IL-15 TRANS-PRESENTATION IS AN AUTONOMOUS, ANTIGEN-INDEPENDENT PROCESS

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Interleukin-15 plays a pivotal role in the long-term survival of T-cells and immunological memory. Its receptor consists of three subunits (IL-15Rα, IL-2/15Rβ, γc). IL-15 functions mainly via trans-presentation (TP), during which an APC expressing IL-15 bound to IL-15Rα presents the ligand to the βγc receptor-heterodimer on a neighboring T/NK cell. To date, no direct biophysical evidence for the intercellular assembly of the IL-15R heterotrimer exists. Antigen presentation (AP), the initial step of T-cell activation is also based on APC – T-cell interaction. We were compelled to ask whether AP has any effect on IL-15 TP or they are independent processes. In our human Raji B-cell – Jurkat T-cell model system we monitored inter/intracellular protein interactions upon formation of IL-15 TP and AP receptor complexes by Förster resonance energy transfer measurements. We detected enrichment of IL-15Rα and IL-2/15Rβ at the synapse and positive FRET efficiency if Raji cells were pretreated with IL-15, giving direct biophysical evidence for IL-15 TP. IL-15Rα and MHC II interacted and translocated jointly to the immunological synapse when either ligand was present, whereas IL-2/15Rβ and CD3 moved independently of each other. IL-15 TP initiated STAT5 phosphorylation in Jurkat cells, which was not further enhanced by AP. Conversely, IL-15 treatment slightly attenuated antigen-induced phosphorylation of CD3ζ chain. Our studies prove that in our model system IL-15 TP and AP can occur independently, and although AP enhances IL-15R assembly, it has no significant effect on IL-15 signaling during TP. Thus, IL-15 TP can be considered an autonomous, antigen-independent process.