PTEN loss affects the immune and inflammatory response in prostate cancer

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Abstract/Resumo

Loss of the PTEN tumor suppressor gene occurs in 20-30% of prostate cancer (PCa) cases and is associated with worse disease outcome. Recent evidence highlights the role of inflammation in the tumor microenvironment (TME) and its association with PCa disease progression. The aim of this study is to determine if PTEN genomic loss is associated with the inflammatory response mediated by IFN regulated pathways in the TME. We performed an in silico analysis of genomic and corresponding transcriptomic profiles PCa tumors (n=493) from the Genomic Data Commons (GDC) cohort to identify significant alterations in immune response pathways when PTEN was lost. We identified 449 genes of interest using the Gene ontology (GO) Biological Function in Nexus Expression 3.0 with the keywords “Immune” and “Inflammatory”. We detected that 104 tumors (21%) had either homozygous or hemizygous loss of PTEN. We also found significant associations between PTEN loss, 17p loss and 21q loss (TMPRSS2-ERG fusion gene). PTEN loss was directly associated with worse PCa outcome. Of the 449 selected immune genes, 124 (28%) were differentially expressed when the PTEN loss group was compared to the PTEN intact group. Different cytokines and chemokines presented differential expression by comparing PTEN loss vs. PTEN intact PCa samples. IL13RA1, CXCL9, CXCL10, CXCL11 and CXCL14 showed upregulation in PTEN loss group ($P<0.0001$), while CXCL12 was found to be downregulated in PTEN loss group. DAVID enrichment analysis showed upregulation of 16 pathways, including RIG-I-like signaling pathway ($P<0.0001$), chemokine signaling pathway ($P<0.0001$), and toll-like receptor signaling pathway ($P<0.0001$). In addition, we identified ten downregulated pathways, including cytokine-cytokine receptor interaction pathway ($P<0.003$) and intestinal immune network for IgA production pathway ($P<0.006$). The 25 most differentially expressed genes were associated directly with type I and II IFN response. Collectively, our findings based on in silico studies suggest that PCa with PTEN loss exhibits dysregulated Type I and II IFN response that permits progression to an aggressive disease phenotype. Future investigations will be required to define the mechanisms underlying these correlations, and their role in PCa disease progression so that inflammation biomarker can be therapeutically exploited using immunotherapies.

Keyword/Palavras-chave: Silico studies; Disease progression; Inflammation biomarker; Immunotherapies

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