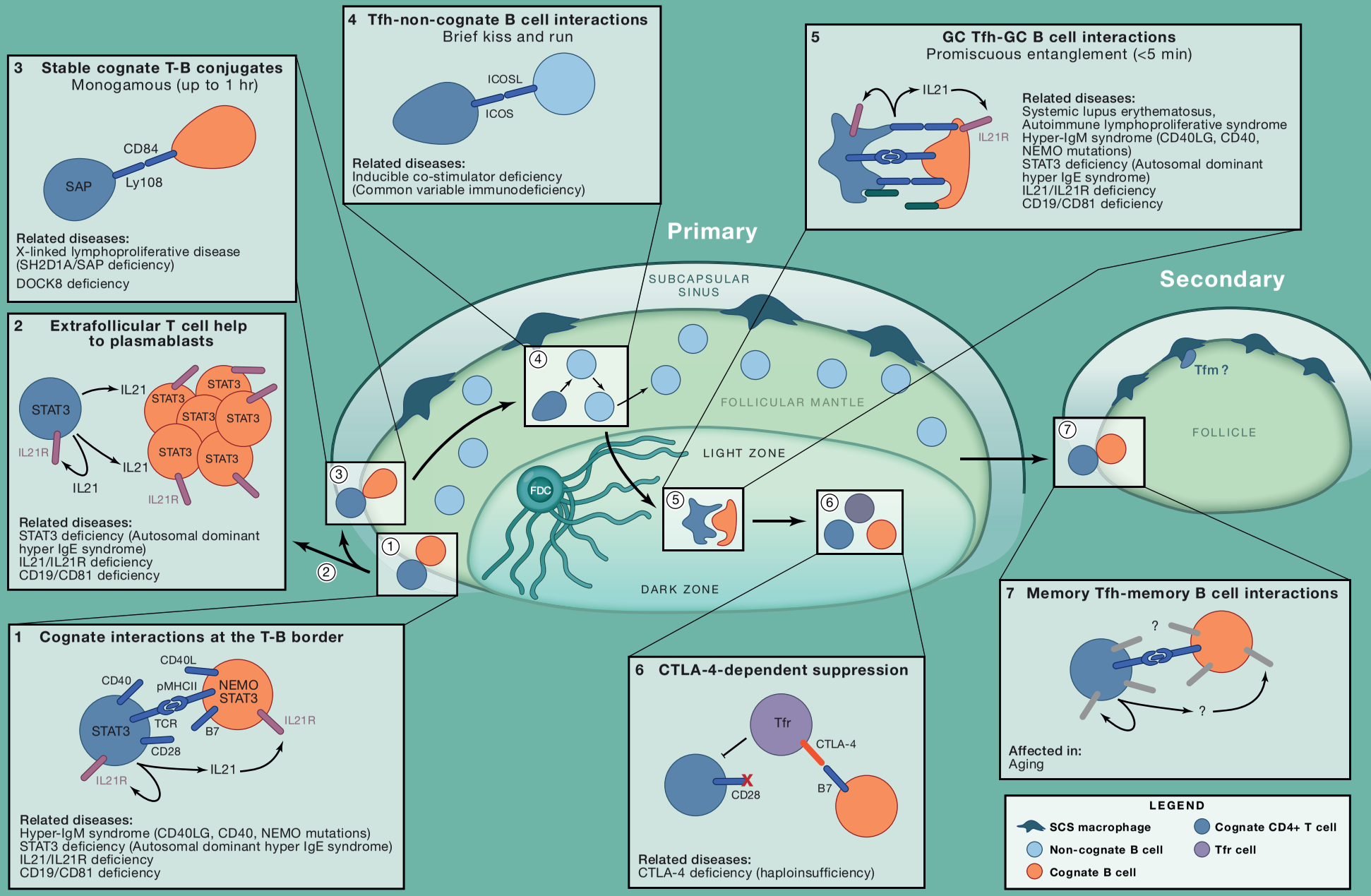
926 Cell 162, August 13, 2015 ©2015 Elsevier Inc. DOI http://dx.doi.org/10.1016/j.cell.2015.07.055

SnapShot: Interactions between B Cells and T Cells

Stuart G. Tangye,[1,2] Robert Brink, [1,2] Christopher C. Goodnow,[1,2] and Tri Giang Phan[1,2]
[1]Immunology Division, Garvan Institute of Medical Research, Darlinghurst NSW 2010, Australia; [2]St Vincent's Clinical School, 2010 UNSW, Australia

Cell



See online version for legend and references.

SnapShot: Interactions between B Cells and T Cells

Cell

Stuart G. Tangye,[1,2] Robert Brink, [1,2] Christopher C. Goodnow,[1,2] and Tri Giang Phan[1,2]
[1]Immunology Division, Garvan Institute of Medical Research, Darlinghurst NSW 2010, Australia
[2]St Vincent's Clinical School, 2010 UNSW, Australia

Interactions between B and T cells are critical for germinal center (GC) reactions and subsequent generation of long-lived memory and plasma cells (PCs). This requires Ag presentation to T cells and serial interactions between receptor/ligand pairs belonging to cytokine, chemokine, CD28/B7, and TNF/TNFR superfamilies that co-operate to induce requisite transcriptional programs in each cell type. In addition to BCR activation, B cell differentiation requires signals provided by T follicular helper (Tfh) cells at multiple spatially distinct checkpoints to ensure the quantity and quality of the antibody response. Tfh cells co-ordinately express molecules that allow them to co-localize with B cells in follicles and GCs of secondary lymphoid tissues and provide stage-specific helper signals to cognate B cells. This process is regulated intrinsically by specific transcription factors and extrinsically by T follicular regulatory (Tfr) cells. The importance of molecular interactions between B and T cells is evidenced by immunodeficient and autoimmune diseases that develop when these interactions are perturbed.

Spatiotemporal Control of Tfh Induction and Fate Commitment

Initial activation of CD4+ T cells occurs in interfollicular and paracortical T cell zones following recognition of specific Ag presented by dendritic cells (DCs). Interactions between CD28/B7, ICOS/ICOS-L and OX40/OX40L on CD4+ T cells and DCs upregulate expression of the transcriptional repressor BCL-6 and the chemokine receptor CXCR5, and downregulate CCR7, in CD4+ T cells to facilitate their migration to the B-cell follicle (panels 1-3).

While commitment to a Tfh fate is B cell independent, full Tfh differentiation requires B cells. At the T-B border, B cells present Ag in the form of peptide: MHC class II (pMHCII) complexes to T cells and form long-term (~1 hr) stable synapses. These cell conjugates require T cell expression of the intracellular adaptor SAP, acting downstream of CD84 and Ly108, since abortive interactions between SAP- or CD84-deficient CD4+ T and B cells impair B cell help and preclude B cells from providing reciprocal signals to maintain Tfh cells (panel 3). DOCK8 may also be important for intercellular interactions at T/B/DC synapses. The most critical interaction at the T-B border involves ICOS-L on cognate B cells and ICOS on activated T cells, which promotes further expression of key Tfh molecules. Engaging ICOS by ICOS-L on non-cognate bystander B cells is also essential for Tfh formation, as it mediates PI3K-dependent migration of CD4+ T cells into the follicle (panel 4).

Focused Delivery of Help to B Cells by Tfh Cells within the GC

In addition to changes in responsiveness to CCL19/CCL20 (via CCR7) and CXCL13 (via CXCR5), the repositioning of activated B and T cells to the follicle is directed by increased expression of EBI2, the receptor for 7α,25-dihydroxycholesterol. Subsequent migration of activated T and B cells into the GC is mediated by increased CXCR4 and S1PR2 and loss of EBI2. These mature Tfh cells are confined to the GC, where they express high levels of *Bcl6*, *Pdcd1*, and *Il21*. In contrast, less mature Tfh cells in the follicular mantle (FM) express lower levels of these genes. Accordingly, only GC B cells can access IL-21/STAT3 signals that are critical for their differentiation into PCs (panel 5). Inside the GC, cognate T-B interactions now take the form of multiple short-lived but extensive surface contacts that are integrated over time to mutually benefit both partners. Thus, GC B cells present pMHCII to activate the TCR and mobilise intracellular CD40L stores in GC Tfh cells. This increases ICOS-L on GC B cells, which further maintains a Tfh fate by repressing KLF2 via FOXO1. Engaging CD40 and BCR promotes GC B cell survival and primes responsiveness to Tfh cytokines (panel 5). A key question from this dynamic model is how GC Tfh cells discriminate and selectively deliver helper signals only to high-affinity non-self-reactive GC B cells and select them for PC differentiation. This partly involves the efficient removal of self-reactive B cells from the GC in a process that requires in situ expression of target self-antigens.

IL-21 produced by Tfh cells induces BCL-6 to maintain GC B cells, AID to induce somatic hypermutation, and BLIMP-1 to drive PC differentiation and Ig secretion. These processes are modulated by additional Tfh cytokines—IL-4, IL-10—which favor IgG and IgA production, respectively. IL-21 also maintains B7.2 expression on activated B cells, which favors Tfh formation. Interestingly, Tfh-derived IL-21 can directly promote PC survival, indicating that Tfh cells also help B cells beyond the GC (panels 2 and 5).

Applying Newton's Law to T-B Interactions

Just as there are myriad requirements to generate Tfh cells, numerous checkpoints are placed on them to prevent excessive B cell activation and autoantibody production. Interactions between PD-1 on T cells and PD-L1 on GC B cells restrain Tfh formation and function. IL-2/CD25/STAT5 signaling also attenuates Tfh formation by inducing BLIMP-1, antagonizing BCL-6. Tfr cells limit Tfh-mediated B cell responses via a mechanism requiring intrinsic CTLA-4 expression (panel 6). However, it is unknown whether this is achieved by competing with CD28 on Tfh cells for B7 on B cells or DCs. Tfr cells might also suppress Tfh cells via cell-cell interactions or soluble mediators. For instance, TGFβ can impede Tfh formation in spleen and lymph nodes; however, it can also promote Tfh differentiation by impairing CD25 upregulation and thus IL-2 signaling.

Interactions between Memory B and T Cells and the Secondary Antibody Response

Adaptive memory is a critical output of the GC and underpins most successful vaccines. Adoptive transfer studies showed that $CXCR5^{+}PD\text{-}1^{+}$ "memory Tfh cells" generate more robust Tfh responses than $CXCR5^{neg}PD\text{-}1^{neg}$ "non-Tfh memory cells" upon Ag recall. However, these memory Tfh cells also generated conventional T helper cells, indicating a high level of heterogeneity. Memory Tfh cells could localize to the splenic T-B border, where they are reactivated by memory B cells. Memory Tfh cells also persist in draining lymph nodes and occupy a niche beneath the subcapsular sinus (SCS). These follicular memory T cells (Tfm) are reactivated by SCS macrophages to initiate secondary antibody responses to rapidly generate "secondary" Tfh cells (panel 7). Interestingly, secondary Tfh cells are not confined to the GC and can egress the follicle via lymphatic flow in the SCS. Where and how these secondary Tfh cells interact with memory B cells to generate secondary responses remains to be established.

ACKNOWLEDGMENTS

The work performed in the authors' labs is supported by research grants and fellowships awarded by the National Health & Medical Research Council of Australia.

REFERENCES

Crotty, S. (2011). Annu. Rev. Immunol. 29, 621–663.

Goodnow, C.C., Vinuesa, C.G., Randall, K.L., Mackay, F., and Brink, R. (2010). Nat. Immunol. 11, 681–688.

Hale, J.S., and Ahmed, R. (2015). Front. Immunol. 6, 16.

Qi, H., Kastenmüller, W., and Germain, R.N. (2014). Annu. Rev. Cell Dev. Biol. 30, 141–167.

Sage, P.T., and Sharpe, A.H. (2015). Trends Immunol. 36, 410–418.

Suan, D., Nguyen, A., Moran, I., Bourne, K., Hermes, J.R., Arshi, M., Hampton, H.R., Tomura, M., Miwa, Y., Kelleher, A.D., et al. (2015). Immunity 42, 704–718.

Tangye, S.G. (2015). Curr. Opin. Immunol. 34, 107–115.

Tangye, S.G., Ma, C.S., Brink, R., and Deenick, E.K. (2013). Nat. Rev. Immunol. 13, 412–426.

Vinuesa, C.G., and Cyster, J.G. (2011). Immunity 35, 671–680.

Weber, J.P., Fuhrmann, F., Feist, R.K., Lahmann, A., Al Baz, M.S., Gentz, L.J., Vu Van, D., Mages, H.W., Haftmann, C., Riedel, R., et al. (2015). J. Exp. Med. 212, 217–233.

  DOI http://dx.doi.org/10.1016/j.cell.2015.07.055