Pairing, an economic way for cytokine carrier transportation and fusion

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$CD4^+$ T helper cells establish immunological synapses and secrete cytokines following antigen recognition at the late stage of TCR signaling [1]. It is already known that T cells use two directionally distinct pathways for cytokine secretion. Some cytokines, like interleukin 2(IL-2), can be delivered exclusively to the immunological synapse (IS), whereas others, like tumor necrosis factor α (TNFα), are delivered multi-directionally in $CD4^+$ T cells[2]. However, mechanisms coordinating these two secretion patterns are not yet uncovered. Here, we show that temporally the expression of TNFα and IL-2 in primary human $CD4^+$ T is induced differently upon stimulation. Spatially, both of $TNF\alpha^+$ and $IL\text{-}2^+$ carriers are transported to their secretion sites tethering with lysosome-related organelles (LROs) and are released prior to LROs fusion with the plasma membrane. Like pairing between CD3 and lytic granule (LG) mediated by SNARE protein Vti1b in $CD8^+$ T cells [3], the tethering between cytokine carriers and LROs is highly dependent on Vti1b via interaction with EpsinR. Using super-resolution structured illumination microscopy (SIM), we found that in most cases endogenous kinesins reside exclusively on LROs but not $TNF\alpha^+$ carrier for TNFα/LRO pairs; in comparison the single $TNF\alpha^+$ carriers also did not colocalize with endogenous kinesin. As predicted by our mathematical model, the following experiments proved that the two directionally distinct secretion patterns are mainly determined by the count of cytokine carriers via tethering with LROs. Thus our findings unveil that tethering of cytokine carriers with LROs is essential for cytokine delivery in $CD4^+$ T cells and the delivery pattern of cytokines is mainly determined by the count of newly derived cytokine carriers.

References

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