CYTOKINES

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It is known that interleukin-15 receptor α (IL-15Rα) presents IL-15 in *trans* to neighbouring cells, and that both IL-15 and IL-15Rα support natural killer (NK)-cell homeostasis in resting conditions. However, how this cytokine–receptor pair functions during inflammation is not fully understood. Now, Mortier *et al.* show that the IL-15–IL-15Rα complex is preassembled in dendritic cells (DCs) following Toll-like receptor (TLR) stimulation, and that only membrane-bound complexes, and not secreted complexes, can provide the stimulatory signal necessary for NK-cell activation *in vivo*.

First, the authors measured the mRNA and protein levels of IL-15 and IL-15Rα in DCs following stimulation with TLR ligands. They found increased levels of mRNA expression of both the cytokine and receptor following stimulation, but only detected increased levels of the IL-15Rα protein. This led the authors to suggest that the IL-15 protein might be complexed with IL-15Rα in DCs following TLR-ligand stimulation, thereby blocking its detection. By developing a new 'complex' ELISA, the authors showed that this was indeed the case. The IL-15–IL-15Rα complexes formed in the endoplasmic reticulum or the early Golgi, and IL-15Rα was required for the secretion of IL-15 under inflammatory conditions. In addition, both IL-15 and IL-15Rα needed to be expressed by the same DC for *trans*-presentation, refuting the idea that IL-15 could be secreted by one cell and subsequently bind to IL-15Rα on another cell. However, membrane-expressed or secreted IL-15Rα could be detected in the absence of IL-15.

Further analyses showed that the coordinated expression of both IL-15 and IL-15Rα specifically by DCs in response to TLR ligands was required for NK-cell activation *in vitro* or *in vivo*. However, only membrane-bound IL-15–IL-15Rα complexes, and not the secreted complexes, could activate NK cells and induce interferon-γ and granzyme-B production *in vivo*.

So, the data show that IL-15 and IL-15Rα are preformed as complexes in DCs following TLR-ligand stimulation, that IL-15Rα acts as a chaperone for IL-15 secretion, as well as a scaffold protein for the *trans*-presentation of IL-15 to NK cells, and that cell-contact between IL-15-presenting cells (for example, DCs) and IL-15-responsive cells (for example, NK cells) is required to deliver IL-15-induced signals.

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ORIGINAL RESEARCH PAPER Mortier, E., Woo, T., Advincula, R., Gozalo, S. & Ma, A. IL-15Rα chaperones IL-15 to stable dendritic cell membrane complexes that activate NK cells via *trans* presentation. *J. Exp. Med.* **205**, 1213–1225 (2008)