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Arsenic trioxide induces autophagic cell death in osteosarcoma cells via the ROS-TFEB signaling pathway

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ABSTRACT

Osteosarcoma is a common primary malignant bone tumor, the cure rate of which has stagnated over the past 25–30 years. Autophagy modulation has been considered a potential therapeutic strategy for osteosarcoma, and previous study indicated that arsenic trioxide (ATO) exhibits significant anti-carcinogenic activity. However, the ability of ATO to induce autophagy and its role in osteosarcoma cell death remains unclear. In the present study, we showed that ATO increased autophagic flux in the human osteosarcoma cell line MG-63, as evidenced by the upregulation of LC3-II and downregulation of P62/SQSTM1. Moreover, the pharmacological or genetic blocking autophagy decreased ATO -induced cell death, indicating that ATO triggered autophagic cell death in MG-63 cells. Mechanistically, ATO induced $TFEB^{(Ser142)}$ dephosphorylation, activated TFEB nuclear translocation and increased TFEB reporter activity, which contributed to lysosomal biogenesis and the expression of autophagy-related genes and subsequently initiated autophagic cell death in MG-63 cells. Importantly, ATO triggered the generation of ROS in MG-63 cells. Furthermore, NAC, an ROS scavenger, abrogated the effects of ATO on TFEB-dependent autophagic cell death. Taken together, these data demonstrate that ATO induces osteosarcoma cell death via inducing excessive autophagy, which is mediated through the ROS-TFEB pathway. The present study provides a new anti-tumor mechanism of ATO treatment in osteosarcoma.

1. Introduction

Osteosarcoma (OS) is the most prevalent bone malignancy in childhood and adolescence, which most commonly occurs in the long bones of the limbs, with highly aggressive and early systemic metastases [1]. Standard osteosarcoma therapy generally involves a combination of surgery, multi-therapeutic agents, and ionizing radiation, and these treatments have improved the benefit of osteosarcoma patients [2]. However, over the last decades, there have been no noticeable improvements in patient survival, suggesting that it is important to discover new agents for the better treatment of breast cancer.

Arsenic trioxide (ATO) is a chemical with the formula As_2O_3, which has been clinically used as part of the standard treatment for patients with acute promyelocytic leukemia (APL). This compound has recently attracted considerable attention because of accumulating data demonstrating its strong inhibitory effect on various solid tumors, including osteosarcoma. ATO prevents osteosarcoma growth by the inhibition of GLI transcription via DNA damage accumulation [3]. Additionally, ATO induces apoptosis of osteosarcoma MG-63 cells through the inhibition of catalase [4]. Although these findings suggest that ATO could exert its anti-tumor activities by targeting multiple pathways, further investigations are required

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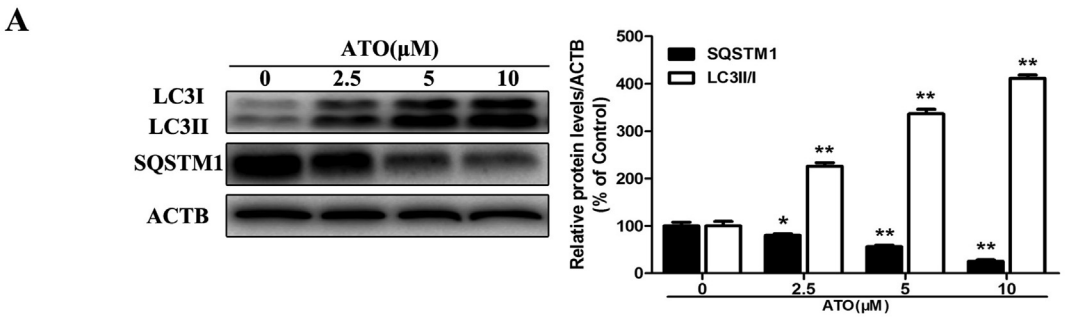

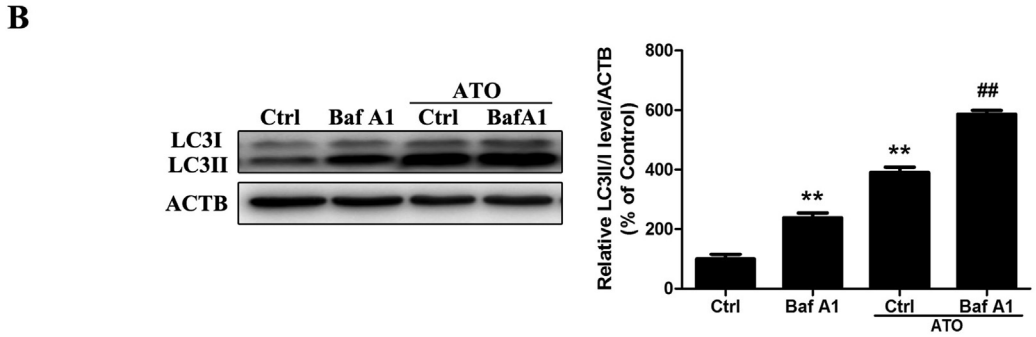

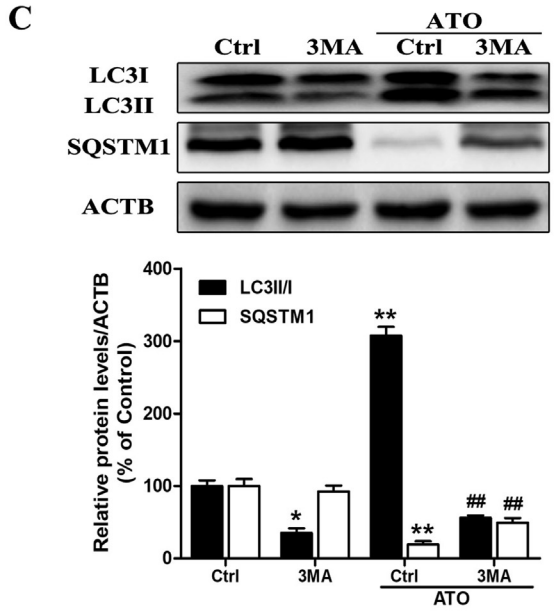

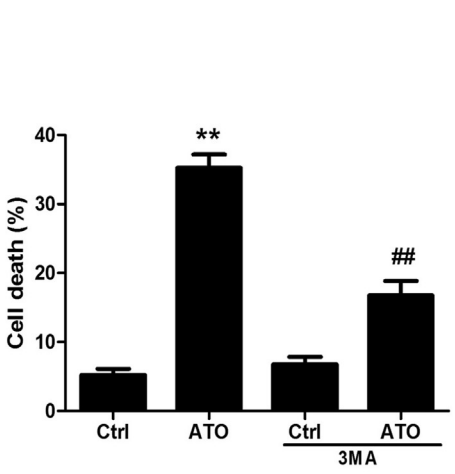

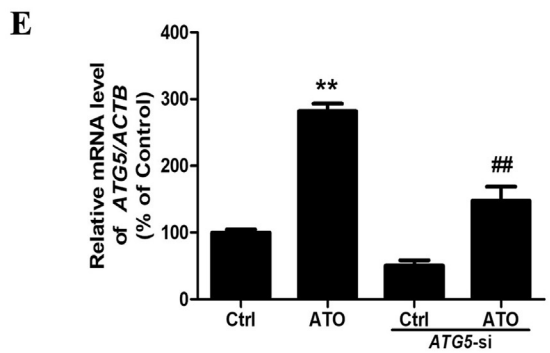

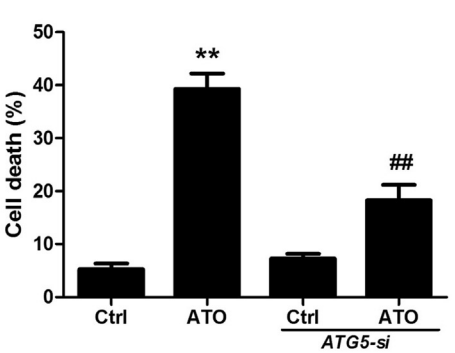

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