Reviewer's report

Title: Characterization of early host responses in adults with dengue disease

Version: 2 Date: 18 February 2011

Reviewer: Beatriz Sierra

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Overall comment:
The paper by Tolfvenstam et al characterizes the early host responses in adults with dengue disease, and reports a strong activation of the innate immune response in the early dengue fever phase, an activation of genes related to biosynthesis and metabolism as well as adaptive immune response genes at defervescence. They also report an individual gene level, significant predominance of CCL2, CCL8, CXCL10, CCL3, antimicrobial peptide #-defensin ,desmosome/intermediate junction component plakoglobin and a microRNA.
The authors deserve credit for addressing a highly relevant and clinically important disease.. The title and abstract express what has been found and the writing is suitable.
The questions posed by the authors are well defined. The methods are advanced, appropriate and well described. The data are truly sound, since this referee agrees with the authors that assessment of dengue-elicited early host responses is difficult as patients rarely seek healthcare during the first days of infection, and this response is critical for the disease outcome. The discussion and conclusions are well balanced and adequately supported.

Discretionary Revisions
Authors did not explore the previous dengue immune background of the patients included in the study, which could be done using neutralization assay. This means to define if they were suffering a primary or a secondary infection, and in this last case, what was the primarily infecting dengue serotype. This referee considers this very important, since it has been demonstrated that dengue immune response notably differs among primarily or secondarily infected patients. Epidemiological observations indicate that 90% of the cases of severe disease (DHF) occur during secondary heterologous DENV infections and that the risk of DHF is increased 15–80 times in secondary DENV infections. During a secondary heterologous infection enhancing heterologous antibodies, via antibody-dependent enhancement (ADE) of infection, are able to facilitate dengue virus (DENV) growth in Fc-bearing host cells. Memory dengue virus–specific T cells induced during a primary dengue virus infection are reactivated by the heterologous viral serotype during a secondary infection to expand to high levels and produce a skewed cytokine profile. So, the characteristics of the early immune response events during secondary DENV infection are likely influenced by both the preexisting DENV-specific B and T cell
repertoire. Besides, the immune response during a secondary infection greatly also depend of the combination of dengue serotypes causing the primary and the secondary infection. DENV-2 after DENV-1 have been frequently associated to dengue hemorrhagic fever, while DENV-2 as primary infection could implies a mild secondary infection.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests