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Dynamic RNA binding protein interactions to cytokine mRNA govern human T cell effector function

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T cells are critical in killing infected and malignant cells. The clearance of target cells depends on the capacity of T cells to produce ample amounts of effector molecules, including the key pro-inflammatory cytokines IFN-γ, TNF-α and IL-2. We recently showed that the production levels and kinetics of these three cytokines rely on post-transcriptional mechanisms, a feature largely defined by RNA-binding proteins (RBPs). Which RBPs modulate the cytokine production in T cells is however not well understood. Here we employed an RNA-aptamer-based capture assay with human T cell lysates to map RBP interactors with the 3'untranslated regions (3'UTRs) of *IFNG*, *TNF* and *IL2*. We found both promiscuous and cytokine-specific binding of RBPs. Intriguingly, the composition of RBP binding to cytokine 3'UTRs altered upon T cell activation. Genetic deletion of confirmed mRNA-binders in primary T cells uncovered RBP-specific activity in modulating the protein output in response to target tumor cells. For instance, the RBPs ZFP36L1, ATXN2L and ZC3HAV1 dampen the production of all three cytokines, whereas HuR enhances the protein production. Intriguingly, only ZFP36L1 destabilizes cytokine mRNA. ZC3HAV1 and ATXN2L employ an mRNA degradation-independent mechanisms to block cytokine production. In fact, ZFP36L1 and ATXN2L double deletion shows synergistic effects on the protein production. In conclusion, identifying the RBPs that fine-tune cytokine production in T cells should help define novel targets to improve T cell responses against pathogens and malignant cells.