The Role of Antibody in Dengue Viral Infection

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***Short Abstract* — Dengue virus has four distinct serotypes whose cross-reactive immune responses contribute to increased disease severity following heterologous infections. Since cross-reactive antibodies may play a role in disease enhancement, we develop a mathematical model of host-virus interaction and predict the mechanisms responsible for virus expansion and loss during primary and secondary dengue infections. We use the model to determine the role of cross-reactive antibodies during dengue fever and dengue hemorrhagic fever-inducing secondary infections, and compare the model to patient data. We predict that the cross-reactive antibodies interfere with the non-neutralizing antibody effects by reducing the phagocyte-mediated removal of antibody-virus immune complexes.**

I. Background

IN recent years, dengue viral infection has become one of the most widely-spread mosquito-borne diseases in the world, with an estimated 50-100 million cases annually, resulting in 500,000 hospitalizations [1]. Dengue viruses (DENV) cause mild dengue fever (DF) and severe dengue hemorrhagic fever (DHF). Dengue virus has four distinct serotypes, DENV 1-4, whose cross-reactive immune responses contribute to increased disease severity following heterologous infections. One current hypothesis postulates that cross-reactive antibodies are responsible for the enhancement of the infection, in a mechanism known as "antibody-dependent enhancement" (ADE) [1,2]. When a patient is first infected with one dengue strain, the host produces neutralizing antibodies specific to that strain. After the primary infection is eliminated, long-lived antibody-producing plasma cells specific to the first strain persist in the body. When infection with a second dengue serotype occurs, antibodies from the primary infection bind the second virus but do not neutralize it. Instead, phagocytes recruited to clear the virus antibody immune complexes internalize non-neutralized virus and become infected in the process [1,2]. The result is higher levels of viremia, which in turn is associated with more severe infection [3].

II. Results

We first model both the neutralizing and non-neutralizing antibody effects in dengue primary infection. Due to observed host-virus characteristics such as high level viremia followed by virus clearance and delayed antibody responses which become detectable after virus resolution [4], we are able to determine unknown parameters in our model. We find that the neutralizing rate has the strongest effect on viral reduction in primary infection.

We next develop a model for secondary infection of a heterologous serotype, taking into account that both strain-specific and cross-reactive antibodies are produced during secondary dengue infection [5]. We then fit the model to published patient data [6] in order to determine the role of the cross-reactive antibodies in both secondary DF and secondary DHF. We find that if the neutralizing rate of the antibody in secondary infection is enhanced as described in ADE, the model gives results which contradict clinical reports [4,6]. However, we are able to fit the known biological data when the cross-reactive antibody results in the decrease of the overall heterologous virus clearance. This suggests that the non-neutralizing antibody effects have more of a role in explaining the difference between secondary DF and secondary DHF. One biological explanation for this result may be that by binding heterologous virus, cross-reactive antibodies render it unavailable for binding and subsequent removal by strain-specific antibodies.

III. Conclusion

We developed mathematical models of antibody response (including both neutralizing and non-neutralizing effects) to model both primary dengue infection and secondary dengue infection. In primary dengue infection, the neutralizing antibody effect was shown to have the strongest effect on viral reduction. In secondary dengue infection, the difference between mild and severe disease can be attributed to the non-neutralizing antibody effect.

References

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