Title of the Contribution:
PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis.

Abstract:
T cell non-Hodgkin lymphomas are a heterogeneous group of highly aggressive malignancies with poor clinical outcomes. T cell lymphomas originate from peripheral T cells and are frequently characterized by genetic gain-of-function variants in T cell receptor (TCR) signalling molecules. Although these oncogenic alterations are thought to drive TCR pathways to induce chronic proliferation and cell survival programmes, it remains unclear whether T cells contain tumour suppressors that can counteract these events. Here we show that the acute enforcement of oncogenic TCR signalling in lymphocytes in a mouse model of human T cell lymphoma drives the strong expansion of these cells in vivo. However, this response is short-lived and robustly counteracted by cell-intrinsic mechanisms. A subsequent genome-wide in vivo screen using T cell-specific transposon mutagenesis identified PDCD1, which encodes the inhibitory receptor programmed death-1 (PD-1), as a master gene that suppresses oncogenic T cell signalling. Mono- and bi-allelic deletions of PDCD1 are also recurrently observed in human T cell lymphomas with frequencies that can exceed 30%, indicating high clinical relevance. Mechanistically, the activity of PD-1 enhances levels of the tumour suppressor PTEN and attenuates signalling by the kinases AKT and
PKC in pre-malignant cells. By contrast, a homo- or heterozygous deletion of PD-1 allows unrestricted T cell growth after an oncogenic insult and leads to the rapid development of highly aggressive lymphomas in vivo that are readily transplantable to recipients. Thus, the inhibitory PD-1 receptor is a potent haploinsufficient tumour suppressor in T cell lymphomas that is frequently altered in human disease. These findings extend the known physiological functions of PD-1 beyond the prevention of immunopathology after antigen-induced T cell activation, and have implications for T cell lymphoma therapies and for current strategies that target PD-1 in the broader context of immuno-oncology.

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