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Abstract 7322: Polygenic adaptation and co-regulatory dynamics in Chernobyl wolves: Unveiling immune and oncogenic stress interactions with implications for human cancer resilience FREE

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Abstract

Wolves living in the Chernobyl Exclusion Zone (CEZ) for at least six generations have adapted to high radiation exposure and are a unique model for studying genetic selection under extreme conditions of oncogenic stress. The objective of this study was to build off previously described signatures of adaptation in CEZ wolves, identify networks of genes associated with immune adaptation in CEZ wolves, and determine prognostic significance of these genes in human cancer datasets to provide insight into immune adaptation and cancer immunity.

RNA from blood samples of wolves in CEZ, Belarus (BLR), and Yellowstone (YLS) were sequenced previously. Here we analyzed these data by mapping wolf transcripts to human orthologs. Radiation exposure (in CEZ and BLR) was quantified by intramuscular Cesium-137. Differential gene expression (DESeq2), network co-expression analysis (lmQCM), and gene set variation analysis (GSVA) assessed transcriptomic changes between populations. Germline single nucleotide polymorphism (SNP) for all three populations were inferred from RNA-seq data.

Genes differentially regulated between populations, including gene modules showing signatures of polygenic selection through increased rates of genetic divergence (p< 0.05) in CEZ wolf populations, were deemed as outlier genes. Those n=3,180 CEZ outlier genes were then investigated in human cancer data from The Cancer Genome Atlas (TCGA) to determine prognostic impact in 10 tumor types highly conserved between human and canines.

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GSVA confirmed activation of neutrophil and macrophage signatures in CEZ wolves and suppression of several adaptive immune-related signatures ($p < 0.05$ vs BLR and YLS). A signature including immune checkpoint targets was also significantly differentially expressed in CEZ wolves. In TCGA, Cox PH analysis identified 23 genes over-expressed in CEZ wolves with significant positive prognostic impact in ≥ 2 human tumor types. PTPN6, previously identified to have positive prognostic value in bladder cancer[1], was also prognostic in three additional tumor types. In human bladder cancer, genes identified as differentially regulated in CEZ wolves were disproportionately associated with improved survival.

As predicted, gene signature variations in CEZ wolves reveal a distinct immune profile, likely shaped by prolonged radiation exposure. These findings, along with evidence of polygenic selection, suggest adaptation to multigenerational radiation exposure (an oncogenic stress). Notably, the enrichment of genes with positive prognosis in human cancer overexpressed in CEZ wolves present a valuable model to explore genetic underpinnings of cancer immunity and advance our understanding of cancer resilience in humans.

Reference: [1]Shen C. et al. The Analysis of PTPN6 for Bladder Cancer: An Exploratory Study Based on TCGA. Dis Markers. 2020.

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