TSPYL2, a sex specific player in the DNA damage response of cancer cells

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TSPY-Like 2 (TSPYL2) is a nuclear protein, encoded by an X-linked gene, that belongs to the testis-specific protein Y-encoded (TSPY-L) nucleosome assembly protein-1 superfamily. Members of this family are involved in cell cycle regulation, transcription and chromatin remodeling through the modulation of histone acetylation.

Published data suggest that TSPYL2 is implicated in the DNA damage response (DDR), a network of molecular pathways that cells have evolved to prevent the replication of a damaged and therefore potentially harmful cell. Indeed, TSPYL2 is involved in the maintenance of G1/S checkpoint in response to ionizing radiation and regulates p53 activity upon camptothecin treatment. In cancer, TSPYL2 expression has been found reduced in glioma, lung, breast and hepatocellular carcinoma and mutated in endometrial cancer. Moreover, TSPYL2 reduces the growth of lung and breast cancer cells and a reciprocal regulation with TGFβ has been reported. However, the physiological functions of TSPYL2 in both DDR and cancer are still unknown and need to be clarified.

Sexual dimorphism has been demonstrated to play a critical role in cancer incidence and survival. Interestingly, at present, no sexual dimorphisms have been reported in DDR pathways. Recently we demonstrated that TSPYL2, by inhibiting SIRT1 and promoting p300 function, regulates p53 activity and apoptosis induction in response to different genotoxic stress. During these studies, we have also found that TSPYL2 protein is induced in untransformed cells after etoposide treatment, whereas in cancer cells TSPYL2 induction is specific for female cells or for male cells that lost the Y chromosome during the oncogenic process. However, TSPYL2 mRNA is induced also in those cell lines where the protein does not accumulate and, specific siRNAs transfection, revealed that E2F1 is the transcription factor responsible for TSPYL2 expression regulation upon genotoxic stress. Moreover, experiments performed with TSPYL2-KO cells, obtained by CRISPR/Cas9, show that TSPYL2 induction increases cell survival upon DNA damage. The obtained results suggest for TSPYL2 a tumor suppressor role and crucial functions in the DDR, possibly gender specific at least in cancer cells.

Therefore, the aims of our studies are to clarify the mechanisms regulating TSPYL2 expression upon DNA lesions and to elucidate the sex specific function of TSPYL2 in the DDR. Results of these studies will increase the knowledge of DDR activation, tumorigenesis and cancer progression, possibly explaining the mechanisms at the basis of cancer sexual dimorphism. In addition, this research will provide useful insights for the development of new and personalized anti-cancer strategies, revealing also if TSPYL2 could be in the future a target for cancer therapy or a marker for patients’ diagnosis and prognosis.


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