Single Gene Inactivation with Implications to Diabetes and Multiple Organ Dysfunction Syndrome

Abstract
Nutritional and environmental epigenetics are involved with the repression of anti-aging genes that are linked to the chronic disease epidemic. Unhealthy diets inactivate the calorie sensitive gene Sirtuin 1 (Sirt 1) involved in epigenetic processes that promote immune system alterations, mitochondrial apoptosis, Non-alcoholic Fatty Liver Disease (NAFLD), diabetes and Nitric Oxide (NO) modification with relevance to core body temperature involved with appetite regulation, glucose homeostasis and hepatic xenobiotic metabolism. The interplay between NO and epigenetics has attracted interest with relevance to autoimmune disease and mitophagy that has become of critical concern to diabetes and the development of MODS. Future research involved with nutritional research and the maintenance of Sirt 1 transcriptional control is critical to the prevention of MODS that is linked to the immune system and insulin resistance. In the developing world bacterial lipopolysaccharides a critical repressor of Sirt 1 is now involved with NAFLD and various organ diseases relevant to tissue accumulation of xenobiotics from various environments with relevance to MODS and the global chronic disease epidemic.

Keywords: Diet; Sirtuin 1; Suprachiasmatic nucleus; Circadian; Xenobiotic

Introduction
Specific genes that are involved in epigenetics are sensitive to nutritional regulation, oxidative stress and the development of insulin resistance that can result from changes in cellular chromatin structure, DNA methylation and histone modifications with relevance to the global chronic disease epidemic [1-7]. Epigenetic modifications in specific cells such as the brain, adipose tissue and liver are more sensitive than other tissues [4]. Epigenetic modifications induced by unhealthy diets or environmental xenobiotics involve the anti-aging genes [8] that alter gene expression in the Suprachiasmatic Nucleus (SCN) in the brain [4,5] with effects on peripheral lipid metabolism and energy expenditure that involve the adipose tissue and liver with immune alterations [9-11] that determine the survival of cells in various tissues (Figure 1).

In the developing world with urbanization and increased access to food epigenetic and immune system alterations are associated with increased chronic disease susceptibility. Down regulation of anti-aging genes reduces hepatic xenobiotic (soil, air, water) metabolism and may promote multiple organ dysfunction syndrome (MODS) [12-14]. These toxic compounds are involved in nuclear receptor dysfunction such as the nuclear receptor Sirtuin 1 (Sirt 1) [5] that determines the survival of man and various species with relevance to toxicity to mitochondria in neurons [15,16] and cells in peripheral tissues [17-27].

Sirt 1 Repression with Accelerated Brain Aging and Organ Disease
The defective gene in various chronic diseases [28-38] is Sirt 1 a NAD(+) dependent class III histone deacetylase (HDAC) protein that targets transcription factors to adapt gene expression to metabolic activity, insulin resistance and inflammation. Interests in Sirt 1 have increased since it may override the effects of other anti-aging genes such as Klotho, p66Shc (longevity protein) and Fork head box proteins (FOXO1/FOXO3a) [8]. In adipose tissue gene expression profiles of Klotho, p66Shc (longevity protein)
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Maintenance maintains chromosome stability and its regulation of telomere length may be nullified by increased xenobiotics with telomere length shortening [4,5,67,68].

Sirt 1 effects on p53 gene regulation supersede micro RNA (miRNAs) regulation of p53 [69-71] with relevance to their role in various chronic diseases [17-27]. MiRNAs such as miR-34a [72] and miR-122, miR-132 [73,74] inhibit Sirt 1 and may inactivate p53-miRNA interactions. Interference with cellular miRNA by diet, drugs and xenobiotics are now relevant to Sirt 1/p53 dysregulation and cell apoptosis. MiRNAs may regulate Sirt1/p53 regulation of nuclear receptors such as peroxisome proliferator-activated receptor-gamma co-activator (PGC-1 alpha) and Pregnane X Receptor (PXR) with interference with xenobiotic metabolism relevant to mitochondrial biogenesis [4,5,75,76].

Other nuclear receptors such as peroxisome proliferator-activated receptor gamma (PPAR gamma), PPAR alpha, beta/ delta, liver X receptors (LXR)/liver receptor homolog-1 (LRH-1) involved in energy, glucose, cholesterol, fatty acid metabolism are regulated by Sirt1 with connections between hepatic nutrient and xenobiotic metabolism (PXR, CAR and xenobiotic sensing nuclear receptor) involved in the expression of cytochrome p 450 (CYP 450) enzymes [5]. Increased levels of xenobiotics in the plasma and various tissues may lead to increased reactive oxygen species associated with low Sirt1 activity [77,78] which is associated with chronic diseases in developing countries.

**SCN dysfunction in diabetes with relevance to MODS**

Insulin resistance and beta cell dysfunction has been associated with the development of MODS [79,80]. In Type 2 diabetes more than 150 genetic loci are associated with the development of diabetes and 50 candidate genes have shown to play a major part in the development of the disease [81]. These genes are involved in pancreatic β cell function, insulin action and glucose metabolism in metabolic conditions. In Type 1 diabetes the HLA class genes have been associated with Type 1 diabetes with differences in haplotypes in ethnic groups such as Caucasians, African, Americans, Japanese and Chinese [46]. Sirt 1 regulation of the MODY gene via transcription factors hepatocyte nuclear factor 1 has been shown with evidence of genetic regulation of liver and pancreas in Type 1 diabetes [81]. Nutritional dysregulation of Sirt1 and the SCN may now involve Type 1, Type 2 and Type 3 diabetes (Figure 2) [63,82] and induce MODS that involves accelerated organ diseases with hepatic xenobiotic metabolism (NAFLD) completely inhibited in these individuals. Sirt 1 repression induces mitophagy with the development of MODS and may supersede the connections between diabetic genes (Type 1 and 2) and their associated diseases (Figure 2). Sirt 1 plays an important role in the regulation fibroblast growth factor 21 [82-84] and the apelinergic pathway [85] with connections to brain insulin resistance (stroke, dementia, AD) [86]. In Type 2 diabetes the relevance of stress, anxiety and hyperphagia are associated with defective apelinergic pathways [85] and severity of diabetes (post-transcriptional defect) associated with Sirt 1-apelinergic system defects in mental disorders [87].

Dysregulated Sirt 1 on adipocyte differentiation and senescence involves gene expression and secretion of adiponectin with effects...
on the release of adipokines and cytokines that are implicated in NAFLD and chronic diseases [88-97]. Sirt 1 interactions with forkhead transcription factor O1 (FOXO1), C/EBP alpha may involve Klotho C/EBP alpha and peroxisome Proliferator-Activated Receptor (PPAR) interactions [98-103] important to mitochondrial function and adipocyte differentiation. Furthermore miR-122 and miR-132 [4] have been shown directly inhibit Sirt 1 and may interfere with adipose tissue adiponectin release. FGF21 binds to FGF receptor and beta klotho receptor complex [104-108] and activates adipose tissue Sirt 1/p53 with interactions with relevance to PGC1-alpha, peroxisome proliferator activated receptor gamma, FOXO 1 [109-111] and AMP activated protein kinase (AMPK) involved in adipocyte tissue transformation. FGF21 and Sirt 1 are essential for liver mitochondrial function (Figure 2) and regulate pancreas mitochondrial biogenesis and beta cell insulin secretion [112].

Sirt 1 effects on hepatic cholesterol metabolism and NAFLD are mediated via Sirt 1 and transcription factor C/EBP alpha that regulates the transcription of the apolipoprotein B gene [113]. The protein kinase c-jun amino-terminal kinase 1 (JNK1) can phosphorylate Sirt 1 with phosphorylation of Sirt 1 important to p53 activation with relevance to NAFLD and the metabolic syndrome [46]. Sirt 1 and its connections to NAFLD may involve Brd4/p53 interactions with relevance to Brd 4-P-TEFb involvement in mitotic progression [46,114]. The control of the adipose tissue-liver crosstalk (gene expression) by the SCN is defective in diabetes (Type 3) and related to excess calorie consumption or core body temperature that overrides the Sirt 1 related SCN entrainment [61]. SCN defects are related to the peripheral circadian clock dyssynchrony [115] (adipose tissue-liver cross talk) that determine Sirt 1 regulation of low adiponectin and melatonin levels involved in the metabolic syndrome, NAFLD and reverse cholesterol transport [61,83,116] with relevance to diabetes and the severity of MODS (Figure 2).

Epigenetic Modifications Involve Nitric Oxide and Immune Dysregulation in Diabetes

Induction of epigenetic alterations that determine brain dysfunction involve Nitric Oxide (NO) homeostasis and effect the adipose tissue-liver crosstalk with relevance to immune alterations that determine the survival of cells in various tissues. Diabetic individuals with defective SCN and brain-liver crosstalk involve immune imbalances as the primary cause of MODS. In Type 3/Type 2 individual’s reduced xenobiotic metabolism is associated with NAFLD and the induction of MODS connected to the immune system. Sirt 1/p53 transcriptional responses are involved in NO metabolism [85,117-119] and immunometabolism regulated by diet, drugs and the environment are critical to mitochondrial apoptosis and the induction of NAFLD in the developed world. Sirt 1 is connected to immunometabolism [9] and adipogenesis disorders with adipose tissue release of adipoctines, inflammatory cytokines, heat shock proteins and natural killer cells relevant to mitophagy in diabetes and MODS. Sirt 1 is essential to maintain the SCN, NO homeostasis [85] and its dysfunction is critical to the defective circadian rhythm of heat shock proteins [60-63] with relation to cellular immune response [9,120]. Sirt 1 and its regulation of autoimmune disease is central to defective liver fat metabolism [9] with maintenance of Sirt 1 in adipose tissue and the liver of critical importance to MODS. Heat/cold stress inactivate the heat shock gene Sirt 1 [60-63] with NO dyshomeostasis, immune system imbalances connected to mitophagy (Figure 3) [4,5,9]. NO regulation of p53 [117-119] is important to epigenetic regulation and Sirt 1 post-transcriptional regulation by NO [85,121-123] involves p53/miRNA [4,124,125], anti-aging gene p66shc [126-128], klotho [129-131], FOXO 3a [132,133], transcription factors PGC1 alpha [132,134,135], PPAR [136-138], LXR-ABCA1 [139,140], AMPK signalling [85,141,142], HSP/body temperature regulation [143-146] and glucose homeostasis [147,148]. The importance of Sirt 1 and the immune response is now consistent with its interplay between NO and epigenetics [149,150] with relevance to human health and disease (Figure 3). The role of NO and cytochrome p450 complex formation [151-153] has become relevant to xenobioc metabolism [5] with increased liver NO [85] implicated in the inactivation of Sirt1/PXR’s control of xenobiotic metabolism [4,5,154,155]. Sirt 1 and its regulation of immunometabolism [9] are connected to xenobiotic metabolism with implications to MODS and xenobiotic induced immune alterations [156,157]. Xenobiotics may nullify Sirt 1’s role in NO homeostasis and vasodilation in the heart [85] with relevance to interference of therapeutic drugs for blood vessel dilation [158]. NO regulates calcium signalling in various cells [159-161] and in the SCN alterations in cell calcium is critical to circadian dys synchrony [162].

Lifestyle factors with Nutritional interventions may reverse Global chronic disease Low calorie diets that upregulate Sirt 1 promote anti-aging gene therapy, miRNA function, transcriptional factor
control and interactive nuclear receptor signalling in various cells and tissue with relevance to maintenance of immune response and prevention of autoimmune disease that may be connected to global chronic disease and the development of MODS (Figure 3). Bacterial LPS is involved with NAFLD and interference with hepatic xenobiotic metabolism is relevant to increased mitophagy and neurodegeneration. Nutritional diets with Sirt 1 activators have become important to molecular and genetic medicine.

**Conclusion**

Global chronic diseases involve cellular immune alterations that lead to mitophagy in various tissues. High calorie diets are involved with transcriptional dysregulation and defective hepatic xenobiotic associated with immunometabolism disorders in genetic medicine. Nutritional regulation of Sirt 1 is essential to maintain the interplay between NO, glucose homeostasis, immune system and various nuclear receptors, transcription factors/signalling factors and miRNA involved in epigenetics with relevance to human diabetes. Bacterial LPS induced Sirt 1 repression in Type 3/Type 2 diabetes induce NAFLD with increased xenobiotic levels linked to the development of MODS and global chronic disease in the developing world.

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