

ENHANCED MITOCHONDRIAL BIOGENESIS AND FUNCTIONS MEDIATE KERATINOCYTE PROLIFERATION IN ARSENIC-INDUCED BOWEN'S DISEASE

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Background:

Multiple Bowen's disease is a hallmark of skin cancer caused by arsenic and it has been reported that arsenic-mediated genotoxicity requires normal mitochondrial functions. Recently, accumulated mitochondrial DNA mutations and loss of mitochondrial function are present in many types of skin cancers. In addition, early carcinogenesis requires the enhanced proliferation mechanism and increased oxidative DNA damages, necessitating the participation of mitochondrial role in biogenesis and generation of reactive oxygen species (ROS), respectively. Moreover, in the pathology of arsenic-induced Bowen's disease (As-BD), clues of abnormal mitochondrial functions come from aberrant cellular proliferation and oxidative DNA damages.

Objectives:

The study aims to investigate if arsenic interferes with mitochondrial biogenesis and functions, leading to cell proliferation in As-BD.

Methods:

Tissues from patients with As-BD and control skin are used for immunohistochemistry for cytochrome c oxidase (Complex IV), a major component of mitochondrial respiratory chain. Mitochondrial DNA (mtDNA) copy numbers, mitochondrial-related biogenesis genes, mitochondrial oxygen consumption rate, and cellular ATP production level are determined in arsenic-treated keratinocytes and As-BD. Keratinocytes are treated with arsenic with or without mitochondrial inhibitors for mitochondrial biogenesis.

Results:

We found an increase in epidermal thickness and cytochrome c oxidase expression in the tissue of patients with As-BD. Cellular proliferation, accompanied with increased mitochondrial biogenesis and its key regulatory factor, mitochondrial transcription factor A (mtTFA) which mediates mtDNA transcription and translation, is significantly promoted in both As-BD and arsenic-treated keratinocytes. Besides, increased oxygen consumption and ATP production also reflect enhanced mitochondrial functions in both As-BD and arsenic-treated keratinocytes. Targeting mtTFA by interference RNA or blocking of mitochondria function by oligomycin abolishes the proliferation effect by arsenic.

Conclusions:

We demonstrate that increase in numbers and functions of mitochondria contribute to arsenic-induced cell proliferation. Aberrant mtTFA upregulation augments mitochondrial biogenesis and contributes to arsenic-induced keratinocyte proliferation in arsenic skin cancers. Taken together, targeting to mitochondrial biogenesis may provide a therapeutic modality to inhibit arsenic skin carcinogenesis in the early stage of Bowen's disease.

Keyword:

Arsenic; Bowen's disease; Carcinogenesis; Mitochondrial biogenesis; Mitochondrial transcription factor A (mtTFA)