SKIN CANCER (OTHER THAN MELANOMA)

THE ROLE OF TOX AND TOX-REGULATED GENES IN MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

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Background: Mycosis fungoides (MF) is the most common type of primary cutaneous T cell lymphoma (pCTCL), and Sézary syndrome (SS) is another type of pCTCL which is related to MF. In MF, the DNA-binding protein TOX is overexpressed, corresponding with both disease severity and prognosis. TOX plays an oncogenic role in pCTCL, but the specific mechanism is still unclear.

Objectives: To find downstream target genes of TOX and explore their effects on cellular functions. To investigate the expression levels of these TOX-regulated genes in MF patients. Further on, to clarify the pathogenic mechanism of TOX and TOX-regulated genes in MF/SS.

Materials and Methods: Overexpression and knockdown of TOX in MF cell lines were performed by viral vector transduction. Transcriptome sequencing data was analyzed by Software EdgeR and GO Enrichment. Quantitative reverse-transcription polymerase chain reaction (qRT-PCR) and western blot were used to detect the expression of TOX-regulated genes in MF/SS cell lines and skin tissues. Cell proliferative activity was investigated by CCK8 cell proliferation assay. In situ expression of TOX-regulated genes in skin tissues was evaluated by immunohistochemical staining.

Results: Multiple genes were regulated by TOX in MF cell line, with an enrichment in 36 gene ontology (GO) terms regarding cellular compartments and biological processes. Among these genes, the expression of 25 genes was significantly altered by TOX, including PRKAR2B, CDCA7L, DPP4, CTLA4 and TNIK. Down-regulation of PRKAR2B, CDCA7L, DPP4 and TNIK inhibited cell proliferation in MF/SS cell lines, and the expression of PRKAR2B, DPP4, CTLA4 and TNIK in the skin lesions from MF patients tended to be greater compared to control.

Conclusions: TOX may participate in the onset and progression of MF/SS through up-regulation of PRKAR2B, DPP4 and TNIK, which promote proliferative tumor cell activity.