A Mathematical Model of Germinal Center Formation

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***Short Abstract* — In this study, we investigate the host-pathogen dynamics leading to successful antibody responses capable of clearing an infection and make predictions on how these mechanisms are altered during chronic infections with viruses such as the human immunodeficiency virus (HIV) and hepatitis B virus (HBV). We develop mathematical models of (antibody producing) B cells that incorporate the interactions between antigen, CD4 T cells, T follicular helper cells and B cells of various levels of specificity to the antigen. We determine the characteristics of B cell and T follicular helper cell interactions during non-chronic infections by fitting the model to human germinal center B cells data. We then study how this prediction changes during chronic HIV infection.**

***Keywords* — T follicular helper cells, Germinal Centers, Theoretical immunology, Differential Equations, HIV.**

I. Purpose

THE main goal is to determine how B cell selection and competition for T follicular helper cells influences germinal center formation in natural infections and how a persistent antigen (such as HIV) can change the expansion-contraction program into highly mutated but protective responses or into dysfunctional responses.

Recent experiments have identified correlations between the density, function, and infection status of T follicular helper cells and the development of mature adaptive immune responses [4]. T follicular helper cells and B cells interact to form germinal centers.

Germinal centers are the anatomical structures where B cells undergo somatic hypermutation, immunoglobulin class switching, and antigen-specific selection [3]. Somatic hypermutations are random therefore emergence of non-autoreactive, high-affinity B cell clones requires strong selection through competition for survival signals [5]. The exact nature of these survival signals is poorly understood. Mathematically we aim to model and better predict these signals to gain a deeper understanding of germinal centers in chronic and non-chronic infections.

II. Results

We developed a system of ordinary differential equations that investigated the contribution of T follicular helper cells in the development, size and resolution of B cells inside the germinal centers. We performed stability and numerical analysis of the system and the theoretical predictions were validated against total germinal center B cell population data collected during non-chronic infections [1].

By comparing the model to the data we estimated B and T follicular helper cells proliferation rates and the recruitment rate into higher affinity classes. For the estimated parameters we found that the germinal centers achieve a maximum of 1037 B cells eleven days after non-chronic infection and germinal centers are lost 27 days following non-chronic infections. Moreover, our model shows that somatic hypermutated clones can proliferate faster than cells of lower affinity. Consequently, B cells that undergo many rounds of somatic hypermutations dominate the overall germinal center B cell population.

We aim to determine how these results apply to chronic infection such as HIV. If we allow for many rounds of somatic hypermutation (as in HIV patients that develop broadly neutralizing antibodies) than the parameters obtained in non-chronic infections cannot explain the size and duration of germinal centers. We determine the changes in these parameters under high rounds of clonal selection and give preliminary predictions on the biological mechanisms that allow for high proliferation while maintaining the germinal center structures. This is work in progress.

III. Conclusion

Our goal is to understand the differences in germinal center formation between uninfected individuals, HIV infected patients, and HIV infected patients who develop broadly neutralizing antibodies. We aim to predict the mechanisms responsible for the growth of mature and effective germinal centers in non-chronic and chronic disease.

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