Selection In Germinal Centers as Reflected by the Shape Characteristics of Immunoglobulin Gene Lineage Trees: A Multi-Scale Simulation

Gitit Shahaf[1], Michal Barak[1], Neta S. Zuckerman[1], Naamah Swerdlin, Malka Gorfine[2] and Ramit Mehr[1]

***Short Abstract* — Somatic hypermutation (SHM) and antigen-driven selection of immunoglobulin genes in germinal centers is crucial for immune protection and humoral immune learning and memory. We have developed lineage-tree based methods for analysis of the dynamics of SHM and selection. Here we show, based on multi-scale simulations of the humoral immune response, that several quantitative measures of lineage trees are correlated with biological parameters of the response.**

I. Background

During the immune response, the generation of memory B lymphocytes in germinal centers involves affinity maturation of the cells' antigen receptors, based on somatic hypermutation of receptor genes and antigen-driven selection of the resulting mutants. Affinity maturation is vital for immune protection, and is the basis of humoral immune learning and memory. Lineage trees of somatically hypermutated immunoglobulin (Ig) genes from B lymphocytes often serve to qualitatively illustrate claims concerning the dynamics of affinity maturation in germinal centers (GC). Using a novel method for graphical quantification of lineage tree properties [1], we have in past studies demonstrated that lineage tree analysis detects fine differences in Ig gene intraclonal diversity between B cell clones generated under different conditions. We found age- and tissue-related differences in the dynamics of the normal humoral immune response in humans [2], unique features of Ig gene diversification in B cell malignancies [3,4] and autoimmune or chronic responses [5,6], and characteristics of B cell diversification in other species which utilize gene conversion rather than rearrangement as the main primary diversification mechanism [7].

II. Simulation

In order to test quantitative claims regarding the GC response and affinity maturation, we created a computer simulation which combines mathematical models for all mature B cell populations, stochastic models of hypermutation and selection, and lineage tree generation and measurement. We ran this program over a large space of the values of dynamical parameters (such as the proliferation, differentiation and mutation rates, initial affinity of the Ig to the antigen, and selection thresholds), creating almost a million simulated lineage trees [8]. We analyzed the data in order to identify the ranges of dynamic parameters that yield biologically correct results based on experimental data regarding germinal center responses, obtaining interesting insights regarding response dynamics. mechanism.

III. Results and Conclusions

We found statistically significant correlations between quite a few tree characteristics and the initial affinity and selection threshold, which seem to be the main parameters that affect lineage tree shapes, in both primary and secondary response trees. We found that GC cells may be divided into a subset possessing low values of selection threshold and mutation rate, and a second, small subset with high values of these parameters. Finally, analysis of correlations between tree properties removed redundant properties, improving the statistical power of this method.

[1] The Mina and Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Ramat-Gan 52900, Israel. E-mail: mehrra@mail.biu.ac.il

[2] Faculty of Exact Sciences, Dept of Mathematics & Statistics, Bar-Ilan University, Ramat-Gan 52900, Israel.

References

[1] Barak M, Zuckerman NS *et al.* (2008) IgTree©: Creating Immunoglobulin Variable Region Gene Lineage Trees. *J. Immunol. Methods* **338**, 67-74.

[2] Banerjee M, Mehr R *et al.* (2002) Age and tissue-specific differences in human germinal centre B cell selection. *Eur. J. Immunol.* **32**, 1947-1957.

[3] Abraham RS, Manske MK *et al.* (2007) Novel analysis of clonal diversification in blood B cell and bone marrow plasma cell clones in immunoglobulin light chain amyloidosis. *J. Clin. Immunol.* **27**, 69-87.

[4] Zuckerman NS, Howard WA *et al.* (2010) Ectopic germinal centers in the thymus of Myasthenia Gravis patients show characteristics of normal germinal centers. *Eur. J. Immunol.*, *in press*.

[5] Steiman-Shimony A, Edelman H *et al.* (2006) Lineage tree analysis of immunoglobulin variable-region gene mutations in autoimmune diseases: chronic activation, normal selection. *Cell. Immunol.* **244**, 130-136.

[6] Tabibian-Keissar H, Zuckerman NS *et al.* (2008) B cell clonal diversification and gut-lymph node trafficking in Ulcerative Colitis revealed using lineage tree analysis. *Eur. J. Immunol.* **38**, 2600-2609.

[7] Mehr R, Edelman H, Sehgal D, Mage R. (2004) Analysis of Mutational Lineage Trees from Sites of Primary and Secondary Immunoglobulin Gene Diversification in Rabbits and Chickens. *J. Immunol.* **172,** 4790-4796.

[8] Shahaf G, Barak M *et al.* (2008) Antigen-driven selection in germinal centers as reflected by the shape characteristics of immunoglobulin gene lineage trees: a large-scale simulation study. *J. Theor. Biol.* **255**, 210-222.