ACOX1 destabilizes p73 to suppress intrinsic apoptosis pathway and regulates sensitivity to doxorubicin in lymphoma cells

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Lymphoma is one of the most curable types of cancer. However, drug resistance is the main challenge faced in lymphoma treatment. Peroxisomal acyl-CoA oxidase 1 (ACOX1) is the rate-limiting enzyme in fatty acid β-oxidation. Deregulation of ACOX1 has been linked to peroxisomal disorders and carcinogenesis in the liver. Currently, there is no information about the function of ACOX1 in lymphoma. In this study, we found that upregulation of ACOX1 promoted proliferation in lymphoma cells, while downregulation of ACOX1 inhibited proliferation and induced apoptosis. Additionally, overexpression of ACOX1 increased resistance to doxorubicin, while suppression of ACOX1 expression markedly potentiated doxorubicin-induced apoptosis. Interestingly, downregulation of ACOX1 increased resistance in lymphoma cells, while downregulation of ACOX1 inhibited proliferation and induced apoptosis. Additionally, overexpression of ACOX1 increased resistance to doxorubicin, while suppression of ACOX1 expression markedly potentiated doxorubicin-induced apoptosis. Importantly, downregulation of ACOX1 destabilized p73 to suppress intrinsic apoptosis pathway and regulates sensitivity to doxorubicin in lymphoma cells.

INTRODUCTION

Malignant lymphoma is one of the most common hematologic malignancies and comprises 3.37% of all malignancies globally (1). Incidence rate of all lymphoma, Non-Hodgkin or Hodgkin lymphoma is approximately 20.3%, 17.37% or 2.92% (2), respectively. Incidence of malignant lymphoma globally increased at a rate of approximately 3-4% per year (1). Overall five-year survival rate for people with Non-Hodgkin or Hodgkin lymphoma is 53.7% or 78.9% (2), respectively. Standard treatments for lymphoma are anthracycline-based combinatorial chemotherapy regimens. Although patients achieve complete response after initial treatment, a substantial proportion of patients relapse. Relapsed lymphomas are refractory to subsequent treatments and exhibit cross-resistance to a variety of anti-cancer drugs (3, 4). Emergence of acquired chemoresistance poses a challenge in successful treatment of lymphoma. Thus, understanding the mechanism of drug resistance is crucial for successful treatment of lymphoma.

Acyl-CoA oxidase 1 (ACOX1) is a flavoenzyme that catalyzes the first and rate-limiting reaction of desaturation of very-long-chain acyl-CoAs to 2-trans-enoyl-CoAs and transfers electrons to molecular oxygen to generate hydrogen peroxide (5). ACOX1 deficiency usually causes peroxisomal disorders and has been linked to human diseases, such as pseudo-neonatal adrenoleukodystrophy (6). Recent studies indicate that ACOX1 may involve in cancer development. ACOX1 knockout mice display growth retardation, infertility, excess very-long-chain fatty acids in the blood, microvesicular steatohepatitis, apoptosis, liver regeneration, and oxidative stress (7, 8). ACOX1 knockout mice eventually develop hepatocellular carcinoma (9). Findings suggest that peroxisomal ACOX1 dysfunction contributes to development of chronic liver disease and hepatocarcinogenesis. Currently, little is known about the role of ACOX1 in other cancers, including...
lymphoma, and the mechanism behind it remains to be elucidated.

p73, a member of the p53 family of tumor suppressors, shares a remarkable homology in DNA sequence and protein structure with p53 (10). p73 displays a certain degree of functional overlap with p53 (10). p53 is usually inactivated in human cancer by point mutations, but the p73 gene is rarely mutated in human cancers (10). Currently, p73 was found to be suppressed through various mechanisms including epigenetic silencing and post-translational modifications (11). In malignant lymphoma, mechanisms of epigenetic silencing or deletion are commonly responsible for inactivation of the p73 gene (12). However, how post-translational modifications regulate p73 protein stability has not been fully elucidated in malignant lymphoma.

In this study, we examined the role of ACOX1 in lymphoma cells. We found that ACOX1 was essential for proliferation of lymphoma cells. Overexpression of ACOX1 reduced the sensitivity of lymphoma cells to doxorubicin. While downregulation of ACOX1 significantly enhanced doxorubicin-induced apoptosis. Additionally, ACOX1 participated in regulation of apoptosis by regulating activation of caspase-9 and caspase-3, and mitochondrial membrane potential. Importantly, p73, but not p53, was critical for mediating ACOX1 regulated apoptosis response. ACOX1 reduced p73 expression by destabilizing p73 protein. Our data indicated that ACOX1 could be a novel target for increasing drug sensitivity and improving treatment of lymphoma.

RESULTS

ACOX1 regulates proliferation and apoptosis

To evaluate the role of ACOX1 in lymphoma, ACOX1-Flag or ACOX1 shRNA were stably expressed via lentivirus-mediated gene transfer in lymphoma cells. As shown in Fig. 1A and Supplementary Fig. 1A, ACOX1-Flag was overexpressed in lymphoma cells. Overexpression of ACOX1-Flag significantly promoted proliferation in lymphoma cells (Fig. 1B, Supplementary Fig. 1B). While knockdown of ACOX1 expression (Fig. 1C, Supplementary Fig. 1C) markedly suppressed proliferation of lymphoma cells (Fig. 1D, Supplementary Fig. 1D). These data indicated that ACOX1 was essential for regulating lymphoma cell proliferation. We further examined if ACOX1 may participate in regulation of apoptosis. As shown in Fig. 1E, F and Supplementary Fig. 1E, F, overexpression of ACOX1-Flag did not cause apoptosis. While downregulation of ACOX1 slightly induced apoptosis as compared with negative control (NC) group (Fig. 1G, H, and Supplementary Fig. 1G, H). To further confirm the effect of ACOX1 on apoptosis, TUNEL assay was performed. Consistently, upregulation of ACOX1 did not cause apoptosis (Fig. 1I, J), while downregulation of ACOX1 induced apoptosis (Fig. 1K, L). These data implied that ACOX1 may participate in regulation of apoptosis in lymphoma cells.

ACOX1 modulates doxorubicin-induced cytotoxic effect

Anthracycline-based combinatorial chemotherapy regimens are the most commonly used and efficacious regimens in lymphoma. Due to ACOX1 participation in regulation of apoptosis (Fig. 1G, H, and Supplementary Fig. 1G, H), we next evaluated if ACOX1 may affect cytotoxic effects of doxorubicin. As shown in Fig. 2A, B and Supplementary Fig. 2A, B, 0.6 μM doxorubicin treatment alone induced significant apoptosis in lymphoma cells. However, overexpression of ACOX1 markedly reduced doxorubicin caused apoptosis (Fig. 2A, B and Supplementary Fig. 2A, B). Also, our data showed...
ACOX1 destabilizes p73 to suppress intrinsic apoptosis
Fei-Meng Zheng, et al.

Fig. 2. ACOX1 modulates doxorubicin-induced cytotoxic effect. (A, B) ACOX1 expressed Raji cells and control cells (Con.) were treated with doxorubicin (0.6 μM) or control solvent for 48 hours. Cells were subjected to apoptosis analysis (A). Statistical results are shown (B). (C, D) shACOX1 expressed Raji cells and control cells (NC) were treated with doxorubicin (0.1 μM) or control solvent for 48 hours. Cells were subjected to apoptosis analysis (C). Statistical results are shown (D). (E, F) Treatment was the same as (A) and (B). Cells were subjected to TUNEL assay analysis (E). Statistical results are shown (F). (G, H) Treatment was the same as (C) and (D). Cells were subjected to TUNEL assay analysis (G). Statistical results are shown (H). The bar represents mean ± SD of three independent experiments (*P < 0.05, **P < 0.01, ***P < 0.001, The ANOVA test, followed by Least Significant Difference test, were used to make statistical comparisons).

Fig. 3. Downregulation of ACOX1 induced apoptosis through the intrinsic pathway. (A) shACOX1 expressed Raji cells (sh) and control cells (NC) were treated with doxorubicin (0.1 μM) or control solvent for 48 hours. Cells were subjected to WB analysis. (B) shACOX1 expressed Raji cells (sh) and control cells (NC) were treated with LEHD, DEVD, IETD or control solvent for 24 hours. Cells were subjected to apoptosis analysis. Statistical results are shown. (C) shACOX1 expressed Raji cells (sh) and control cells (NC) were subjected to total protein extraction or cytoplasmic/mitochondria protein extraction. These proteins were subjected to WB analysis. (D) Treatment was similar with (A). Cells were subjected to mitochondrial membrane potential analysis. (E) ACOX1 expressed Raji cells and control cells (Con.) were treated with doxorubicin (0.6 μM) or control solvent for 48 hours. Cells were subjected to WB analysis. (F) The treatment was similar with (E). Cells were subjected to mitochondrial membrane potential analysis. The bar represents mean ± SD of three independent experiments (*P < 0.05, **P < 0.01, ***P < 0.001, The ANOVA test, followed by Least Significant Difference test, were used to make statistical comparisons).

that the combination of ACOX1 downregulation and doxorubicin treatment resulted in greater apoptosis in lymphoma cells than was achieved with either ACOX1 downregulation or doxorubicin alone (0.1 μM) (Fig. 2C, D and Supplementary Fig. 2C, D). To further confirm the above results, the TUNEL assay was performed. Consistently, upregulation of ACOX1 reduced doxorubicin-induced apoptosis (Fig. 2E, F), while downregulation of ACOX1 enhanced doxorubicin-induced apoptosis (Fig. 2G, H). These data indicated that ACOX1 could be a potential target to enhance cytotoxic effects or prevent drug resistance of doxorubicin.

Downregulation of ACOX1 induced apoptosis through the intrinsic pathway
We next examined the mechanism of ACOX1 regulated apoptosis. As shown in Fig. 3A and Supplementary Fig. 3A, downregulation of ACOX1 significantly increased activities of caspase-9 and caspase-3, correlating with increased PARP cleavage. Cleavage of procaspase-8 was not significantly altered after downregulation of ACOX1 (Fig. 3A and Supplementary Fig. 3A). We confirm this by using different caspase inhibitors, including LEHD (inhibition of caspase-9 or caspase-3), DEVD (inhibition of caspase-3) and IETD (inhibition of caspase-8). As shown in Fig. 3B, LEHD or DEVD effectively reversed shACOX1 induced apoptosis. While IETD did not reverse shACOX1 induced apoptosis (Fig. 3B). These data imply that ACOX1 mainly regulated apoptosis through the intrinsic apoptotic pathway. Consistently, the combination of ACOX1 downregulation and doxorubicin treatment induced a more significant increase of activated caspase-9 and
ACOX1 destabilizes p73 to suppress intrinsic apoptosis

We found that p53 expression was not induced by downregulating ACOX1 (Fig. 4A and Supplementary Fig. 4A), while p73 expression was enhanced by downregulating ACOX1 (Fig. 4A and Supplementary Fig. 4A). We also examined the expression of two p53 phosphorylated sites (Ser15 and Ser20) required for p53-dependent apoptosis. A previous study showed that PPARα expression may counteract the apoptotic effect. Interestingly, our data shows that overexpression of ACOX1 effectively rescued doxorubicin-induced reduction of caspase-9 and caspase-3 and PARP cleavage. Consistently, overexpression of ACOX1 reversed doxorubicin-induced activation of caspase-9 and caspase-3 and PARP cleavage. Thus, overexpression of ACOX1 destabilizes p73 to reduce apoptosis.

In this study, we elucidated the oncogenic role of ACOX1 in lymphoma. Our data shows ACOX1 was essential for proliferation of lymphoma cells. Additionally, overexpression of ACOX1 alleviated doxorubicin-induced apoptosis, while downregulation of ACOX1 aggravated doxorubicin-induced apoptosis. Also, ACOX1 participated in regulation of apoptosis by modulating mitochondrial membrane potential and activation of caspase-9 and caspase-3. Importantly, ACOX1 regulates p73 expression at the post-translational level.

**DISCUSSION**

In this study, we elucidated the oncogenic role of ACOX1 in lymphoma. Our data shows ACOX1 was essential for proliferation of lymphoma cells. Additionally, overexpression of ACOX1 alleviated doxorubicin-induced apoptosis, while downregulation of ACOX1 aggravated doxorubicin-induced apoptosis. Also, ACOX1 participated in regulation of apoptosis by modulating mitochondrial membrane potential and activation of caspase-9 and caspase-3.
destabilizes p73 to suppress activation of the intrinsic apoptosis pathway.

Peroxisomes play a critical role in metabolism of reactive oxygen species, bile acids, very-long-chain, and branched-chain fatty acids (16). Cancer cells usually reprogram metabolism to support their malignant phenotype. Dysfunction of peroxisomes may lead to metabolic alterations and contribute to cancer development (17). Current study suggests that deregulation of peroxisome function may contribute to drug resistance in lymphoma cells (18). Peroxisomal ACOX1 is commonly expressed in most tissues and is critical for desaturation of very-long-chain acyl-CoAs to 2-trans-enoyl-CoAs. ACOX1 deficiency caused endoplasmic reticulum stress, accumulation of reactive oxygen species, VLCFAs and enlarged peroxisomes and is connected with human disease (19, 20). In this study, we show that ACOX1 functioned as an oncogene in lymphoma cells to promote proliferation and counteract doxorubicin-induced apoptosis. Our data implies that suppression of ACOX1 could be a novel and effective approach for treatment of lymphoma. Deficiency of ACOX1 results in activation of PPARα and induces progressive endoplasmic reticulum stress contributing to hepatocarcinogenesis (9). The lack of ACOX1 and PPARα causes absence of spontaneous peroxisome proliferation in aged mice (21), indicating that PPARα is critical for ACOX1 regulated effects. In our study, upregulation of PPARα was also observed when ACOX1 expression was downregulated. In this situation, upregulation of PPARα may be a protective mechanism for lymphoma cells to escape apoptosis. This phenomenon implies that the combination of ACOX1 and PPARα suppression could achieve more significant anti-cancer effects.

Expression of p73 is maintained at low levels in mammalian cells and is usually controlled through mechanisms including epigenetic silencing and post-translational modifications (11). In this study, our data suggests that p73 was destabilized via a proteasome related-degradation mechanism during ACOX1 overexpression in malignant lymphoma cells. The mechanism of p73 degradation has not been fully elucidated. A previous study showed that Itch, a Nedd4-like HETC-E3 ubiquitin ligase, selectively binds and ubiquitinates p73 to induce proteasome-dependent degradation of p73 (22). Also, NEDL2 binding and stabilization in a NEDL2-dependent manner (23). Additionally, NQO1 physically interacts with p73 in an NADH-dependent manner and protects it from 20S proteasomal degradation (24). Additionally, DNA damage can induce phosphorylation of p73 by c-Abl, leading to stabilization of p73 protein (25). Our data provides a novel ACOX1-related mechanism to demonstrate deregulation of p73 expression in lymphoma. p73 is induced in response to DNA damage. A previous study showed that deficiency of ACOX1 results in increased intracellular H2O2 levels (9), usually causing DNA damage and stress. We speculated that destabilization of p73 may be caused by downregulating ACOX1 induced DNA damage and stress response. Besides, our data indicates that ACOX1 interacted with p73, implying that interaction between ACOX1 and p73 may interfere with degradation of p73 protein via proteasome related-mechanism. However, more data about the physical interaction between ACOX1 and p73 is needed to elucidate the mechanism.

In conclusion, our study uncovers a previously unknown oncogenic function of ACOX1 in lymphoma. We anticipate that our findings will provide a new target for overcoming drug resistance of traditional chemotherapy in lymphoma.

MATERIALS AND METHODS

Detailed information is provided in the Supplementary Information.

Reagents and cell culture

Doxorubicin, Cycloheximide (CHX), MG132, HW-14643, and Annexin V-FITC Apoptosis Detection Kit were purchased from Sigma-Aldrich (MA, USA). Antibodies against Flag, Caspase-3, Caspase-8, Caspase-9, PARP, Bax, phospho-Bad (Ser112), Cytochrome C, p53, p53(Ser15), p53(Ser20), p73, and GAPDH were purchased from Cell Signaling Technology (Boston, USA). Antibodies against ACOX1 was purchased from Abcam (Cambridge, U.K.). Antibody against puromycine was purchased from Merk (Darmstadt, Germany). LEHD, DEVD, and IETD were purchased from R&D Systems (MN, USA). Raji and Daudi cells were obtained from the ATCC (Manassas, VA, USA) and were cultured in RPMI-1640 (Thermo Fisher Scientific, USA) supplemented with 10% fetal bovine serum (Thermo Fisher Scientific, USA). Cells were maintained at 37°C in a humidified 5% CO2 atmosphere.

Western blot (WB) analysis

Cells were lysed in RIPA buffer containing protease inhibitors. Equal amounts of protein were analyzed by electrophoresis in SDS-PAGE gels. Proteins were transferred to nitrocellulose membrane. Nitrocellulose membranes were blocked by 3% BSA in TBST at RT and then were incubated with indicated antibodies at 4°C overnight. Nitrocellulose membranes were incubated for one hour at room temperature with secondary antibodies. Antibody binding was evaluated with an enhanced chemiluminescence kit (Pierce, USA).

Lentivirus preparation and transfection

Lentivirus preparation and transfection were described previously (26). 5 × 10⁶ 293T cells were transfected with 12 µg lentiviral vector, 9 µg psPAX2 (Addgene, MA, USA) and 3 µg pMD2.G (Addgene, MA, USA). Supernatants were collected every 24 hours after 12 hours transfection and concentrated via ultracentrifugation. Viral titer was determined by serial dilutions. Multiplicity of infection for transfection was 10.

Statistical analysis

Statistical analyses were performed using SPSS software,
version 16.0 (SPSS Inc.). The ANOVA test, followed by Least Significant Difference test, was used when performing multiple comparisons (27). Level of significance was set at P < 0.05.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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