Role of FOXO3a in the Liver

Subjects: Toxicology

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Forkhead box O (FOXO) transcription factors are members of the forkhead box (FOX) family that have a highly conserved forkhead DNA-binding domain (DBD). FOXO transcription factors have been discovered in several species, including the worm (daf-16), the fly (dFoxO), zebrafish, rodents, and humans. To date, four key elements of the mammalian FOXO subfamily have been found, including FOXO1, FOXO3a, FOXO4, and FOXO6. These proteins have a high level of profile similarity and vary mainly in their tissue-specific expression. FOXO3a has been investigated extensively as a special and crucial regulator of cellular homeostasis, lifespan, and stress response. FOXO3a is regarded as a crucial regulator of many essential cellular processes, including cell proliferation, apoptosis, autophagy, and ROS detoxification. FOXO3a's subcellular distribution, protein–protein interactions, stability, and transcriptional selectivity may be influenced by ROS through post-translational modifications (PTMs) and epigenetic processes, as shown by accumulating data.

oxidative stress FOXO3a transcription factor liver injury mitochondria cell survival

1. FOXO3a-Autophagy Axis

Autophagy is a progressively preserved lysosomal degradation procedure that removes long-lived toxic aggregates of cellular proteins, lipids, injured organelles, and intracellular pathogens. Autophagy serves as a critical adaptive event in response to changed cellular signaling or stresses and has a crucial function in cellular renovation and preservation of cellular homeostasis [1][2][3][4][5][6]. FOXO3a has been implicated in autophagy in a variety of cells to protect them from various stresses [7][8][9][10]. Notably, several studies have revealed that FOXO3a induces the expression of numerous autophagy genes, such as genes related to autophagy initiation (Atg101, Ulk1/2), vesicle nucleation (Atg14, Vps34), elongation (LC3b, Atg5), and mitophagy (Bnip3, Beclin1, Pink1), through binding to the promoter regions and transactivating the expression of autophagy genes in response to oxidative stress.

Ethanol treatment has the potential to produce excessive reactive oxygen species (ROS) in hepatocytes, particularly superoxide ($O_2^{\bullet-}$), and to elicit significant liver oxidative injury, such as steatosis, inflammation, fibrosis, and cirrhosis, through mitochondrial damage and endoplasmic reticulum stress. Interestingly, it has been revealed that acute ethanol treatment modulates autophagy as a compensatory pathway to mitigate ethanol-induced liver injury [11]. Acute ethanol treatment significantly increased the expression of many key autophagy-related genes, including Ulk1, Atg5, Beclin1, Bnip3, Bnip3L, Atg7, LC3b, Atg14, and Vps34, which were induced by nuclear translocation of FOXO3a in primary cultured mouse hepatocytes and in the liver. Multiple post-translational modifications (PTMs), such as Akt- and Sirt1-mediated reduced phosphorylation and enhanced deacetylation of FOXO3a, were discovered to defend against alcohol-induced liver damage through nuclear translocation and

transcriptional regulation of those autophagy-related genes. FOXO3a$^{-/-}$ mice treated acutely with ethanol demonstrated lower expression of autophagy-related genes, but elevated liver damage. These findings indicate that FOXO3a is a crucial factor in regulating in vitro and in vivo ethanol-induced autophagy and cell survival [12]. Furthermore, another study indicated that the Farnesoid X Receptor (FXR) mediated the stimulation of FOXO3a in ethanol-induced autophagy and hepatotoxicity. Acute alcohol treatment in Farnesoid X Receptor (FXR) KO mice was found to stimulate Akt, enhance FOXO3a phosphorylation, and reduce FOXO3a nuclear retention, in addition to the transcription of autophagy genes Atg5, Becn-1, and MAP1LC3B, thereby inducing hepatic mitochondrial spheroid formation, which may be utilized as a compensatory substitute mechanism to eliminate damaged mitochondria induced by ethanol [13]. According to these findings, the lack of FXR disrupted FOXO3a-mediated autophagy, which, in turn, increased alcohol-induced liver damage. Furthermore, the AMPK–FOXO3a axis has been revealed to regulate autophagy-related genes, including Beclin-1 and LC3B, in both primary rat hepatocytes and human liver cells [14].

Mitophagy, the selective destruction of damaged mitochondria by autophagy, is necessary to maintain healthy mitochondria. Mitophagy dysfunction in hepatic cells has been identified in several liver disorders [15]. Defective mitophagy leads to increased ROS production, ATP depletion, apoptosis-related protein production, and dysregulated stress signaling transduction [16]. By inhibiting mitophagy, 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47) has been shown to induce mitochondrial dysfunction, redox state imbalance, and accompanying liver oxidative damage. Evident liver injuries were observed in BDE-47-treated mouse livers, and the ROS production and MDA content were markedly increased, while the expression and activity of mitochondrial antioxidative enzyme MnSOD were notably decreased in the livers. These results indicate that BDE-47 induces mitochondrial dysfunction and related liver oxidative injury in mice. Additionally, in the livers of mice supplemented with BDE-47, Parkin, an E3 ubiquitin ligase, was significantly down-regulated. Furthermore, BDE-47 dramatically decreased both the LC3II/LC3I ratio and the expression of mitochondrial LC3II protein. Furthermore, it is demonstrated that BDE-47 significantly inhibited the expression and activity of Sirt3, resulting in a substantial rise in the protein expression of Ac-FOXO3a and a reduction in the protein expression of PINK1 in vivo. Notably, miR-34a-5p significantly inhibited Sirt3/FOXO3a/PINK1-mediated mitophagy in BDE-47-treated mouse liver to enhance mitochondrial dysfunction and hepatotoxicity [17]. These results demonstrate that FOXO3a is essential for the control of mitophagy to protect the liver from xenobiotic-induced oxidative stress.

A study by Zhou Y. et al. discovered FOXO3a to be a direct downstream target of miR-223, mediating the decrease in the LC3-II/LC3-I ratio and the elevation of p62 expression, leading to the suppression of doxorubicin-induced autophagy in hepatic cells [18]. Interestingly, FOXO3a also has been implicated in the promotion of a specific form of autophagy known as lipophagy in the liver. In vitro and in vivo analyses established that FOXO3a could positively regulate Atg14 gene expression via a reaction with the cis-elements of proximal insulin response elements (IRE) [19]. Notably, the expression of many autophagy-related genes, such as LC3B, Gabarapl1, Bnip3, and Bnip3l, can contribute to FOXO3a in the circadian induction of autophagy. In a recent work, the authors found that insulin controls the molecular clock in a PI3K- and FOXO3a-dependent method, suggesting a critical function for the insulin-FOXO3a-clock signaling mechanism in the regulation of circadian rhythms [20]. FOXO3a is also implicated in connecting the circadian clock to metabolism in the mouse liver [21]. All these studies suggest that the

FOXO3a-autophagy axis is pivotal in regulating liver oxidative injury. Although it is well recognized that FOXO3a can directly cause the expression of autophagy genes throughout its transactivation processes in xenobiotic-induced liver injury, the regulation of its own gene expression and the underlying mechanisms of specificity based on the stress trigger and physiological context are widely undefined.

2. FOXO3a-Regulated Apoptosis

Apoptosis is a spontaneous and orderly programmed cell death modulated by related genes, resulting in the self-elimination of excessively damaged or nonfunctional cells [22]. Oxidative stress can trigger excessive apoptosis by modifying critical cellular components via the mitochondrial pathways [23]. Multiple signaling mechanisms are involved in oxidative-stress-induced hepatocyte death, including the ERK1/2, SGK, JNK, and FOXO3a signaling mechanisms. The suppression of autophagy enhances the accumulation of FOXO3a and the transactivation of many proapoptotic genes by FOXO3a in response to oxidative stress. There is evidence that FOXO3a is a crucial transcriptional regulator of Bim and PUMA expression. Due to its ability to bind to and neutralize all prosurvival Bcl-2 members, it is regarded as the most effective of the proapoptotic BH3-only proteins. Even so, the particular cell signal mechanism differs based on the intensity and period of oxidative stress as well as the cell type, and the underlying mechanisms of the balance between proapoptotic and pro-survival activities of FOXO3a remain obscure. A better understanding on how FOXO3a-dependent apoptosis is differentially controlled in the liver may provide insight into the etiology of xenobiotic-induced liver oxidative damage.

Wnt/β-catenin and FOXO3a have been revealed to have a crucial function in protecting the liver versus 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) and paraquat [24]. The stimulation of Wnt/β-catenin signaling inhibits FOXO3a-induced cell death by up-regulating the β-catenin target gene serum/glucocorticoid regulated kinase 1 (SGK1). Conversely, SGK1 was considerably reduced, which prevented it from inactivating FOXO3a, leading to the nuclear retention of FOXO3a and elevated proapoptotic target gene expressions of p27 and Bim in β-catenin KD livers exposed to oxidative stress. In addition, the removal of FOXO3a boosted hepatocyte resistance to oxidative-stress-induced apoptosis, validating FOXO3a's proapoptotic involvement in the stressed liver. These data imply that the phosphorylation of FOXO3a by SGK1 inhibits its apoptotic activity, hence increasing hepatocyte survival [24].

Ac-FOXO3a is more likely to cause cell death, while deacetylated FOXO3a exhibits activated transcriptional function and antioxidant potential [25]. Recent research suggests that the environmental contaminant hexavalent chromium (Cr(VI)) generated an elevation in acetylated FOXO3a by suppressing Sirt1 expression and activating the Bim/PUMA axis, culminating in oxidative-stress-mediated death in hepatocytes. Treatment with resveratrol, a Sirt1 activator, significantly reduced acetylation and reversed liver damage, indicating that resveratrol may have a therapeutic effect on Cr(VI)-induced liver injury. In contrast, suppression of Sirt1-mediated deacetylation of FOXO3a exacerbates oxidative stress and the development of Cr(VI)-induced hepatotoxicity. These investigations established the connection between acetylation of FOXO3a and apoptosis triggered by environmental contaminants, establishing the foundation for a more complete comprehension of chemical hepatotoxicity [26].

Interestingly, FOXO3a expression is highly associated with enhanced cell death in the liver of chronic ethanol-fed rats and negatively related with suppressed β-catenin signaling. Ethanol exposure reduced the phosphorylation of FOXO3a and increased nuclear localization of FOXO3a, as well as the exhibition of liver injury and apoptosis in rats. The proapoptotic protein Bim, a downstream target gene of FOXO3a, was up-regulated, together with antiapoptotic signals modulated by Bcl-2, Bcl-XL, and pro-caspase 3 which were inhibited in the liver. Moreover, it demonstrated that SGK1 functional kinase activity, but not Sirt1, was needed for FOXO3a-induced apoptosis. Chronic ethanol consumption inhibited β-catenin signaling and resulted in SGK1 expression reduction, which in turn supported FOXO3a increase to cause hepatocyte death, suggesting that FOXO3a has a key function in promoting the death of hepatocytes [27].

Although it is known that the dephosphorylation of FOXO3a caused by a decrease in SGK1 in response to alcohol exposure promotes the expression of proapoptotic genes over antioxidant genes, the precise locations necessary for this interaction remain unknown. Recent evidence indicates that ethanol stimulates the JNK-dependent phosphorylation of FOXO3a at serine-574, and that p-574-FOXO3a preferentially attaches to promoters of proapoptotic genes but not to antioxidant targets in hepatocytes, showing that p-574-FOXO3a is exclusively pro-apoptotic. The Bcl-2 promoter was bound by both unphosphorylated and p-574-FOXO3a, but the unphosphorylated form was a transcriptional activator and the p-574-FOXO3a form was a transcriptional repressor. In addition, targeted alterations at S-574 reveal that the charge at this position is a crucial determinant of FOXO3a's proapoptotic action. It is indicated that S-574 phosphorylation creates a particularly apoptotic form of FOXO3a after ethanol treatment in hepatocytes [28]. Interestingly, a recent study has demonstrated that acute ethanol gavage induced FOXO3a-dependent Kupffer cell apoptosis in mice and subsequently protected against ethanol-induced liver injury via attenuating the liver pro-inflammatory phenotype mediated by promoting infiltrating macrophage differentiation [29]. Although the finding explored the link between FOXO3a and inflammation in xenobiotic-induced liver injury, a better understanding of the potential pathways remains to be determined.

In addition, the transcriptional regulation of Bim by FOXO3a has also been implicated in lipoapoptosis in some hepatocytes treated with saturated free fatty acids (FFA). FFAs induced FOXO3a dephosphorylation/activation by protein phosphatase 2A (PP2A), but not a reduction in the phosphorylated form of Akt and SGK in Huh-7 cells, HepG2 cells, and murine hepatocytes, highlighting the PP2A–FOXO3a–Bim pathway as a critical toxicity pathway in the regulation of apoptosis [30]. A similar study showed that the decrease in the phosphorylation of FOXO3a at Thr32, modulated by stimulation of the phosphatase PP2A, which is needed for 14-3-3 binding, suppressed FOXO3a turnover, caused a nuclear gathering of p53, inhibited cytoplasmic p53, and suppressed mitochondrial-mediated cell death. These data indicate that interactions between p53, FOXO3a, and 14-3-3 lead to reduced benzo[a]pyrene (BaP)-caused death in cells co-exposed to TCDD, PCB 153, or estradiol, and targeting FOXO3a might thus damage a cell's capability to carefully handle xenobiotics via the weakening of cell death [31].

Although autophagy and apoptosis have been extensively investigated in xenobiotic-induced liver injury, the coordination and interplay between FOXO3a and the processes of oxidative damage are complicated and are not fully understood. In general, both autophagy and apoptosis as partners affect each other, and autophagy tends to be antiapoptotic by elevating the cutoff point of stress needed to cause apoptosis [32]; however, the mechanisms

that determine the basal grades of autophagy and the cutoff point for death are still in their infancy. Taken together, these studies establish a dual autophagy–apoptosis regulatory role of FOXO3a to maintain cellular homeostasis to further regulate liver oxidative injury, but the interaction between the intrahepatic signaling response and FOXO3a transcriptional programs of different xenobiotics, as well as the specific mechanisms, need further investigation.

3. FOXO3a-Mediated Regulation of the Antioxidant System

Excessive generation of ROS has been widely implicated in the etiology and progression of liver oxidative injury by various chemicals [33][34][35][36]. An increasing number of studies show that the FOXO3a signaling pathway protects hepatocytes from oxidative damage by stimulating the transcription of genes coding for multiple antioxidants and ROS detoxification. Many antioxidant enzymes, such as GSH-Px, MnSOD, Peroxiredoxin (Prx), Catalase, and mitochondrial oxidative phosphorylation (OXPHOS), have been found to be up-regulated at the transcriptional level upon activation of the FOXO3a pathway through the direct or indirect binding of FOXO3a to the promoters of these target genes in the nuclei or mitochondria. Studies show that MnSOD catalyzes dismutation of superoxide to generate oxygen and hydrogen peroxide (H_2O_2). H_2O_2 is further dismutated to water and oxygen in a reaction catalyzed by a peroxisomal heme peroxidase, called catalase. Alternatively, peroxiredoxins are also the major cellular enzymatic scavengers that control H_2O_2 level, which are known gene targets of FOXO3a. The up-regulation of these antioxidant enzymes can reduce cellular ROS production, consequently ameliorating oxidative injury, and raise cellular survival in the stressed liver [12][37][38][39][40]. In this respect, a better understanding is necessary for the function of FOXO3a in mediating nuclear–mitochondrial crosstalk because they can influence each other's activities, such as oxidative stress response.

On the other hand, mitochondria homeostasis preserves the role and integrity of the mitochondria by coordinating its biogenesis and fusion–fission dynamics involving FOXO3a-dependent pathways. FOXO3a controls ROS metabolism by suppressing the expression of a set of nuclear-encoded mitochondrial genes by stimulating the expression of MAX dimerization proteins (MAD/MXD) and modifying the stability/function of the c-MYC protein. In addition, FOXO3a stimulation reduced the mtDNA copy number, the expression of mitochondrial proteins, and the levels of respiratory complexes, therefore significantly lowering ROS formation [41]. Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is a well-characterized master regulator of mitochondrial biogenesis and a set of genes related to mitochondrial function and oxidative metabolism. Significantly, FOXO3a may protect cells from oxidative stress by interacting directly with PGC-1α. FOXO3a and PGC-1α are recruited to the identical promoter regions and trigger a set of antioxidative genes [42], as shown by co-immunoprecipitation and in vitro interaction experiments. In addition, FOXO3a is a direct transcriptional regulator of PGC-1α, indicating that an auto-regulatory loop controls the FOXO3a/PGC-1α regulation of mitochondrial oxidative stress protection [42].

Recent research has demonstrated that the Sirt3-mediated deacetylation of FOXO3a positively modulates related genes in order to coordinate mitochondrial fission and fusion. Mitochondrial fusion is induced by mitofusin 1 (Mfn1), Mfn2, and optic atrophy 1 (OPA1) to mediate the repair of damaged mitochondrial DNA, whereas mitochondrial fission is regulated by dynamin-related protein 1 (Drp1) and Fis1 to initiate the separation of damaged mitochondria from healthy mitochondria. Mitochondrial fission and fusion can be targeted for degradation, the consequences of

which improve mitochondrial efficiency and cellular tolerance to oxidative damage involving FOXO3a in liver oxidative injury caused by chemicals such as senecionine [43][44][45][46].

Overall, FOXO3a functions as a pivotal transcription factor responsible for several transcriptional programs such as cell survival and death. Nonetheless, the precise mechanisms of FOXO3a that govern transcriptional program specificity need to be further investigated, including the basal level of protein expression, different cell types of the liver, special PTMs, epigenetic regulation, key cofactors, stress stimuli, and so on. Moreover, although increased ROS formation has been widely acknowledged as a crucial mechanism underlying the cytotoxicity and liver injury caused by various chemicals, other mechanisms beyond ROS may also be critically involved in FOXO3a-mediated effects for many chemicals.

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