SUPPLEMENTAL MATERIAL

Guy-Grand et al., http://www.jem.org/cgi/content/full/jem.20122588/DC1

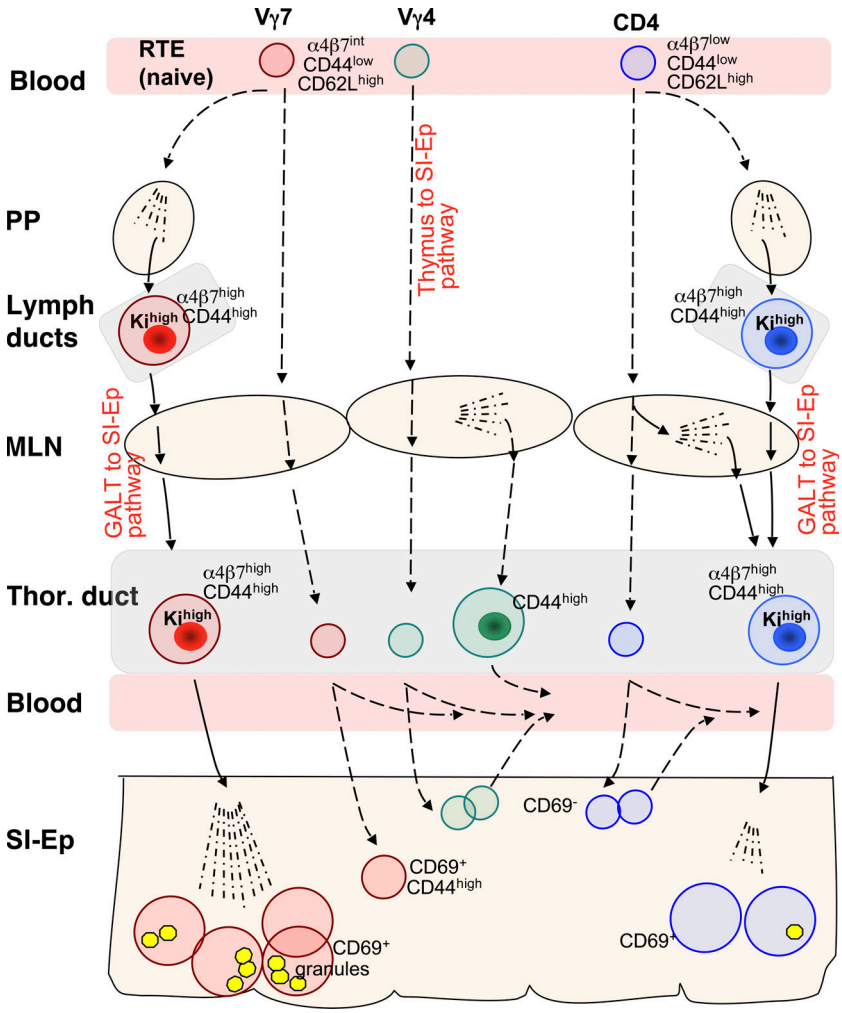

Figure S1. The hemolymphatic cycle of gut-tropic T cells. For clarity, only the circuits of γδ (Vγ7 and Vγ4) and CD4 T cells, representative of unconventional and conventional T cells, are depicted. **The hemolymphatic cycle of naive T cells:** RTEs (or naive cells in general) of all cell types are naive (CD44^{low}) and express high levels of CD62L. They continuously recirculate from blood through LN, whose efferent lymphatics converge to the thoracic duct (lower half of the body), which drains into systemic blood circulation. Recirculation through the GALT also includes PPs, whose efferent lymphatics have the peculiarity of draining into MLNs. Because RTEs also express α4β7, they can also circulate through the SI wall, including the SI-Ep. They enter this site via blood vessels, and exit again probably also via the blood. As such, circulation through the SI wall is here included as part of the general hemolymphatic circuit followed by naive cells. However, the rate of circulation through the SI-Ep is higher for unconventional than conventional RTEs, because the former express higher levels of α4β7, as depicted. Also, γδ RTEs of all families, which express high levels of both CD62L and α4β7, circulate without preference through LN and SI-Ep, irrespective of whether they bear TCR prone to recognize ligands in the SI-Ep. Thus, Vγ7 RTEs, many of which are prone to colonize the SI-Ep, recirculate freely through LN; conversely, Vγ4 RTEs, which are poorly represented in the SI-Ep, efficiently circulate through this site. For RTEs of all types, this general circuit can be "broken" if, upon TCR-mediated ligand recognition, they are either arrested in the SI-Ep, or reprogrammed in the GALT to exclusively home to the SI-Ep, as indicated by the further up-regulation of α4β7 and concomitant loss of CD62L. Therefore, colonization of the SI-Ep involves two circuits: the thymus–SI-Ep pathway (dashed arrows) followed by naive cells (including RTEs), and the GALT–SI-Ep pathway (solid arrows) followed by cells that have been previously activated in the GALT. **Thymus–SI-Ep pathway:** RTEs can enter the SI-Ep, either directly via the blood or, probably for most cells, after rounds of circulation through secondary lymphoid organs. Vγ7 T cells have a higher probability of being arrested and activated through TCR-mediated interactions, as indicated by the expression of CD69. However, these cells proliferate poorly and do not contribute to the pool of cytotoxic IELs, represented by yellow granules containing high amounts of granzyme B. Vγ4 and CD4 RTEs have a low probability of being arrested and will return to circulation. **GALT–SI-Ep pathway:** Recirculation through the GALT (solid arrows) is central for the development of Vγ7 and CD4 T cell–mediated immune responses against mucosal antigens, coupled to strong up-regulation of α4β7 and loss of CD62L. However, whereas Vγ7 T cells are activated and proliferate upstream MLN, one possible site being PPs, CD4 T cells do it in both MLNs and PPs. Activated cells reach the thoracic as cycling blasts and will home almost exclusively to the gut wall. In the SI-Ep, cycling Vγ7 T cells expand far more than CD4 homologues, thereby becoming predominant, especially in the pool of Granzyme B^{high} IELs. In contrast, as also depicted, Vγ4 T cell–mediated immune responses occur in contexts leading to complete loss of α4β7, and hence will not migrate into the SI-Ep.