

Christopher Wetherill
TBMH 5054

Immune Dysfunction and SLE Pathogenesis

Systemic lupus erythematosus (SLE) is an autoimmune disorder in which autoantibody production results in chronic inflammatory damage to multiple host organ systems (Dong, Zhu, Wang, & Wang, 2011). Emerging evidence suggests that populations of T_H cells produce IgG class-switched autoantibodies that contribute to the pathogenesis of lupus (Datta, Zhang, & Xu, 2005). In such a model, stylized in Figure 1, we see inappropriate T_H cell activation following inappropriate recognition by B cells (or other antigen presenting cells) of autoantigens and subsequent loading of those peptide epitopes onto MCHII molecules.

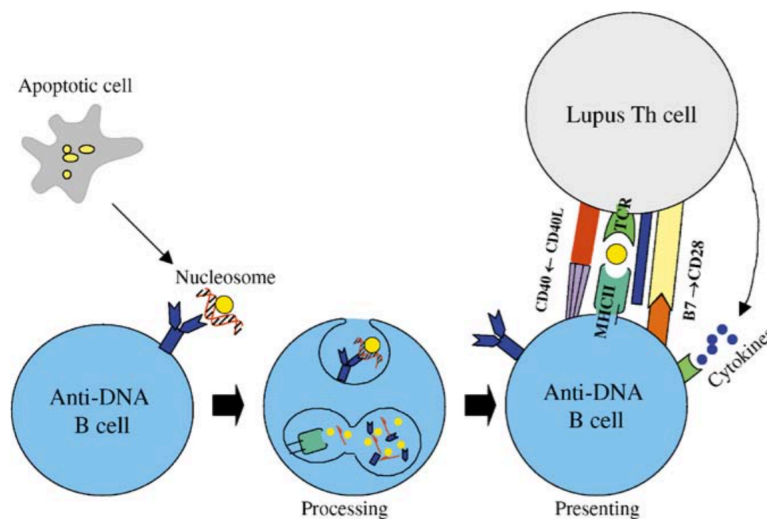


Figure 1: Stylized representation of inappropriate T_H cell activation following B cell sensitization to autoantigens. Taken from Datta, Zhang, and Xu (2005).

Such inappropriate activation of B cells may in part be caused by alterations to T_H cell signaling pathways. For example, it has been reported that in lupus phenotypes there is impaired cAMP-dependent phosphorylation due to reduction of protein kinase A levels; likewise, research has found compromised pathways involving protein kinase C and p56-lymphocyte-specific protein tyrosine kinase (p56lck). Further, in murine models, inhibition of the PI3K pathway and stimulation of MAPK pathways has been shown to ameliorate the disease, potentially indicating some dysfunction there acting to promote the onset of the SLE phenotype (Mak & Kow, 2014).

In further studies, type I interferons have been implicated in moderating T_H cell-B cell interactions promoting autoreactivity. Specifically, triggering of plasmacytoid dendritic cell Toll-like receptors stimulates pDC secretion of IFN- α/β . These interferons are, in turn, are in excess thought to promote development of autoreactive naïve T_H cells. However, the specific role of these molecules in the development and regulation of SLE remain unclear (Mangini, Lafyatis, & Van Seventer, 2007).

Finally, recent studies have implicated T_{FH} cells in the pathogenesis of SLE. Specifically, the expansion of these cell populations has been found to associate with increased production of anti-dsDNA antibodies. It has been additionally hypothesized that these cell populations play a significant role in the loss of tolerance for self-reactive B cells at germinal centers: whereas self-reactive

B cells would normally be excluded by germinal centers, the overabundance of T_{FH} cells may help to promote the survival of these B cell populations (Dong et al., 2011). Moreover, it has been shown that inhibition of T_{FH} cells by inducible $CD8^+$ T_{reg} cells leads to increased self tolerance (i.e., decreased autoreactive immune response) (Kim, Verbinen, Tang, Lu, & Cantor, 2010).

In summary, a wide range of immune cell dysfunctions have been implicated in SLE; however, establishing direct causative links has remained elusive. This may indicate that SLE is more accurately a spectrum of autoimmune disorders that manifest a similar phenotype but maintain separate causative agents. In any event, T_H cells seem to play a crucial role in the development and activation of autoreactive B cells and the ultimate onset of SLE and further research must be done to elucidate their exact role in the pathogenesis of this disease.

References

- Craft, J. (2012). Follicular helper T cells in immunity and systemic autoimmunity. *Nature Reviews Rheumatology*, 8, 337 - 347. doi: 10.1038/nrrheum.2012.58
- Datta, S., Zhang, L., & Xu, L. (2005). T-helper cell intrinsic defects in lupus that break peripheral tolerance to nuclear autoantigens. *Journal of Molecular Medicine*, 83, 267 - 278. doi: 10.1007/s00109-004-0624-2
- Dong, W., Zhu, P., Wang, Y., & Wang, Z. (2011). Follicular helper T cells in systemic lupus erythematosus: A potential therapeutic target. *Autoimmunity Reviews*, 10, 299 - 304. doi: 10.1016/j.autrev.2010.11.004
- Kim, H., Verbinnen, B., Tang, X., Lu, L., & Cantor, H. (2010). Inhibition of follicular T-helper cells by CD8+ regulatory T cells is essential for self tolerance. *Nature*, 467, 328 - 332. doi: 10.1038/nature09370
- Mak, D., & Kow, N. (2014). The pathology of T cells in systemic lupus erythematosus. *Journal of Immunology Research*, 2014. doi: 10.1155/2014/419029
- Mangini, A., Lafyatis, R., & Van Seventer, J. (2007). Type I interferons inhibition of inflammatory T helper cell responses in systemic lupus erythematosus. *Annals of the New York Academy of Sciences*, 1108, 11 - 23. doi: 10.1196/annals.1422.002
- Martin, J., Baeten, D., & Josien, R. (2014). Emerging role of IL-17 and Th17 cells in systemic lupus erythematosus. *Clinical Immunology*, 154, 1 - 12. doi: 10.1016/j.clim.2014.05.004
- Murdaca, G., Colombo, B., & Puppo, F. (2011). The role of Th17 lymphocytes in the autoimmune and chronic inflammatory diseases. *Internal and Emergency Medicine*, 6, 487 - 495. doi: 10.1007/s11739-011-0517-7
- Wahren-Herlenius, M., & Dömer, T. (2013). Immunopathogenic mechanisms of systemic autoimmune disease. *Lancet*, 382, 819 - 831. doi: 10.1016/S0140-6736(13)60954-X