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Unhealthy Nutrigenomic Diets Accelerate NAFLD and Adiposity in Global communities

Martins IJ[1,2,3*]

[1]*Centre of Excellence in Alzheimer's Disease Research and Care, School of Medical Sciences, 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*

[*]**Corresponding author:** Ian Martins, School of Medical Sciences, Edith Cowan University, 270 Joondalup Drive, Joondalup, Western Australia 6027, Australia, Tel: +61863042574; E-mail: i.martins@ecu.edu.au

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Abstract

The understanding of genetic factors involved in the risk for obesity has identified genes that are closely linked to obesity related diseases. A single gene effect versus multiple genes effect may indicate either the interaction unique to various environments that regulate abnormal molecular or cellular events responsible for obesity with several hypotheses proposed in relation to the development of obesity. The understanding of the development of adipogenesis has been the focus of the global community with obesity genetics, epigenetic regulatory mechanisms and transcription factors important to the world-wide obesity epidemic with increased risk for adiposity. The search for specific genes that are sensitive to nutritional regulation, oxidative stress, inflammation, endocrine disease, lipid/glucose metabolism, insulin resistance and Alzheimer's disease has been the focus of the current obesity epidemic in various developed countries. Epigenetics is now considered as an important mechanism for the development of obesity and can result from changes in cellular chromatin structure without alterations in DNA sequence, including DNA methylation, histone modifications and chromatin remodelling. Epigenetic modifications induced by unhealthy diets and the environment effect nuclear/mitochondria interactions and implicate nuclear receptors such as Sirt 1 as a single gene effect with interactions with microRNA and transcription factors such as p53 that regulate cellular and immune events with effects on cellular lipid metabolism and energy expenditure that induce senescence with poor DNA repair. Epigenetic modifications in various communities are now closely involved in NAFLD associated with excess transfer of fat to the adipose tissue and the induction of obesity in developed countries. The failure of various anti-obese drugs has encouraged the use of nutrigenomic diets that reverse senescence and assist in the early nutritional intervention that reverses NAFLD with reduced adiposity.

Keywords: Tumor protein p53; Sirtuin 1; Immune; Nutrition; Obesity; Senescence

Introduction

The global increase in chronic diseases such as obesity, diabetes and neurodegenerative disease is predicted to rise to 1 in 5 individuals by the year 2050 and linked to organ diseases in various countries [1]. Epidemiological studies indicate that human obesity is associated with an increased risk for atherosclerosis and diabetes. In obese individuals the increased adiposity is now associated with epigenetic modifications that involve alteration in chromatin induced by either the environment or unhealthy diets. The genetic modifications that induce abnormal cellular events in adipose tissue are responsible for defective nuclear and mitochondria interactions with decreased energy expenditure. The several hypothesis proposed for the induction of obesity include the telomere hypothesis of cell senescence [2] that link a decline in telomeres to mitochondria function [3,4]. The susceptibility of humans to obesity compared to other mammals indicate that human genes malfunction early in life with mitochondrial apoptosis with increased risk of non-alcoholic fatty liver disease (NAFLD) and degenerative diseases [5].

Furthermore the theory of age-dependent mutation and senescence [6] has become important to explain the increased insulin resistance and severity of obesity and diabetes that may be associated with xenobiotic consumption in these individuals [7]. The Fisher geometrical model of adaptation suggest an aging theory that indicate genetic changes such as mutational distributions early or late in life are induced by excessive dietary fat and sugar consumption that may cause patterns of age-specific mortality in various populations. Evolutionary mechanisms of senescence by the aging theory include the classical quantitative genetic approaches that can provide information about the age-specific distribution of genetic effects that may segregate in populations. New quantitative genetic methods such as the use of the DNA and RNA microarrays could be applied to examine changes in genetic interactions to explore age-related changes. Interest in genomics has led to identification of novel genetic pathways (Figure 1) that are age independent and indicate that disturbance in the mutation equilibrium in life increase with a single gene involved in various chronic diseases such as NAFLD and obesity in the developing and developed world.

Diets and lifestyles in global populations may prevent decreased senescence and mutations related to the age related theory with the prevention of telomere shortening and improvement in adaptation of the organism to the environment. A single gene such as sirtuin 1 (Sirt 1) in humans and mammals involved in longevity may determine the expression of various genes with gene silencing relevant to organ diseases in obesity and diabetes. Sirt 1 may be relevant to the telomere hypothesis [2] and the mitochondrial theory of aging [3,4].

In various communities adipose tissue transformation in obesity with poor glucose homeostasis has become important to diabetes and hepatic regeneration related to defective Sirt 1's involvement in insulin resistance.

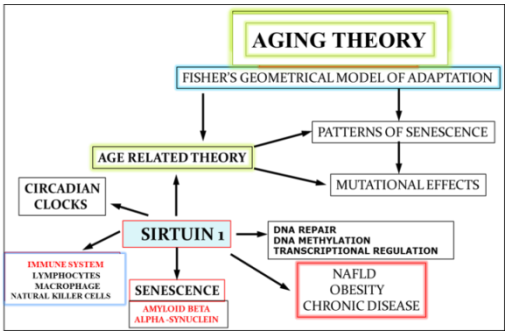

Figure 1: In populations in the developed and developing world the theory of age-dependent mutation and senescence has become important to explain increased insulin resistance and severity of obesity and diabetes. Adaptation to genetic changes by transcriptional dysregulation early or late in life induced by nutritional intake may determine age-specific mortality in various populations. Interest in genomics has increased with the identification of age independent genetic pathways that indicate the disturbance in the mutation equilibrium increase with dysregulation of the gene Sirt 1 that is involved in various chronic diseases associated with immune dysregulation, obesity and neurodegeneration.

Sirt 1 dysregulation connected to appetite control and NAFLD in mice possibly involves other genes such as the obese (ob), leptin, fat, agouti and New Zealand Obese genes [8]. Sirt 1 dysregulation and insulin resistance can be associated with diabetes and involve genes such as the human leukocyte antigen class 1, II, mature-onset diabetes of the young genes and other candidate genes [9]. In obesity and diabetes alterations in Sirt 1 involve the transcription factor tumor protein p53 (p 53) that may transform adipose tissue by abnormal transcription regulation with an increased release of adipocytokines that are linked to NAFLD. Fisher's model of adaptation may target the importance of the adipose tissue to transformation as the organ that has failed to adapt to maintain organism survival with increased age dependent mutations associated with defective transcriptional regulation and gene expression in various tissues [6].

Sirt 1's involvement in the adipose tissue and liver crosstalk has become important with adipose tissue lipid metabolism related nuclear and mitochondria abnormalities that are possibly connected to increased adiposity with the induction of NAFLD and the development of obesity. Futhermore, the interest in bacterial lipopolysaccharides, the immune system and nuclear gene dysfunction associated with adipogenesis and glucose dyshomeostasis has also increased in relation to the adipose tissue-liver cross talk. Anti-obese drugs with poor clinical outcomes and unhealthy complications has prevented the continued use of these drugs in various developed countries. The use of nutrigenomic diets [8] that maintain the Sirt 1 function and promotes its binding to chromatin have become of interest with genomic regulation involved in the reversal of liver dysfunction and adipose tissue transformation. The role of Sirt 1 in the immune system has also been identified as important to adaptation versus the defective genomic regulation in NAFLD, obesity and Alzheimer's disease (Figure 2).

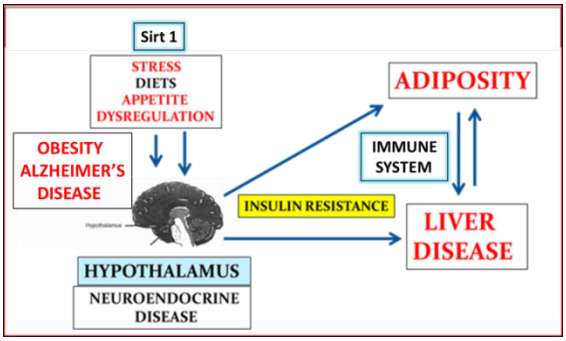

Figure 2: Interests in environmental factors such as stress, diet and appetite that affect the hypothalamus and the suprachiasmatic nucleus (SCN) closely regulate peripheral clocks (amyloid beta dynamics) in the periphery such as in the liver (NAFLD) and adipose tissue (increased adiposity). Peripheral genomic modulation of Sirt1 involved in abnormal immune responses override brain regulation of the adipose tissue and liver crosstalk with the development of increased adiposity (obesity) and NAFLD.

Effects of food restriction on adipose tissue and liver crosstalk in genetically obese/diabetic mice and man

Interests in the current global obesity epidemic has escalated with the metabolic syndrome and NAFLD that may involve 40% of individuals in developed and developing countries [7,8]. Lipoprotein and glucose metabolism is disturbed in obese individuals [10] with increased lipid accumulation and excess lipids that are stored in adipose tissue. In obese individuals the classification of obesity is with a body mass index (BMI) that is greater than 30.0 Kg/m^2 [8]. Nutrigenomic diets have become important for the treatment of NAFLD in obese individuals and also in lean individuals with BMI (25 kg/m^2) [11] with the reversal of adipose tissue transformation linked to improvements in glucose metabolism, immune system and NAFLD (Table 1).

The abnormal liver lipid metabolism may be responsible for the increased adiposity in obese individuals and food restriction studies have become important to improve hepatic lipid metabolism and adipose tissue transformation linked to the altered immune response in obesity [12-16]. The gene-environment interaction identifies Sirt 1 as the defective gene involved in the global obesity and NAFLD epidemic [7]. Sirt 1 dysregulation is now considered important to the development of obesity with chromatin alterations (modelling) that influence the DNA sequence, DNA methylation and histone modifications. As with nuclear liver receptors [7] the adipose tissue nuclear receptors undergo deacetylation of histone and non-histone targets by Sirt 1 (nicotinamide adenine dinucleotide dependent class III histone deacetylase) that target transcription factors such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC 1-<alpha>), p53, pregnane X receptor (PXR) to adapt gene expression to metabolic activity, insulin resistance and inflammation [7,8,10]. Figure 3 shows that Sirt 1 is involved with appetite regulation linked to the obese and diabetic genes [8] and DNA repair. Transcriptional regulation of metabolism involves the peroxisome

proliferator-activated receptor gamma (PPAR<gamma>) isoforms with nuclear- mitochondria interactions (tissues) that involve 5′-monophosphate-activated protein kinase (AMPK) activation regulated by nutrient availability. Sirt 1 deacetylation of Forkhead box protein O1 (FOXO1) control apoptosis with regulation of xenobiotic metabolism and inflammation. Sirt 1 involvement in adipose tissue transformation is by p53 transcriptional dysregulation that involves the repression of PPAR<gamma>nuclear receptor and FOXO1 that are responsible for adipocyte lipid metabolism [17-19]. Furthermore Sirt 1/p53 interactions may regulate adipocytokines and immune responses that may be important to the abnormal adipose tissue-liver crosstalk that promotes NAFLD in obesity [20-29].

Individuals	NAFLD	Organ Disease	Adipose Tissue Transformation Immune Disorders
Lean Individuals (25 Kg/m^2)	No/Yes	Liver?	No
Overweight obesity (30 Kg/m^2)	Yes	Adipose Tissue, Liver, Kidney, Heart, Brain	Yes
Morbid obesity (>35 Kg/m^2)	Yes	Adipose Tissue, Liver, Kidney, Heart, Brain	Yes
Severe obesity (>40 Kg/m^2)	Yes	Adipose Tissue, Liver, Kidney, Heart, Brain	Yes
Childhood obesity	Yes	Adipose Tissue, Liver, Kidney, Heart, Brain	Yes

Table 1: Defective adipose tissue immune responses are associated with insulin resistance, NAFLD and various organ diseases in overweight individuals, morbid and severe obesity.

In rodent models of obesity and diabetes the disturbed adipogenesis linked to NAFLD [8,30] may be associated with the abnormal release of adipocytokines (leptin, adiponectin, apelin and angiotensin II) related to hepatic fibrogenesis, NAFLD and neurodegenerative diseases [31,32]. As shown in Table 2, food restriction that activates Sirt 1 and PGC 1-<alpha> in tissues of mice (fat/NZO) corrected the dysregulated adipose tissue-liver crosstalk associated with the improved body weights and hepatic lipid metabolism with relevance to NAFLD in obese individuals. Food restriction increased liver fatty acid oxidation in obese and diabetic mice but adipose tissue mass (body weights) was not altered in ob, db, and Ay mice connected to leptin resistance [30] and associated with poor activation of PGC 1-<alpha>by leptin (Figure 3). The increased hepatic lipid metabolism was not associated with improved adipocyte metabolism in obese, diabetic and agouti mice after the 6 week of food restriction with the degree for NAFLD persistent in these mice (Table 2). Leptin resistance may also involve the immune system and the duration of food restriction (fat and carbohydrate content) may determine immune responses and improved fatty acid oxidation in both the adipose tissue and the liver.

The brain-liver pathway for the metabolism of the Alzheimer's disease peptide amyloid beta involves Sirt 1 (peripheral sink amyloid beta hypothesis) [9] with the abnormal peripheral amyloid beta metabolism associated with adipose tissue transformation [12,31,32] connected to leptin resistance and NAFLD (Tables 1 and 2).

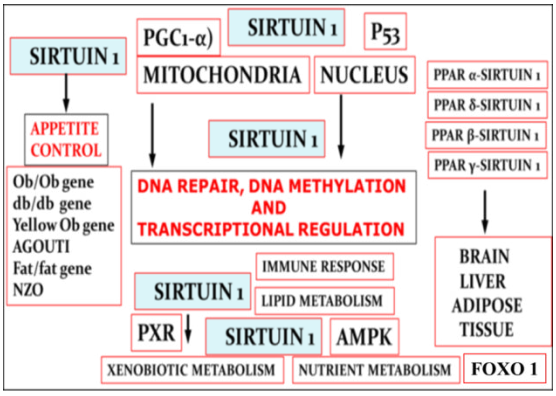

Figure 3: Epigenetic modifications are associated with the malfunction of the gene Sirt 1 with p53 dysregulation associated with the abnormal release of adipocytokines and inflammatory mediators from the adipose tissue with the increased risk to liver disease A. Chromatin alterations that influence the DNA sequence (repair systems), DNA methylation and histone modifications involve the gene Sirt 1. B. Nuclear receptors undergo deacetylation of histone and non-histone targets by Sirt 1 (nicotinamide adenine dinucleotide dependent class III histone deacetylase) and target transcription factors PGC 1-<alpha>, p53, PXR, to adapt gene expression to metabolic activity, insulin resistance, xenobiotic metabolism and inflammation. C. Sirt 1 is involved with appetite regulation linked to the obese/diabetic genes D. Nuclear and mitochondria interactions in various tissues involve AMPK, PGC 1-<alpha>, PPAR<gamma>, FOXO1 regulation by Sirt 1 expression and activity (nutrients). E. Adipose tissue release of adipocytokines (adiponectin, leptin) and altered immune response may be important to the adipose tissue-liver crosstalk that promote NAFLD in obesity.

Obese/Diabetic mice	Liver Metabolism	Adipose tissue Metabolism
ob/ob	Increased Fatty acid oxidation	Adipocyte Abnormal transformation
fat/fat	Increased Fatty acid oxidation	Adipocyte Normal lipid metabolism
Ay	Increased Fatty acid oxidation	Adipocyte Abnormal transformation
db/db	Increased Fatty acid oxidation	Adipocyte Abnormal transformation
NZO	Increased Fatty acid oxidation	Adipocyte Normal lipid metabolism

Table 2: Liver lipid metabolism and adipocyte lipid metabolism in genetically obese (ob) and diabetic (db) mice models after pair-feeding to control mice (3.5 gm/day). In all obese and diabetic mice pair-feeding was associated with increased liver lipid metabolism but adipose tissue metabolism was not changed in ob/ob, Ay and db/db mice with no significant changes in body weight.

Food restriction improves Sirt 1/ PGC 1-<alpha>regulation of adipose tissue and liver (lipid/amyloid beta metabolism) [32] and involves the immune response (Figures 2 and 3) with support for the relevance of the immune system to Alzheimer's disease progression in the developing and developed world [32,33].

Abnormal post-transcriptional regulation of p53 determine liver disease and adipose tissue transformation in obesity

Abnormal gene regulation involved in adipose tissue metabolism is now closely linked to hepatic lipid metabolism associated with an individual's failure to adapt to the environment with accelerated senescence and obesity. In obesity the response to stress signals involve Sirt1 and the p53 tumor suppressor protein associated with insulin resistance [34], metabolic processes, cancer and DNA damage. p53 deficiency is associated with cancer and indicate poor regulation of Sirt 1 may be involved in cancer predisposition. Interests in the nutritional regulation of obesity and diabetes has increased with the effects of feeding on Sirt 1 and p53 that are involved in nuclear-mitochondria interactions, mutations, cell death (apoptosis) or permanent cellular senescence [35-41]. Sirt 1 and its post-transcriptional regulation of p53 [42,43] is closely involved in adipogenesis and adipocyte lipid metabolism [44-48] with implications for abnormal Sirt 1 deacetylation of p53 that links lipid metabolism with adipocyte transformation and liver disease. Sirt 1 knockout mice and p53 knockout mice develop NAFLD [49-52] and indicate close connections between liver disease and adipocyte transformation may involve Sirt 1/p53 effects on mitochondrial function [53-56].

The leptin gene is one of a number of genes that determine food intake and body weight maintenance with adipose tissue transformation associated with p53 events that override leptin or Sirt1's control [57] of adipose tissue metabolism of glucose, lipids and amyloid beta. Furthermore the adipocyte derived leptin and its increased secretion in obesity is associated with the inflammatory [58] or immune responses with the increased release of inflammatory derived cytokines [12,16,20]. Hyperleptinemia has been associated with p53 and NAFLD with close links between leptin, inflammation and Kupffer cell activation [59]. Food restriction studies in genetically obese/diabetic mice (Table 2) showed no change in body weight (abnormal adipogenesis) and leptin disorders in these mice may have relevance to obesity in man [60]. In obese mice and man the associated NAFLD and hyperleptinemia are related to the lack of hepatoprotective effects of the adipose tissue derived adiponectin [61-63] with the reduced ability to prevent inflammation in the liver.

A variety of interactions between the p53 and the innate immune system [64-67] indicate the role of p53 in immune homeostasis/ inflammatory disease associated with liver cell senescence, lipid metabolism and the recruitment of natural killer (NK) immune cells [68,69]. The persistence of cellular senescence that determines the adipose tissue-liver crosstalk does not involve the elimination of the senescent cells but allow p53 in the promotion of adipose tissue adipogenesis with the development of NAFLD. p53 activates and suppresses (transcriptional suppressor) target genes such as Sirt 1 involved in the innate immune response [70,71] and sterol regulatory element-binding protein-1 (SREBP-1) [45,52] a key transcriptional regulator of adipocyte triglyceride synthesis. Sirt 1 and its importance in adipose tissue lipid metabolism is also connected to adiponectin release via Sirt 1/FOXO1 transcriptional complex [72,73] with maintenance of hepatic function. Metabolic regulation of the liver and adipose tissue become important as the p53 release from the nucleus to the cytoplasm becomes abnormal and implicates p53 and microRNA (miRNA) in the abnormal regulation of fatty acid metabolism in the mitochondria (Figure 4).

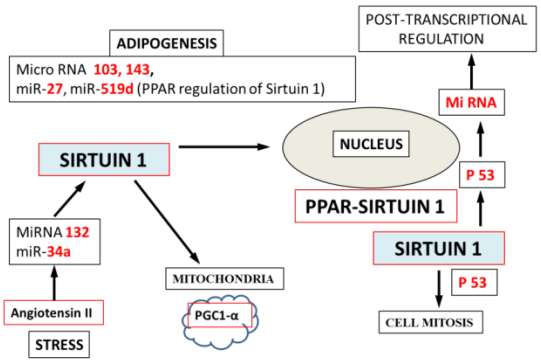

Figure 4: In the liver and adipose tissue the nuclear and mitochondria interactions are determined by effects of p53 on the altered expression of multiple miRNA that involve the immune system in obesity. A. MiRNAs 103 and 143 are important in the acceleration of adipogenesis in association with miRNAs such as miR-27 and miR-519d involved in the transcriptional regulation of PPAR<gamma>. B. PPAR<gamma> is strongly expressed in adipocytes and plays a significant role in the Sirt1 transcriptional activation of adipocytokines (adiponectin, leptin, angiotensin II) and oxidation of fatty acids. C. p53 involved in miRNA dysregulation is important in the abnormal metabolism of adipocyte lipids associated with the inactivation of the nuclear-mitochondria crosstalk and the development of obesity. The p53 effects on miR-34a transactivation involve Sirt1 expression associated with insulin resistance increased adiposity, immune dysregulation and NAFLD.

Effects of p53 on gene regulators include miRNAs [74] and their role in the induction of obesity [75] indicates altered expression of multiple miRNAs in metabolic tissues [76,77] that also involve the abnormal immune system [78-80]. MiRNAs 103 and 143 are important in the acceleration of adipogenesis [81] with other miRNAs such as miR-27 and miR-519d [82] involved in the transcriptional regulation of PPAR<gamma> [83] and determine adipocyte development and fat cell numbers. PPAR<gamma> is strongly expressed in adipocytes and plays a significant role in the Sirt 1 transcriptional activation of adipocytokines (adiponectin and leptin). PPAR<alpha> activation of Sirt 1 causes increased lipid clearance via β-oxidation enhancement and p53 associated miRNA dysregulation is important in the abnormal metabolism of adipocyte lipids associated with the inactivation of the nuclear-mitochondria crosstalk (Figure 4). Angiotensin II derived from the adipocytokine Apelin [31] effects PPAR<gamma>-Sirt1 expression in adipose tissue [32,84,85] and plays a central role in adiponectin release [31,32]. Furthermore miRNAs such as miR-34a [86] and miR-122, miR-132 [87,88] that directly inhibit Sirt 1 affect adipose tissue adiponectin release associated with poor activation of hepatic genes involved in glucose and lipid metabolism [62] with an increase in acetylated p53 involved with cell apoptosis and NAFLD [51,52]. The p53 effects on miR-34a transactivation involve Sirt1 expression with the development of metabolic disease [89-92]. Other transcription factors such as

CCAAT/enhancer binding protein alpha (C/EBP<alpha>) have been shown to activate Sirt 1 expression linked to adipogenesis via PPAR<gamma>regulation [93,94] with possible involvement by miR-34a.

LPS regulation of Sirt 1/p53 interactions is connected to dietary fat, immune system disorders and liver disease

The immune theory involves Sirt 1/p53 dysregulation and failure to adapt to the environment implicates an abnormal immune system in the pathogenesis of insulin resistance and aging [95,96]. Diets high in fat and low in fibre are associated with an increase in gut microbiota in the plasma with effects on the immune system, insulin resistance and energy homeostasis in animals and humans [97-103]. In particular in mice high fat high cholesterol diets increased the levels bacterial endotoxins, also known as lipopolysaccharides (LPS) with sensitivity of LPS to the severity of inflammation [104-106]. LPS and cytokines have been shown to stimulate hepatic sphingolipid synthesis with the production of lipoproteins with altered ceramide and sphingomyelin content [107,108]. In obese mice altered inflammatory responses were found to LPS administration when compared with control mice [109,110] with intestinal microbiota and NAFLD closely linked with connections to the systemic inflammation and the metabolic syndrome [111-116]. The immune system and its involvement in the adipose tissue-liver crosstalk strongly implicate LPS in the pathogenesis and development of NAFLD and obesity.

LPS are endotoxins and essential components of the outer membrane of all Gram-negative bacteria [117,118]. Bacterial LPSs are dimeric molecules consisting of a polysaccharide moiety linked to a lipid core termed lipid A which is anchored within the cell membrane [118,119]. LPS has been shown to effect hepatic genomic stability [120] with effects on reverse cholesterol transport (RCT) in macrophages by downregulation PPAR <gamma> with relevance to the role of the adipose tissue inflammatory responses in RCT [121-130]. LPS has been shown to have direct effects on mitochondria DNA synthesis associated with mitochondria dysfunction [131]. LPS have also been implicated in the adipocyte-macrophage interaction with upregulation of systemic inflammatory responses [132] associated with mononuclear DNA damage [133]. Interests in LPS and fat absorption has increased with the effects of LPS on Sirt 1 regulation of reverse cholesterol homeostasis and on alpha synuclein and amyloid beta metabolism [134].

LPS binding protein (LBP) bind LPS and modify the inflammatory response [135]. LBP and leptin are both elevated in obesity with relevance to LPS effects on leptin expression, appetite and obesity induced inflammation [136-140]. LPS has been shown to effect cholesterol efflux by the modulation of the liver X Receptors (LXR) and ATP-binding cassette transporter 1 (ABCA1) [141,142] pathways overriding Sirt 1 effects on LXR-ABCA1 interactions. Reduction of fat intake [135] may lower plasma LPS content and has become important to reduce metabolic diseases. LPS effects macrophage SREBP expression and inhibits liver PGC 1-<alpha>expression [129,142,143] linked to abnormal Sirt 1 cell regulation [27,144]. LPS mediated corruption of cholesterol efflux in macrophages has been reported with the importance of cholesterol-rich lipoprotein interactions [145-147] for the neutralization of LPS in metabolic diseases and diabetes [148-150].

LPS induction of interferon-gamma (IF-γ) has been shown in NK cells and T lymphocytes with the effects of IF-γ on inflammatory cytokine genes, glucose homeostasis and macrophage function with relevance to adipogenesis [151,152]. IF-γ has been shown to suppress genes such as Sirt 1 involved in metabolic dysfunction and induce p53 apoptosis related genes [153-155]. Effects of IF-γ on chromatin modelling promotes the activation of macrophages with relevance to transcriptional control in the regulation of inflammatory cytokine production in activated macrophages [156,157]. MiR-34a and other microRNAs are involved in the regulation of IF-γ involved in the innate immune response [158,159]. The inverse relationship between adiponectin and inflammatory cytokines has been shown with adiponectin levels closely linked to NK cell activation [160-162]. In obesity the role of LPS involves adiponectin inflammatory responses with effects of IF-γ on insulin resistance, lipid metabolism and macrophage activation [163].

LPS effects on p53 induce apoptosis in the liver [164,165] overide Sirt 1's role in the deacetylation of p53 with effects on reduced hepatic lipid metabolism (nuclear-mitochondria interactions) with relevance to increased adiposity. p53 association with PXR and down regulation of PXR activity [166,167] is independent of Sirt1/PXR effects [7] (Figure 3) with implications of LPS to poor hepatic xenobiotic, bile metabolism linked to the immune system [168-173]. The abnormal p53/PXR interactions that induce NAFLD are associated with altered miRNA expression connected to xenobiotic metabolism [174-176]. Xenobiotics such as bisphenol A (BPA) have been shown to be abnormal in obesity with increased secretion in the urine associated with adipogenesis [177] immune disorders [178] and p53 associated apoptosis [179,180]. Phthalates found in various foods (milk, butter, meats) are linked to the Sirt 1/p53 interactions with effects of phthalates on p53 transcriptional activity [181-183] and links phthalates to NAFLD and adiposity in global communities [184]. Interests in alpha-synuclein and its relevance to the immune system in the periphery [134,185] and brain [186,187] have increased with alpha-synuclein regulation of p53 transcriptional regulation of apoptosis. Sirt 1 effects on hepatic alpha- synuclein and amyloid beta metabolism are closely linked to LPS [134], metabolic disease and obesity with effects of p53 transcriptional regulation by intracellular alpha-synuclein and amyloid beta metabolism in the liver and brain linked to cellular apoptosis [188-191].

Nutrigenomic diets prevent liver and adipose tissue senescence in obesity

The failure of various anti-obese drugs [192] in the treatment of obesity has encouraged the use of nutrigenomic diets to prevent senescence of various tissues involved in chronic disease [1]. In obese individuals the importance of early treatment of NAFLD may reside in individuals [7,8] with BMI between 25-30 kg/m^2) with reversal of adipose tissue transformation linked to improvements in glucose metabolism, the immune system and NAFLD. In individuals with BMI greater than 30 kg/m^2 unhealthy diets that induce abnormal Sirt 1/p53 interactions are associated with alterations in microRNA with the failure of DNA repair systems that accelerate liver senescence with effects on adipose tissue inflammatory responses, lipid metabolism and energy expenditure.

Diets that contain appropriate protein, carbohydrate and fat (low) upregulate Sirt 1 expression and activity in cells with effects on nuclear and mitochondria events to maintain lipid metabolism and energy expenditure. Food restricted diets in young genetic obese and diabetic mice indicate that reversal of liver lipid metabolism that involves the Sirt 1/p53 interactions and may allow improvements in adipogenesis

in man (BMI 25-30 kg/m^2). Nutritional regulation may maintain p53 deacetylation by Sirt 1 and prevent glucose dyshomeostasis associated with the rapid hepatic and adipose tissue lipid metabolism. Diets that contain high amounts of (-)-epigallocatechin-3-gallate a polyphenolic compound found in green tea may have deterimental effects to p53 transcriptional activity and acetylation [193-195] with detrimental effects on the Sirt 1 deacetylase activity associated with apoptosis linked to NAFLD.

Furthermore, food consumption [32] that prevent programmed cell death pathways in mouse and man may be relevant to Sirt 1 gene expression that activate the adipose tissue to release factors such as adiponectin [32] and suppress inflammatory cytokines to maintain liver function and to prevent NAFLD in man. Nutrigenomic diets such as the consumption of high fibre diets [196] are involved in metabolic engineering that allow physiological nuclear and mitochondria interactions that activate the PPAR<gamma>-Sirt 1 and Sirt1-PXR interactions (Figure 3) linked to therapeutic nutrient and xenobiotic metabolism (BPA) that are associated with effects on p53 half-life and cell apoptosis [197].

Diets and the immune system have become important with dietary fat and composition associated with NK cell activity and adipose tissue immune responses [198-202]. Suppression of Sirt 1 expression by dietary fat can be associated with the abnormal p53 post-transcriptional regulation of NK cells [69,203]. Furthermore dietary fat may facilitate the absorption of LPS in rodents and man with effects on suppression of Sirt 1 effects and promotion of p53 apoptotic effects in cells. Food restriction diets delay LPS absorption with the prevention of LPS inhibition of cholesterol homeostasis in macrophages by promotion of reverse cholesterol transport (RCT).

Multiple theories of aging have been proposed and the immune theory of aging may involve adipose tissue transformation with activation of immune responses that involve macrophages and immune cells. Fisher's model of adaptation may also target the importance of the adipose tissue as the organ most susceptible to programmed cell death pathways and transformation associated with mutations in genes in various cells and tissues [6]. Diet and the immune system are closely linked with endogenous intestinal microflora (gram negative bacteria) and environmental factors that influence dietary composition (fatty acid composition) that may play a central role in immune homeostasis and reactivity in the liver. In support of Sirt 1's involvement in the mitochondria theory with aging provide close links to mitochondria dysfunction (Sirt 1 downregulation) and abnormal immune response [68,204-206].

Essential requirement of the amino acids such as leucine [207-213] may maintain the nuclear and mitochondria p53 transport with an increase in p53 half-life and prevention of immune dysfunction and NAFLD. Nutrigenomic diets such as low calorie diets that activate Sirt 1 reduce plasma cholesterol levels [30] prevent hepatic p53 induced apoptosis by xenobiotics and LPS. Drugs such as suramin are Sirt 1 inhibitors [214,215] prevent leucine activation of Sirt 1 and xenobiotics such as phthalates may modify Sirt1 chromatin association with induction of p53 apoptotic responses [181-184,216,217] in liver and adipose tissue.

Conclusion

The increase in NAFLD and obesity in global communities indicate that epigenetic modifications are associated with the malfunction of the gene Sirt 1 with p53 dysregulation linked to the defective adipose tissue-liver crosstalk in obesity. Healthy low calorie diets and active lifestyles early in life that maintain healthy Sirt 1/p53 interactions in individuals with BMI (25-30 kg^2) will decrease organ senescence and age related mutations. The use of healthy diets that do not contain elevated components (sugar, fats, xenobiotics, LPS, (-)-Epigallocatechin-3-gallate, drugs) may prevent the induction of p53 cell apoptosis and Sirt 1 suppression but increase liver cell telomere length and improve hepatocyte nuclear and mitochondria interactions. Activators of Sirt 1 such as leucine and resveratrol will increase hepatic xenobioitic metabolism and prevent mitochondrial apoptosis connected to NAFLD dysfunction. Nutritional diets that promote Sirt 1 binding to chromatin and prevent its disassociation by various drugs and unhealthy diets will prevent adipose tissue transformation and activation of immune responses that involve macrophages, NK cells and lymphocytes that are linked to NAFLD and other organ diseases in various communities.

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