin and palmitic acid should be avoided to prevent defective liver and brain cell ontogeny in the young and the elderly to prevent hyperglycemia induced oxidative stress and myocardial infarction.

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