Why we Itch: A structural exploration of Interleukin-31

Maintaining homeostasis requires our cells to react to extracellular cues and communicate with neighbouring cells. Cytokines are small proteins that modulate the activity of the immune system by binding to their cognate receptors on the cell surface triggering a signalling cascade in the process. We set out to answer key questions on the structural and molecular basis of the signalling assembly mediated by the acute pruritogenic cytokine Interleukin-31 (IL-31) and by extension the related IL-6 family. This research remains very timely with potential antibody-based therapies neutralizing IL-31 signalling actively progressing through clinical trials to treat patients affected by moderate to severe atopic dermatitis and prurigo nodularis. In dogs, monoclonal antibody therapy neutralizing IL-31 is in fact an already recognized and available therapy.

Receptor sharing by different cytokines is a common feature within the IL-6 family of cytokines. In case of IL-31, the cognate receptors are the specific IL-31Ra and OSMR, which it shares with Oncostatin-M. We can now present in crystal clear detail the structures of IL-31 and its complex with receptors. In addition, we have characterized the molecular determinants of the cytokine receptor assembly as well as the structural basis for the neutralization of each of the components by antibodies.

Our findings provide several unanticipated insights into the structural landscape of IL-31 and its receptors, including new opportunities for structure-based drug design.

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