An agent-based model for investigation of immunological synapse patterns

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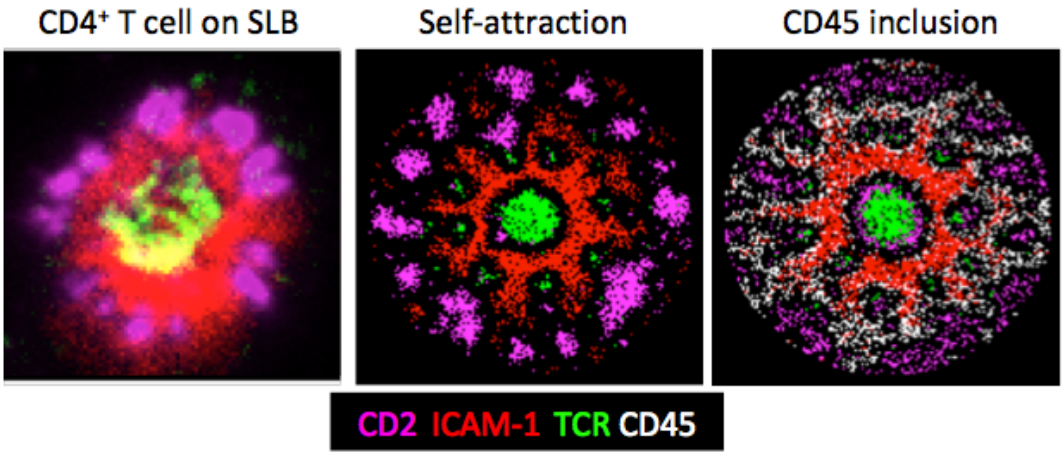
We have previously published agent-based models for the immune synapse[1,2]. The first generation model focused on development of the bull's eye pattern generated by a system with small (~13 nm) TCR-ligand complexes, which are transported towards the central supramolecular activation cluster (cSMAC) and accumulate there, and large (>20 nm) LFA-1-ICAM-1 complexes that provide a "back-fill" of adhesion in the peripheral SMAC (pSMAC)[1]. The second generation incorporated a weak central transport for LFA-1-ICAM-1, enabling formation of a realistic radial distribution of interactions in the pSMAC[2]. Furthermore, we incorporated CD28-CD80 complexes, which are less abundant than LFA-1-ICAM-1 complexes and are the same size as the TCR-ligand complexes and thus could passively follow TCR-ligand complexes toward the center[2]. An intermediate ring of CD28-CD80 interactions between the cSMAC and pSMAC was consistently formed when a weak coupling of CD28-CD80 complexes to actin was incorporated[2]. Surprisingly, addition of an alternative small molecular pair, CD2-CD58, which forms more interactions than LFA-1-ICAM-1, to the experimental model resulted in CD2-CD58 clusters outside the pSMAC in the most distal aspect of the immunological synapse (dSMAC)[3]. The left panel of the Figure shows one example of experimental data demonstrating the "corolla" of CD2-CD58 interactions



(magenta), mostly outside the LFA-1-ICAM-1 interactions (red) and the central TCR-ligands interactions (green). The displacement of CD2-CD58 interactions to the dSMAC due to the centripetal movement of TCR-ligand and LFA-1-ICAM-1 interactions takes place naturally

in the model due to the larger area needed for the more abundant CD2-CD58 interactions. The corolla pattern could be further refined by self-attraction of CD2-CD58 interactions (central panel) or through inclusion of large molecules like CD45 (white) that must be moved away in order for CD2-CD58 clusters to form (right panel), resulting in a similar confinement of CD2-CD58 interactions into clusters within the dSMAC. The functional implications of the model for the ability of T cell to integrate distinct signals will be discussed.

1 Figge, M. T. & Meyer-Hermann, M. Geometrically repatterned immunological synapses uncover formation mechanisms. *PLoS Comput Biol* **2**, e171, doi:10.1371/journal.pcbi.0020171 (2006).

2 Siokis, A., Robert, P. A., Demetriou, P., Dustin, M. L. & Meyer-Hermann, M. F-Actin-Driven CD28-CD80 Localization in the Immune Synapse. *Cell reports* **24**, 1151-1162, doi:10.1016/j.celrep.2018.06.114 (2018).

3 Demetriou, P. *et al.* CD2 expression acts as a quantitative checkpoint for immunological synapse structure and T-cell activation. *bioRxiv*, 589440, doi:10.1101/589440 (2019).

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