Structural basis for IL-33 recognition and its antagonism by the hookworm effector HpARI

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Abstract

Interleukin 33 (IL-33) plays a major role in inflammation, allergy, and host defence against parasitic hookworms. As a result, *Heligmosomoides polygyrus* (Hp) is armed with a potent effector called Alarmin Release Inhibitor (HpARI) which contributes to suppression of protective immune responses in its host by antagonizing IL-33. As a side effect, recombinant HpARI administration also reduces host asthma and allergy. Here we present the first crystal structure of HpARI bound to mouse IL-33. HpARI is a CCP domain containing protein and the structure reveals that that it contacts IL-33 primarily through second and third CCP modules. In particular, the binding site on IL33 occupied by a large loop from the third CCP domain of HpARI overlaps with the binding site for the IL-33 receptor, ST2. Therefore, this structure reveals how HpARI prevents the IL-33-ST2 interaction, reducing host innate defences. It also provides a structural framework for rational design of inhibitors against IL-33 for treating certain inflammatory conditions and diseases.