

Orchestrators of TCR Signal Specificity and Functional Output

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The TCR can discriminate subtleties in antigen/MHC affinity and presentation context and appropriately induce T cell activation, inactivation or development into distinct T effector and memory subsets. A primary goal of my laboratory has been to understand the molecular basis of TCR signal specificity and elucidate molecular mechanisms for selectively coupling TCR engagement to specific downstream signals and functions. Experiments aimed at identifying the basis by which the SH3 domain of Lck SH3 selectively couples to downstream TCR signals and functions led to our identification Dlg1, a MAGUK scaffold, as an orchestrator of T cell polarity and TCR signal specificity (Round et al. 2005, Round et al. 2007). Together with recent publications elucidating a role for the MAGUK family member CARMA in selectively augmenting downstream TCRs signals, these studies identify a role for MAGUK scaffolds in orchestrating synaptic organization and TCR signal specificity. Our studies on the endogenous lectin, galectin-1, have also lead to its identification as a novel T cell regulator, capable of tuning polarity and TCR signals to selectively modulate functional outcome. Our most recent studies have demonstrated that galectin-1 regulates TCR-driven CD8 thymocyte development, primary CD8 expansion and CD8 effector burst size (Liu et al, 2008 and unpublished data). We find that gal-1 differentially affects TCR binding, output and T cell survival, depending on the developmental and activation stage of the T cells. These findings highlight a role for glycosylation and lectin binding in specifying TCR output in distinct T cell subpopulations and in response to qualitatively distinct peptide/MHC ligands. It is becoming increasingly clear that multiple processes contribute to the organization of TCR, co-stimulators and signal transducers at the TCR contact. Organization afforded by liganded co-stimulator engagement, membrane microdomain partitioning, glycolattice formation, intracellular protein scaffolding and polarity each contribute to the overall organizational scheme in a given T cell contact. Because the contributions of each of these processes can vary in cells at different stages of development and activation and in differing local microenvironments, we hypothesize that they function as points of control for TCR signal specificity. Thus, we anticipate our continuing studies in this area will be fruitful in understanding basic mechanism of immune regulation as well as in identifying targets for specifically modulating T cell responses.

References:

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