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**Structure and Thermodynamic Analysis of the Interaction between Epstein-Barr Virus IL-10 and IL-10R1.**

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Human interleukin-10 (hIL-10) and Epstein-Barr virus (EBV) interleukin-10 (vIL-10) share 84% sequence identity and modulate diverse immune responses by engaging two cell surface receptors (IL-10R1 and IL-10R2) that activate the Jak/Stat signal transduction pathway. Consistent with the nature of EBV, vIL-10 has retained hIL-10's immunosuppressive functions such as inhibiting pro-inflammatory cytokines, but not its immunostimulatory activities such as thymocyte proliferation. These functional differences have been shown to be modulated by vIL-10/IL-10R1 interactions. To define the molecular basis of these functional differences, crystal structures of vIL-10 and a vIL-10 point mutant which displays "hIL-10 like" properties were determined bound to the IL-10R1 receptor chain. A comparison of the structures with the hIL-10/IL-10R1 complex reveals a series of subtle structural changes between the vIL-10 and hIL-10 complexes. These include the rotation of the ligand on the receptor surface, a change in the dimer domain angle, and disruption of contacts in the ligand-receptor interface. The structural results are confirmed by a thermodynamic analysis of the vIL-10/IL-10R1 interactions.