SKIN CANCER (OTHER THAN MELANOMA)

LOSS OF ZEB1 GENE IN SEZARY SYNDROME

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Introduction: Cutaneous T cell lymphoma (CTCL) is a group of incurable non-Hodgkin lymphomas that develop from the skin-homing CD4+ T cell. Mycosis fungoides and Sézary syndrome (SS) are the most common subtypes. Although next-generation sequencing data provided advances in the comprehension of the genetic basis of CTCL, there is not uniform consensus on the identity and prevalence of putative driver genes for this heterogeneous group of tumors.

Objective: To increase the knowledge about the complex genetic etiology characterizing SS.

Materials and Methods: We used SNP6 array and GISTIC algorithm to prioritize focal somatic copy-number alterations in a dataset of sequential samples from 21 SS patients. Quantitative PCR was used to assess mRNA level, DNA sequence analysis for mutational screening and Kaplan-Meier estimator for survival analysis. Gene Set Enrichment Analysis was employed to identify predefined signatures associated with genotypic/phenotypic differences. Knockout Sézary cell lines were used for validation experiments.

Results: We confirm a prevalence of significant focal deletions targeting tumor suppressor genes (TP53, PTEN and RB1). In our cohort ZEB1 spans a deletion having the highest level of significance; it is affected by deletions and somatic inactivating mutations in 46.5% of cases. We found potentially relevant ZEB1 germline variants and a worse clinical course for patients with ZEB1 bi-allelic inactivation. Multiple abnormal expression signatures were found associated with ZEB1 depletion: we verified that ZEB1 exerts a role in oxidative response of Sézary cells.

Conclusions: We confirmed the importance of deletions in the pathogenesis of CTCL. ZEB1 abnormalities in SS fulfills the criteria of a canonical tumor suppressor gene. Although additional confirmations are needed, we suggest, for the first time, that ZEB1 germline variants might contribute to the risk of developing this disease. We provide evidence that

ZEB1 in Sézary cells influences the reactive oxygen species production affecting cell viability and apoptosis.