

WORKSHOP B

B Lymphocytes - Development and Function

¹Frankfurt Institute for Advanced Studies (FIAS), Goethe-University Frankfurt/Main, Frankfurt/Main, Germany and

²Mathematical Institute, Oxford University, Oxford OX1 3LB, United Kingdom

B.1 Analysis of B cell selection mechanisms in the adaptive immune response

M. Meyer-Hermann¹, P.K. Maini², and D. Iber²

The essential task of a germinal centre reaction is the selection of those B cells that bind the antigen with high affinity. The exact mechanisms of B cell selection is still unknown and rather difficult to be accessed in experiment. With the help of an already established agent-based model for the space-time-dynamics of germinal centre reactions [1,2] we compare the most important hypotheses for what the limiting factor for B cell rescue may be. We discuss competition for antigen sites on follicular dendritic cells, a refractory time for centrocytes after every encounter with follicular dendritic cells, competition for the antigen itself, the role of antigen masking with soluble antibodies, and competition for T cell help. The unexpected result is that neither competition for interaction sites nor competition for antigen nor antigen masking are in agreement with present experimental data on germinal centre reactions. We show that these most popular selection mechanisms do not lead to sufficient affinity maturation and do not respect the observed robustness against changes of initial conditions. However, the best agreement with data was found for the newly hypothesized centrocyte refractory time and for competition for T cell help. Thus the *in silico* experiments point towards selection mechanisms that are not in the main focus of current germinal centre research. Possible experiments to test these hypotheses are proposed.

References:

- [1] Meyer-Hermann, M., A mathematical model for the germinal center morphology and affinity maturation. *J. Theor. Biol.* 216 (2002) 273–300.
- [2] Meyer-Hermann, M., Maini, P.K., Back to “one-way” germinal centers. *J. Immunol.* 174 (2005) 2489–2493.

Institute of Immunology, Otto-von-Guericke University, Magdeburg, Germany

B.2 Analysis of the functional redundancy among the non-raft transmembrane adaptor proteins LAX, SIT and TRIM.

B. Arndt, B. Schraven, and L. Simeoni

To date, 7 Transmembrane Adaptor Proteins (TRAP) have been identified: LAT; LAX, LIME, NTAL, PAG, SIT and TRIM. Among them, LAX, SIT and TRIM are localised in the non-raft fraction of the plasma membrane and may function as negative regulators of antigen receptor-mediated

signalling. In fact, analysis of LAX-deficient mice revealed that LAX inhibits TCR- and BCR-mediated signalling pathways. Similarly, SIT functions as a negative regulator of signals transduced through the TCR and is required to set the threshold for thymocyte selection and peripheral T-cell activation. Conversely to LAX and SIT, TRIM appears to be dispensable for normal T-cell development and T-cell function as TRIM^{−/−} mice show no obvious defects. Although the data from knock-out models indicate that the non-raft-associated TRAPs LAX and SIT are required for proper lymphocyte function, their effects on the immune system are rather mild or even absent as in TRIM-deficient mice. This could suggest that non-raft TRAPs share a functional redundancy in lymphocytes.

While LAX/TRIM double deficient mice are still under investigation, analysis of SIT/TRIM-deficient mice revealed that these two adaptors indeed share redundant functions during thymic selection and mutations in their genes could alter immune tolerance and lead to the generation/activation of autoreactive T cells.

Surprisingly, SIT/LAX double deficient mice show increased proportions of B1 B-cells in the peritoneal cavity and in the spleen, thus indicating that SIT and LAX together regulate the expansion of this particular B-cell subset that has been associated with autoimmune diseases. Conversely to their crucial role in B1 B-cells, LAX and SIT seem not to be redundant for T-cell and conventional B2-cell development and function.

In summary, our data show that non-raft TRAPs play important but redundant roles in finely tuning immune responses. Moreover they also share overlapping functions, by acting as negative regulators, in controlling the development/expansion of distinct lymphocyte subpopulations and in maintaining tolerance.

Immunoregulation, Deutsches Rheuma Forschungszentrum, Berlin, Germany

B.3 B cells activated through TLR produce high amounts of Interleukin-10

T. Roch, K. Hoehlig, V. Lampropoulou, and S. Fillatreau

Interleukin-10 producing B cells can suppress inflammatory immune responses despite persistence of a microbial stimulus. The signals controlling IL-10 production by B cells remain to be determined. Here, we show that only engagement of Toll-Like Receptors (TLRs), but not the two other major pathways involved in B cell activation (B cell receptor and CD40), stimulates B cells to produce high amounts of IL-10. The secretion of IL-10 induced by TLR-signals is strongly diminished when CD40 is concomitantly stimulated. Instead of IL-10, B cells co-stimulated through CD40 and TLRs secrete IL-6. This indicates that T cells control which cytokines are produced by TLR-activated B cells. The secretion of IL-10 by LPS- and CpG-stimulated B cells requires MyD88. The genetic background controls the amount of IL-10 produced: B cells from BALB/c mice secrete around 10 fold more IL-10 than their C57BL/6 counterparts.