ROLE OF PROTEIN KINASE Cβ IN ADULT T-CELL LEUKEMIA LYMPHOMA

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Background:
In ATLL, recurrent somatic mutations in PKCβ and other T-cell receptor (TCR) pathway mediators drive signaling through NFκB to IRF4. We sought to determine if PKCβ represents a therapeutic target for ATLL and to identify downstream effectors and biomarkers of TCR signaling *in vivo*.

Methods:
In order to examine the role of PKCβ and PKCβ D427N, found in ATLL, we performed cell-based FRET kinase assays, and we examined ATLL proliferation and transcriptional profiles in the presence of PKCβ specific inhibitor, enzastaurin. We also transduced mouse hematopoietic stem cells (HSCs) to express PKCβ or PKCβ D427N, and examined transcriptional and hematologic effects. Lastly, we examined PKCβ expression in ATLL subjects.

Results:
The D427N substitution increased basal activity and decreased stimulated activity of PKCβ. Enzastaurin specifically inhibited ATLL proliferation in culture and produced a gene expression signature consistent with ferroptosis. Expression of PKCβ in HSCs led to intrinsic suppression and extrinsic expansion of T cells *in vivo*. Genes expressing checkpoints, including PD1 and TIGIT, as well as the T cell co-stimulator CD28, were suppressed by wild-type PKCβ, but not by the D427N mutant. Additionally, PKCβ expression in patient-derived PBMCs increased 4-fold following treatment with PD-1 inhibitor, nivolumab, coincident with disease progression.

Conclusion:
Although PKCβ is a tumor suppressor, it may play an oncogenic role in ATLL, through TCR activation and inhibition of ferroptosis. Elevated expression of checkpoints may offer a selective advantage of CTL escape to PKCβ D427N expressing cells. These findings support the pursuit of PKCβ as a therapeutic target in ATLL, and provide a mechanism to explain the selective advantage of the D427N substitution in this malignancy.

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