DISSECTING THE HETEROGENEITY OF CD8+ RESIDENT MEMORY T CELLS: UNIQUE DIFFERENTIATION PROGRAMS AND LOCAL ENVIRONMENT SHAPE THE T_{RM} PHENOTYPE.

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We previously compared murine CD8+ T resident memory (CD8+ Trm) cell subsets of the small intestine, liver and lung by whole genome gene expression analysis. We showed that individual Trm subsets of distinct organs clearly differed from each other, involving differential expression of 42 genes related to critical aspects of CTL function.

In this study we sought to clarify whether these differences were exclusive to CD8+ Trm cells, or could be, at least in part, also evoked in other, nonresident CD8+ T cells homing to the same organs. A murine acute GVHD model was set up in that transplanted allogeneic cytotoxic effector T cells (CD8+ Teff) of the graft (OT-I mice) infiltrate and attack various organs of the host (CAG-OVA mice) expressing the chicken ovalbumin$^{257\text{-}264}$ peptide (SIINFEKL). By transplanting GFP- and CD45.1-tagged OT-I CD8+ T cells, in vivo tracking and recollection of activated CD8+ Teff cells was also made possible to study changes in their gene expression patterns upon organ entry.

The data provided by this model suggest that the 42 genes previously found as differentially expressed in CD8+ Trm cell subsets of given organs can be split into two distinct groups.

A large part of these 42 genes showed identical or very similar expression patterns in CD8+ Trm and Teff cells depending on their organ environment. Hence, their differential regulation in distinct organs could not be verified as a unique functional feature exclusive to CD8+ Trm cells. We also found that if differences arose between Trm and Teff cells in such genes, then they were generally less pronounced in Teff than Trm cells of given organs. As Teff cells become promptly exhausted upon organ entry, while their respective Trm counterparts are maintained for extended time, these data suggest that such differences develop locally, and are fully established over longer periods of time.

The remaining genes, however, including multiple members of the granzyme and KLRG families, were confirmed as a specific marker for CD8+ Trm cells of distinct organs, as in contrast to CD8+ Trm cells, they were expressed by Teff cells in a uniform fashion regardless of their organ-level localization. Taken together, our results suggest that differences observed between CD8+ Trm subsets of various organs may be attributed to both local, non-specific adaptation to the environment, and unique, Trm cell-restricted, organ-specific differentiation programs.

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