

Insights from a thirty-year journey of PD-1: function, regulation and therapeutic modulation

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The discovery of PD1 in 1992 as a molecule associated with T cell activation-induced cell death marked the beginning of a 30-year journey of scientific exploration into the function, regulation, and therapeutic modulation of this protein. Over the years, we have uncovered that PD1 plays a critical role in preventing overactivation-induced cell death and autoimmunity, whereas its inhibition can unleash the power of the immune system to fight cancer. In my presentation, I will outline the journey from the discovery of PD1 to its role as a breakthrough target in cancer immunotherapy. I will describe its regulation and function and examine how a mechanistic understanding of PD1 signalling reveals its central function in setting the activation threshold for T cells. By controlling T cell proliferation, differentiation, exhaustion and metabolic status, PD1 helps to maintain immune homeostasis. I will explore how this threshold theory, in combination with new insights into T cell metabolism and the impact of the microbiota on immune cell modulation, can provide guidance for the development of efficient combination therapies. Moreover, I will discuss the mechanisms underlying immune-related adverse events that can occur after PD1-targeted therapy and explore potential treatment options.