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# Introductory Chapter: Obesity—“OMICS” and Endocrinology

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Additional information is available at the end of the chapter

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## 1. Introduction

The comprehension of the genetics or “OMICS” (referring to a field of study in biology ending in -omics, such as genomics, proteomics or metabolomics), serving as a determinant in the development of obesity, has led to the identifications of genes closely associated with obesity-related diseases or ailments. Understanding of the etiology of adipogenesis has been of interest to the global community, i.e., obesity genetics, as well as its regulatory mechanisms, with transcription factors (TFs) being instrumental in the worldwide epidemics of overweight, with an increased risk for adiposity.

The identification of specific genes, sensitive to modulation by nutrients, as well as oxidative stress, inflammation mediators, endocrine factors/diseases, the turnover of lipids and carbohydrates (i.e., glucose and fructose, in particular), and insulin resistance has become a major focal point of the current obesity epidemic in various developed countries. “Epigenetics” is now construed as an important mechanism for the development of obesity, which may emanate from alterations in cellular chromatin structure without “touching” the DNA sequence itself, reaching from DNA methylation, histone modifications, and chromatin remodeling. The epigenetic modifications brought about by unhealthy “eating” affect nuclear and/or mitochondrial interplay, involving nuclear receptors like sirtuins, e.g., Sirt 1, serving as a single gene interacting with microRNAs, as well as transcription factors (TFs), e.g., p53, modulating cellular metabolism. These epigenetic players determine lipid turnover and energy expenditure, thereby inducing senescence followed by incomplete DNA repair. Epigenetic modifications in various social communities are at present believed to induce “nonalcoholic fatty liver disease” (NAFLD), associated with excess fat transfer to white adipose tissues (WATs), thus leading to obesity in developed countries. The overt failure of a series of antiobese drugs advocates the use of so-called nutrigenomic diets, enabling a reverse of the senescence, which ensures an early and successful nutritional intervention combatting NAFLD, preceding a reduction in the number of severe adiposity, worldwide.

The enhancement in chronic diseases, such as obesity and diabetes (including early neurodegenerative diseases), is speculated to multiply by a factor of 5 by the year 2050, and will be linked to various organ diseases in the global population [1]. In overweight individuals, the increased adiposity is thought to be associated with epigenetic modifications, encompassing chromatin alterations induced by the environment and/or unhealthy diets. Genetic modifications inducing abnormal metabolic turnover in white adipose tissue (WAT) consolidate the defective nuclear mitochondrial interplay, leading to decrements in their energy expenditure.

Several hypotheses predicting the induction of obesity encompass the telomere-induced cellular senescence associated with a decline in telomeres and mitochondrial functioning [2, 3]. This phenomenon haunts humans in particular (in comparison to other mammals) and indicates that human genes exhibit malfunctions in early childhood, like mitochondrial apoptosis associated with an enhanced probability of incurring nonalcoholic fatty hepatic disease (NAFLD), as well as degenerative, detrimental diseases [4, 5].

Furthermore, the theoretical aspects of age-related mutations and senescence [6, 7] have proven essential to describe the enhanced insulin resistance and the severity of weight gain and diabetes, which may be linked to xenobiotic ingestion in general [7, 8]. Adaptation model systems allude to theories of aging, postulating genetic alterations, like mutational patterns, which could be induced through excessive ingestion of dietary fats and sugars, which may lead to patterns of age-related mortality in general. Hereditary and/or evolutionary senescence mechanisms encompass known genetic approaches, which may yield information related to age-specific patterns of segregating genetic traits in various populations. Modern genetic analyses, such as DNA or RNA microarray analyses, are now available to aid in pinpointing age-related changes in the genetic "interplay." This has unraveled a solid identification of novel, age-dependent genetic pathways of metabolism, which are associated with disturbances in the steady state of the appearance of new mutations within single genes involved in diseases like NAFLD, as well as obesity worldwide [8].

Various lifestyles in a global population could decrease, or even prevent, senescence as well as mutations, associated with the telomere shortening theory, thus improving in adaptation of man to his environment. A single gene, like Sirt1 (Sirtuin-1), being involved in longevity, may govern the expression of a plethora of genes being of relevance to the triggering of organ diseases in obesity and diabetes. Sirt1 may be of relevance to both (a) the telomere hypothesis [2] and (b) the mitochondrial theories of aging [3, 4].

In different, closed habitats, the phenotypical transformation of a "versatile," i.e., beige adipocyte phenotype, to the traditional white, triglyceride-storing, adipocytes, has been linked to a poor glucose homeostasis. This is now associated to diabetes and hepatic malfunctioning and a defective Sirt1, leading to insulin resistance. Sirt1-mediated malfunctioning with concomitant loss of appetite control and NAFLD development in experimental animals seems to involve other genes, such as the obese (*ob*), leptin, fat, and agouti genes [8]. Sirt1 dysregulation and insulin resistance are linked to diabetes and encompass genes like the "mature-onset diabetes of the young genes," as well as others [9]. In obesity and diabetes, changes in Sirt1 expression is linked to the transcription factor p53, which enables the transformation of the "normal" white adipose into an adipokine secreting tissue type, linked to NAFLD [6].

## 2. Food restriction organ crosstalk in obese/diabetic “mice and men”

NAFLD may involve up to some 40% of individuals in the world population [7, 8]. Lipoprotein and glucose metabolism is disturbed in obese individuals [10] with increased lipid accumulation and excess lipids stored in adipose tissue. In obese individuals, obesity manifests when the body mass index (BMI) reaches 30.0 kg/m<sup>2</sup> [8]. However, nutrigenomic diets have shown good results in the treatment of NAFLD in both lean and obese individuals with BMI-values around 25 kg/m<sup>2</sup> [11], resulting in a back-transformation of adipose tissue transformation (to a more white (WAT) phenotype), which is consequently linked to improved glucose turnover and less conspicuous NAFLD.

Abnormal lipid turnover in the liver may increase adiposity in obese individuals. Food restriction studies have shown to normalize hepatic lipid metabolism, as well as adipose tissue type transformation associated with an altered immune response in obese individuals [12–16]. The observed gene-environment interactions pinpoints Sirt1 as the major defective gene involved in global obesity and NAFLD epidemics. Sirt1 dysregulation is therefore considered as the more prominent facilitators in the development of obesity, affecting the cell epigenetics (i.e., DNA sequence, methylation, and histone modifications). Like for the hepatic nucleoreceptors [7], the adipose tissue counterparts are subjected to histone deacetylation by Sirt1, targeting transcription factors (TFs) like PGC-1 $\alpha$ , p53, the pregnane X receptor (PXR), where the latter is known to bind vitamin K2 (i.e., MK-4 or MK-7) in order to modulate gene expression, adapting metabolic activity, insulin resistance, as well as the level of cellular and body inflammation [7, 8, 10]. It is well known that Sirt1 is linked to appetite regulation through obesity-related and diabetic genes [8], as well as the DNA repair system.

Transcriptional regulation of metabolic processes depends upon isoforms of PPAR $\gamma$ , interacting with nuclear and mitochondrial genes via influence AMPK (5'-AMP activated protein kinase, AMPK) activation regulated by nutrient availability. Furthermore, Sirt1 deacetylation of Forkhead box protein O1 (FOXO1) controls apoptosis with regulation of xenobiotic metabolism and inflammation, as well as vitamin K2 (MK-4/MK-7). The specific effect of vitamin K2 is described in detail in a separate book on vitamin K2, edited by Gordeladze, to be published in early 2017 by InTech Publishing Company. Suffice to mention here is that the involvement of Sirt1 in adipose tissue transformation is mediated by p53 transcriptional dysregulation, which causes repression of PPAR $\gamma$  and FOXO1, both being instrumental in the lipid metabolism of adipocytes [17–20]. Finally, Sirt1/p53 interactions may modulate the adipocytes' levels of adipocytokines, as well as immune responses, being important to maintain an abnormal adipose tissue-liver cross-talk leading to NAFLD in obesity [21–29].

In animal models of both obesity and diabetes, the disturbed adipogenesis being coupled to NAFLD [6, 30] is probably a result of the enhanced release of adipocytokines (i.e., apelin, leptin, adiponectin, and A-II =angiotensin-II), which is seen with the appearance of hepatic fibrogenesis, NAFLD, as well as neurodegenerative diseases [31, 32]. It is well known that food restriction, activating both Sirt1 and PGC-1 $\alpha$  in tissues of transgenic (fat/NZO) mice, normalized adipose tissue-liver cross-talk being associated with improved body weights, as well as hepatic lipid metabolism, reflecting the usefulness of this model system to adapt successful

treatments of NAFLD in obese patients. As expected, food restriction enhanced hepatic fatty acid oxidation in obese and/or diabetic mice; however, adipose tissue mass (body weights) was not altered in transgenic (i.e., ob, db, and Ay mice) expressing leptin resistance [30], which normally is linked to low activation levels of PGC1 $\alpha$  by leptin.

The enhanced hepatic lipid turnover was not associated with improved adipocyte metabolism in obese, diabetic, and/or agouti mice after prolonged food restriction. However, we have shown that treatment by vitamin K2 of both human stem cells and mouse preadipocytes, with gene-manipulated G<sub>s</sub>- and G<sub>i2</sub>-alpha type G-proteins altered their phenotype from white (WAT) to “beige” (BAT-like), reducing the expression of white adipose tissue genes, while those of brown adipose tissue counterparts were enhanced [33].

The brain-liver-based metabolic pathway for the Alzheimer's disease-related peptide  $\beta$ -amyloid also involves Sirt1 [9]. In these patients, the adipose tissue loses its capability to process the  $\beta$ -amyloid in a normal fashion, now bringing about adipose tissue transformation [12, 31, 32], which leads to leptin resistance and NAFLD. Interestingly, food restriction fully restores the Sirt1/PGC-1 $\alpha$  regulation of adipose tissue and liver lipid/ $\beta$ -amyloid turnover [32], thus involving the immune response with support for a mandatory role of the immune system in the progression of Alzheimer's disease in both the developing and developed world [32, 33]. Furthermore, aberrant posttranscriptional modulation of p53 determines liver affection and adipose tissue type transition in obesity.

Hence, abnormal gene regulation of the adipocytes' metabolism seems to be closely linked to the hepatic lipid turnover, which in turn leads to failure to adapt to the environment, causing senescence and obesity. In obesity, the response to stress signals, which involve both Sirt1 and the tumor suppressor protein p53, which are closely linked to insulin resistance [34] and metabolic processes, but also to cancer and DNA damage. Deficiency of p53 is linked to cancer and is interpreted as if a poor regulation of Sirt1 is involved, predisposing for cancer. An interest in the nutritional modulation of obesity, with or without concomitant diabetes, has increased due to the effects of feeding patterns on Sirt1 and p53, being involved in the reciprocal nuclear-mitochondrial interactions, emerging mutations, as well as apoptosis (cell death) and/or responses encompassing permanent cellular senescence [35–41]. Sirt1 and its posttranscriptional impact on p53 [42, 43] is heavily involved in the differentiation of adipocytes, as well as lipid metabolism in general [44–48], with their implications for abnormal Sirt1 deacetylation of p53, linked to lipid metabolism with its characteristic transformation of adipocytes and ensuing liver disease. Interestingly, both Sirt1 and p53 knockout mice develop NAFLD [49–52], which alludes to a close connections between adipocyte phenotype “switch” involving Sirt 1 and/or p53 impact on mitochondrial functioning [53–56].

The leptin gene is but one of a plethora of genes determining food intake and body weight preservation where the transformation of adipose tissue is closely linked to p53-induced events, overriding the intrinsic control function of leptin or Sirt1 [57] in adipose tissue-based metabolism of both glucose and lipids  $\beta$ -amyloid. Additionally, leptin from adipocytes, with its augmented egress in obese subjects, is linked to inflammatory [58] or immune responses characterized by augmented circulatory levels of inflammatory derived cytokines [12, 16, 20]. The condition known as “hyperleptinemia” is paralleled with enhanced

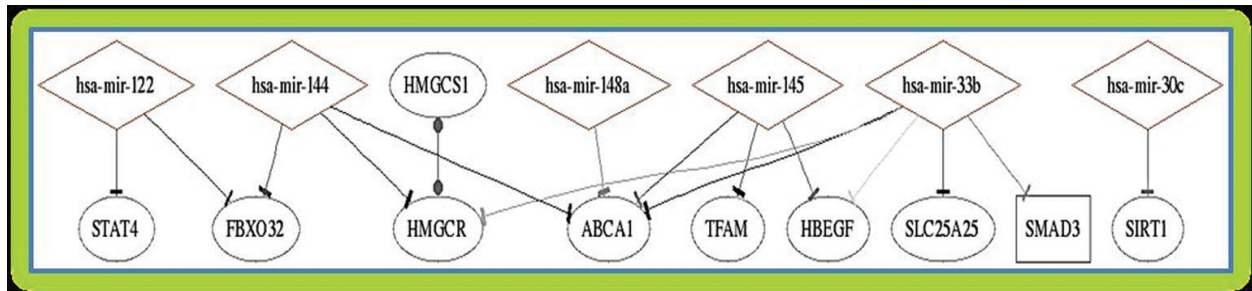
levels p53 and NAFLD, where there is a significant link between peripheral leptin levels, inflammation markers, and Kupffer cell activation [59]. Studies on food restriction in obese/diabetic animals clearly demonstrated a lack of change in body weight, construed as abnormally enhanced adipogenesis with concomitant and leptin disorders, which be relevant to obesity in humans in general [60]. Both in obese animals, as well as in human, a parallel occurrence of NAFLD with hyperleptinemia are construed as being linked to a lack of hepatoprotective ability of the fat cells to secrete adiponectin [61–63], as well as diminished ability to prevent or dampen hepatic inflammation.

A plethora of p53-mediated interactions with the innate immune defense system [64–67] points to a function of p53 leading to immune homeostasis and/or inflammatory disease, which both are associated with hepatocyte senescence, lipid turnover, as well as a recruitment/attraction of natural killer (NK) cells [68, 69]. This persistence of “senescence” characterizing the cross-talk between white adipose tissue (WAT) and the liver does not facilitate the elimination/removal of the senescent cells; however, the p53-related promotion of adipose tissue adipogenesis with the development of NAFLD is allowed to take place. p53 is known to activate and suppress target genes like Sirt1, being associated with the innate immune response [70, 71], as well as and SREBP-1 (sterol regulatory element-binding protein-1) [45, 52], which serves as a key transcriptional regulator of the synthesis of lipids (triglycerides) in adipocytes. Sirt1, with its major role in lipid turnover in adipose tissue, is also metabolically “associated” to adiponectin release via the Sirt1/FOXO1 transcriptional complex [72, 73], known to maintain basic hepatic functions. The regulation of the liver and adipose tissue metabolism becomes evident as the p53 is released from the nucleus, implicating p53 itself and microRNA (miRNA) species in the aberrant regulation of fatty acid turnover in the mitochondria.

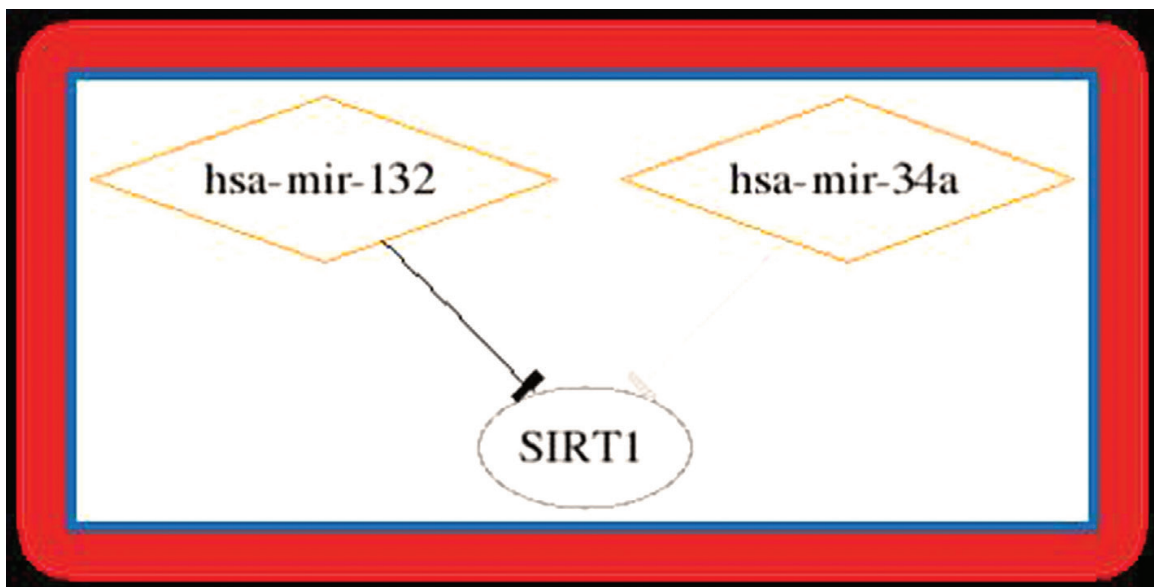
The impact of p53 on gene regulators encompasses miRNAs [74], where their function in the induction of obesity [75] hints to altered expression of multiple miRNA species in metabolic tissues [76, 77]. This also lends an important role to be played by an “abnormal” immune system [78–80]. Hitherto, the following findings pertaining to miRNAs involved are: MiR-103 and -143 have been shown to be important in the “kick-off” and maintenance of adipogenesis [81], where miRNAs, e.g., miR-27 and miR-519d [82] serve as regulators of PPAR $\gamma$  [83], which accounts for the differentiation, as well as the overall number of fat cells. PPAR $\gamma$  is heavily expressed in adipocytes, i.e., especially in WAT, and plays a mandatory role in the Sirt1-mediated transcriptional stimulation of adiponectin and leptin. The PPAR $\alpha$ -mediated activation of Sirt1 yields an increase in lipid turnover through a general enhancement of  $\beta$ -oxidation. Furthermore, p53-associated miRNA dysregulation seems to be of importance, characterizing the aberrant metabolism of adipocyte-derived lipids, linked to the inactivation of nuclear-mitochondrial crosstalk. Angiotensin II (AII, from the adipocytokine Apelin) [31] effectuates PPAR $\gamma$ -Sirt1 expression in the adipose tissue [32, 84, 85], playing a pivotal role in the production and release of adiponectin [31, 32]. Furthermore, miRNA species such as miR-34a [86], miR-122, and miR-132 [87, 88], which directly obliterate the Sirt1-mediated biochemical processes, bring about adiponectin release, to be construed as a poor activation of hepatic genes governing both glucose and lipid turnover [62]. Furthermore, the CCAAT/enhancer-binding protein alpha (C/EBP $\alpha$ ) stimulates Sirt1 expression, which is coupled to adipogenesis through modulation of PPAR $\gamma$  [63], involving miR-34a.

Underneath, a high-stringency emulation (using the Mir@nt@n algorithm), and based on the most recent scientific articles [86–90], the links between microRNA species and genes shown to be implicated in the development of the “fat liver syndrome” are shown in **Figures 1 and 2**, respectively.

Suffice to say, SIRT1, seems to be modulated by hsa-mir-30c, while, ABCA1-levels are determined by the integrated input of signals emanating from micro-RNA species like hsa-MiRs 144, 148a, 145, and 33b. Future studies of these MiRs will show whether they might be targets or markers for gene manipulations normalizing liver metabolism, and thus combatting adiposity, in patients with aberrant lipid metabolism and/or adiposity.



**Figure 1.** High stringency emulation of gene-microRNA interactions, showing the impact of microRNA species on some “master” genes involved in the development of supersized adipocytes with the WAT (white adipocyte tissue-phenotype) alongside a fatty liver in patients developing nonalcoholic fatty liver disease (NAFLD).



**Figure 2.** High stringency emulation of gene-microRNA interactions, showing the impact of microRNA species on some “master” genes involved in the development of a fatty liver in patients developing nonalcoholic fatty liver disease (NAFLD).

### 3. LPS modulation of Sirt1/p53 interactions is coupled to fat ingestion, dysfunction of the immune system, and metabolic liver disease

The immune-based hypotheses involve the aberrant regulation of Sirt1/p53 and a lack of adaptation to the environment, which implicates an abnormally functioning immune system in both the pathogenesis of insulin resistance and aging [85, 86]. Diets, which are high in fat and low in fibrous compounds, are linked to an enhancement of gut microbiota in the circulation, with impact on immune functions, lowered insulin sensitivity, as well as energy homeostasis in both animals and humans [77–83]. Noteworthy, animals fed a high fat/cholesterol diet demonstrated enhanced levels of bacterial endotoxins (known as lipopolysaccharides, LPS) with a parallel enhancement of inflammatory processes [64–66]. In this respect, both LPS and cytokines have been associated with enhanced hepatic sphingolipid synthesis with altered ceramide contents, which has been associated with peripheral insulin resistance. In obese mice, a change in inflammatory responsiveness was demonstrated subsequent to LPS administration [9, 10], followed by an alteration in intestinal microbiota and NAFLD, known to be closely correlated with systemic inflammation and the metabolic syndrome [11–16]. Hence, it was shown (verified) that the immune system is involved in the crosstalk between adipose tissue and liver, which inevitably implicates bacterial toxins in the pathogenesis and further development of NAFLD and obesity.

The LPSs are dimeric polysaccharide moieties linked to a lipid core, anchored within the cell membrane [18, 19], and have been shown to effect hepatic genomic stability [20] affecting reverse cholesterol transport (RCT) in macrophages by downregulation PPAR $\gamma$  [21–30]. LPSs have demonstrated to directly affect mitochondrial DNA synthesis linked to mitochondrial dysfunction [31]. LPSs are also involved in adipocyte-macrophage intercommunication, enhancing systemic inflammatory responses [32], being linked to DNA damage [33]. LPS and fat absorption have received increased interest, related to their effects on the Sirt1-mediated modulation of hepatic cholesterol homeostasis, as well as their impact on  $\beta$ -amyloid metabolism [34].

LPS-binding proteins (LBPs) associate with LPS and alter inflammatory responses [35]. The LBPs, as well as leptin, are both upregulated in the obese, impinging on biological phenomena, like the expression of leptin, appetite, and obesity-provoked inflammatory reactions [36–40]. LPS has, since long, been demonstrated to affect the efflux of cholesterol via the liver X Receptors (LXR) and the ATP-binding cassette transporter 1 (ABCA1) [41, 42] pathways, of which the latter is overriding the Sirt1-mediated impact on LXR-ABCA1 interactions. A lowering of the ingestion of fat [35] suppresses plasma LPS levels, and has therefore become a strong tool in the reduction of both the development and impact of metabolic diseases on health in general. LPS has been shown to modulate SREBP expression in macrophages, while also subduing liver PGC1 $\alpha$  expression [29, 42, 43], and thus being associated with an abnormal Sirt1-regulation of basal adipocyte cell functioning [27, 44]. The LPS-facilitated “blockage” of the elimination of cholesterol from macrophages has been demonstrated to serve as



an important factor in the cholesterol-rich lipoprotein intercommunication network [45–47], thus impacting on LPS neutralization in metabolic diseases, with focus on diabetes [48–50].

LPS-induced production of interferon-gamma (IF $\gamma$ ) has been shown in both NK-cells and T- lymphocytes impacting genes encoding inflammatory cytokines, glucose metabolism, and macrophage-related modulation of genes in adipocytes [51, 52]. IF $\gamma$  has also been shown to affect genes, like Sirt1 and p53 apoptosis coupled genes, whose role are being “dissociated” in dysfunctional stages of metabolism [45–53]. The impact of IF $\gamma$  on chromatin modeling stimulates macrophages, controlling gene transcription, thus regulating inflammatory cytokine production in activated macrophages [46, 47]. In this context, MiR-34a and other MiRs are involved in the modulation of the IF $\gamma$ -mediated innate immune responses [48, 49]. However, one has discovered an inverse correlation between adiponectin and inflammatory cytokines, with adiponectin levels being associated with NK-cell activation [50–52].

The LPS-stimulated biological effect on p53-induced apoptosis in the liver [53, 54] surpasses the effect of Sirt1 as to the deacetylation of p53, reducing the hepatic lipid turnover. Hence, the p53-mediated downregulation of PXR activity [55, 56] is not dependent of the Sirt1/PXR-mediated reactions [57–60]. Therefore, the untoward p53/PXR interactions, which lead to NAFLD, are coupled to an altered expression of miRNA species related to the turnover of xenobiotics [61–63]. In this context, xenobiotic metabolism has been shown to be disturbed in obese individuals, which is associated with enhanced lipid synthesis [63], disturbed immune reactions [62], and marked apoptosis [64, 65]. The high levels of phthalates contained within alimentary like milk, butter, and meats are linked to the Sirt1/p53 interactions [66–68], which couples the phthalates to NAFLD and adiposity in communities worldwide [68].

Furthermore, the focus on  $\alpha$ -synuclein and its impact on the immune system in the periphery [69, 70] and CNS [71, 72] have emerged as knowledge about its regulatory impact on p53 transcriptional regulation of apoptosis has increased. Sirt1-mediated effects on hepatic  $\alpha$ -synuclein and amyloid- $\beta$  turnover are closely linked to LPS [72], metabolic diseases, as well as obesity, with observed impact on p53 transcriptional regulation by both  $\alpha$ -synuclein and amyloid- $\beta$  metabolism in the liver and brain [73–77].

#### **4. Nutrigenomic diets block both hepatic and adipose tissue damage in obese individuals**

A lack of effect of some anti-obese medications [78] in the treatment of obese patients has paved the way for nutrigenomic dieting, hopefully preventing the development of senescence of various tissues being implicated in chronic disease states [1]. In obese patients, the success to be gained in early interventional treatments of NAFLD may depend upon individuals [7, 8] having a BMI value of between 25 and 30 kg/m<sup>2</sup>, with a genuine reversal of adipose tissue transformation being coupled to solid improvements in glucose turnover immunoregulatory capacity, as well as NAFLD. In patients showing BMI values greater than 30 kg/m<sup>2</sup>, unhealthy diets inducing abnormal Sirt1/p53 interactions are often associated with changes in the levels of various microRNAs, inducing a chronic failure in the DNA repair system,

which accelerates hepatic senescence with ensuing adipose tissue inflammatory responses, as well as a dysfunctional lipid metabolism and aberrant energy expenditure.

Diets containing sufficient and appropriate protein “species,” carbohydrates, and low in fat upregulate both Sirt1 expression and activity in cells, leading to a positive effect on nuclear and mitochondria events, thus sustaining both lipid turnover and energy expenditure. And, not to surprise anyone, food-restricted diets in young and genetically obese and diabetic mice, induce a reversal of hepatic lipid metabolism, involving Sirt1/p53 interactions, which yields improved adipogenesis in man. Nutritional regulation may maintain p53 deacetylation by Sirt1, and thus sustain the “healthy” glucose homeostasis, which is paralleled with a swift energy disposal within adipose tissues. Additionally, ingested foods [32], able to block programmed cell death pathways, may be associated with expression of the Sirt1-gene, thus activating adipose tissues to synthesize and release factors (e.g., adiponectin) [32], which will suppress the impact of inflammatory cytokines, in order to sustain “normal” liver function, thus blocking the induction of NAFLD in humans. Nutrigenomic diets, as for instance high fiber diets [79], will kick-start an “engineered” metabolism, allowing for a joint physiological nuclear and mitochondrial interaction, which will stimulate the PPAR $\gamma$ -Sirt1 and Sirt1-PXR interactions coupled to both therapeutic nutrient and xenobiotic metabolism, that are associated with positive effects on p53 half-life and cell apoptosis [80].

Dieting and the immune system serve as synonymous with dietary fat and its composition being associated with NK cell activity and immune responses in the adipose tissue [81–83]. The suppression of Sirt1 expression by dietary fat is now associated with an abnormal p53 mediated posttranscriptional regulation of NK cells [69, 83]. Furthermore, dietary fat may facilitate the absorption of LPS in rodents, but also man, by modulating the suppression of Sirt1 effects, while also promoting p53-mediated cell death. Hence, food restriction slows down LPS absorption, followed by an obliteration of LPS inhibition of cholesterol turnover in macrophages by the promotion of a reverse cholesterol transport.

A plethora of theories describing the process(es) of aging have been launched, however, the “immune theory” involves fat tissue transformation alongside an activation of its inherent immune responses, encompassing macrophages and other immune cells. However, this adaptation model system is furthermore thought to include adipose tissues as the organs showing the highest susceptibility to apoptosis, with pathways of transformation largely linked to various mutations in a plethora of genes in different cells and tissues [6]. Hence, diets and our immune system are efficiently “cooperating” with our endogenous intestinal microbial flora (i.e., Gram-negative bacteria) and environmental factors, impinging on dietary fatty acid compositions, which play a pivotal role in the immune homeostasis and reactivity of the liver. The Sirt1's involvement in the mitochondria theory of aging brings about a close link to mitochondrial dysfunction (i.e., Sirt1 downregulation), as well as an abnormal immune response [68, 84–86]. An essential requirement of some amino acids (e.g., leucine) [93] may sustain a nuclear and mitochondria p53-associated transport, along with an enhancement in the half-life of p53, as well as a blockage of immune dysfunction and development of NAFLD.

Nutrigenomic diets, like the low calorie diets, activating Sirt1, may lower plasma cholesterol concentrations [30], thus preventing hepatic p53-mediated apoptosis by xenobiotics and LPS.

A series of drugs, which inhibit Sirt1 [92] have been developed, which prevent leucine-mediated activation of Sirt1 and xenobiotics (e.g., phthalates), modifying Sirt1 chromatin association, with an ensuing induction of p53-mediated apoptotic responses [91–93] in both the liver and adipose tissue.

## 5. Summary

An increase in NAFLD/obesity in communities around the world, show that epigenetic modifications are linked to malfunctioning of the gene Sirt1 along with p53 dysregulation of a defective adipose tissue-liver crosstalk. Healthy low calorie diets and/or an active lifestyle, maintaining adequate Sirt1/p53 interactions in obese individuals may decrease organ senescence, as well as age-related mutations to occur. The ingestions healthy foods devoid of components like sugars, fats, xenobiotics, and LPS may obliterate the induction of p53 cell-based apoptosis and Sirt1 suppression, but also enhance hepatocyte life span, thus preserving hepatocyte nuclear and mitochondrial interactions. Metabolic stimulators of Sirt1 (i.e., leucine, polyphenols (e.g., resveratrol) and catechins) may enhance hepatic xenobiotic turnover, as well as preventing mitochondrial death, linked to the dysregulation of NAFLD.

Nutritional diets, which promote the binding of Sirt1 to chromatin, thus preventing it from association, induced by various drug regimens, as well as unhealthy diets, will inevitably also prevent adipose tissue transformation, as well as activation of immune responses involving macrophages, NK cells, and lymphocytes that are associated with NAFLD, as well as other diseases seen in various habitats and communities.

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