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A tick's grip on immunity: structural determinants of the Salp15–CD4 interaction and its effect on human CD4+ T cells

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Rationale: As obligate hematophagous ectoparasites, ticks rely on salivary proteins to circumvent host immune defenses while feeding on blood. Tick saliva contains a complex mixture of bioactive molecules, including potent immunomodulators. Among the most well-studied is Salp15, a 15 kDa salivary protein from *Ixodes scapularis* with strong immunosuppressive properties. In murine models, Salp15 has been shown to bind CD4 on T cells, thereby interfering with T cell receptor-mediated signaling and inhibiting $CD4^+$ T cell activation, proliferation, and cytokine production. While these functional effects are well documented in mice, the molecular basis underlying Salp15 activity, as well as its relevance to human T cell responses, remains poorly understood.
Methods: To elucidate the structural determinants of this activity, we focus on resolving the three-dimensional structure of recombinant Salp15 and characterizing its interaction with CD4 and potential additional cellular targets using NMR studies. Biological activity of Salp15 is tested based on IL-2 expression using flow cytometry and qPCR.
Results: Here, we demonstrate for the first time that Salp15 exerts comparable immunomodulatory effects on human $CD4^+$ T cells.

Conclusions: Defining the structure–activity relationship of Salp15 will provide critical insight into its mechanism of immune modulation and may enable the rational development of Salp15-derived molecules as novel immunomodulatory agents in autoimmune disease like graft versus host disease.

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