AOX1 regulates xenobiotic metabolism in Bladder cancer (BCa): Implications for Bladder

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Introduction

Bladder cancer (BCa), the most common cancer of the urinary tract, has higher incidence in men compared to women in western countries. [1]

Etiologically, occupational exposures (aromatic amine and polycyclic aromatic hydrocarbon exposures), tobacco smoking are well known to contribute to the occurrence of BCa. [2]

AOX1 (Aldehyde oxidase1) is a cytosolic phase -I xenometabolic enzyme actively participating in cellular metabolism and xenobiotic metabolism of aldehyde containing compounds, N-Heterocycles, azodyes, nitropolycyclic aromatic hydrocarbons.

Bladder cancer development

Heat map of the altered xenobiotic metabolites in clinically diagnosed BCa tissues.

Expression of AOX1 by TMA

Tissue micro array TMA of 175 from different grade patients show the high expression of AOX1 in low grade than high grade.

Experimental

The Agilent 6490 LC/TQ and 6550 QTOF LC-MS system were used to generate the analytical results.
Results and Discussion

Altered xenobiotic metabolites in BCa tissues.

Heat map of the stages wise altered xenobiotic metabolites in different of clinically diagnosed BCa tissues.

Down regulation of AOX1 in BCa progression

qPCR (A, B) and Immunoblot (C,D) from clinically diagnosed different stage patients and different grade cell lines confirms that the high grade tumors are losing the AOX1. Immuno fluorescence staining (E) of different grade cell lines suggests the low grade cell lines having high expression of AOX1 than high grade cell lines.

Switching of AOX1 associated metabolites in KD and OE BCa cell lines

A and B: Immunoblot confirms the knock down and over expression of AOX1 in benign cell lines (SVHUC) and cancer cell lines (5637) respectively. C and D show the switching of AOX1 associated metabolites in knock down and over expressed cells.
Results and Discussion

Negative correlation of AOX1 with EZH2

Reactivation of AOX1 in methylation inhibited BCa cell lines

BCa cell lines (J82, T24) treated with methylation inhibitors show the over expression suggesting the AOX1 inhibition in high grade cancer through hyper methylation.

Conclusions

- Xenobiotic metabolites are altered during bladder cancer development.
- Loss of AOX1 xenobiotic enzyme and alteration in its associated metabolites during BCa progression.
- Loss of AOX1 expression in higher stages of BCa is probably due to methylation associated epigenetic modification. Further studies are going on to elucidate the loss of AOX1 and its implications in BCa development.

References


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