The role of CD137 and CD137L in the pathogenesis of classical Hodgkin Lymphoma

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Abstract
Hodgkin’s lymphoma (HL) is caused by a minority population of malignant Hodgkin and Reed-Sternberg (HRS) cells that recruit an abundance of inflammatory cells. This extensive tumor stroma is characteristic of HL, and is essential for HL pathogenesis. How HRS cells manage to recruit the multitude of immune cells, and how they can persist in their presence, is only partly understood.

We found that the TNF receptor family member CD137 is expressed on HRS cells, while normal B cells, from which HRS cells are most often derived, do not express CD137. Ectopically expressed CD137 downregulates CD137 ligand (CD137L), which is a powerful stimulator of cellular immune responses, by a process of trogocytic transfer of CD137, complex formation between CD137 and CD137L, internalization and degradation. Disappearance of CD137L reduces co-stimulation of T cells.

In addition, CD137 signaling into HRS cells induces the secretion of IL-13 which further inhibits cellular immune responses. CD137-induced IL-13 also enhances the growth of HRS cell lines. CD137, IL-13 double-positive cells could be detected in the majority of HL patient samples.

As the cause of ectopic CD137 expression in HRS cells we identified Epstein-Barr Virus (EBV), and propose that EBV hijacks a physiological, CD137-based immune-regulatory mechanism to escape immune surveillance. Bispecific antibodies that target CD30 and CD137, a combination that is fairly unique to HRS cells, are being developed for immunotherapy of HL. These data reveal a novel immune escape mechanism based on ectopic CD137 expression, and they identify CD137 as a candidate target for immunotherapy of HL.

Recommended Reading

Rajendran Sakthi, Weng Tong Ho and Herbert Schwarz. CD137 signaling in Hodgkin and Reed-Sternberg cell lines induces IL-13 secretion, immune deviation and enhanced growth. OncoImmunology, 5(6):e1160188, 2016.