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Lect. Dr. Juthathip Mongkolsapaya
Department: Office for Research and Development
Field of interests: Biomedical Research in Dengue Hemorrhagic Fever and Dengue Viruses
Contribution: Corresponding Author

Lect. Dr. Prida Malasit
Department: Office for Research and Development
Field of interests: Biomedical Research in Dengue Hemorrhagic Fever and Dengue Viruses
Contribution: Co-author
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Ponpan Matangkasombut1,2,*, Wilawan Chan-in1, Anunya Opasawaschai1, Pisut Pongchaikul1, Nattaya Tangthawornchaikul1, Siripjitt Vasanawathana2, Wannee Limpitikul3, Prida Malasit4,7, Thaneeva Duangchinda2,4,5, Gavin Screaton2, Juthapit Mongkoltsapaya3,4,7,

1Department of Microbiology, Faculty of Science, Mahidol University, Bangkok, Thailand, 2Systems Biology of Diseases Research Unit, Faculty of Science, Mahidol University, Bangkok, Thailand, 3Center of Emerging and Neglected Infectious Diseases, Mahidol University, Bangkok, Thailand, 4Medical Biotechnology Unit, National Center for Genetic Engineering and Biotechnology, National Science and Technology Development Agency, Pathumthani, Thailand, 5Department of Pediatrics, Khon Kaen Hospital, Khon Kaen, Thailand, 6Department of Pediatrics, Songkhla hospital, Songkhla, Thailand, 7Dengue Hemorrhagic Fever Research Unit, Office for Research and Development, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, 8Division of Immunology and Inflammation, Department of Medicine, Hamersmith campus, Imperial College London, London, United Kingdom

Abstract

Background: Dengue viral infection is a global health threat without vaccine or specific treatment. The clinical outcome varies from asymptomatic, mild dengue fever (DF) to severe dengue hemorrhagic fever (DHF). While adaptive immune responses were found to be detrimental in the dengue pathogenesis, the roles of earlier innate events remain largely uninvestigated. Invariant natural killer T (iNKT) cells represent innate-like T cells that could dictate subsequent adaptive response but their role in human dengue virus infection is not known. We hypothesized that iNKT cells play a role in human dengue infection.

Methods: Blood samples from a well-characterized cohort of children with DF, DHF, in comparison to non-dengue febrile illness (OFI) and healthy controls at various time points were studied. iNKT cells activation was analyzed by the expression of CD69 by flow cytometry. Their cytokine production was then analyzed after α-GaCer stimulation. Further, the CD1d expression on monocytes, and CD69 expression on conventional T cells were measured.

Results: iNKT cells were activated during acute dengue infection. The level of iNKT cell activation associates with the disease severity. Furthermore, these iNKT cells had altered functional response to subsequent ex vivo stimulation with α-GaCer. Moreover, during acute dengue infection, monocyte CD1d expression was also upregulated and conventional T cells also became activated.

Conclusion: iNKT cells might play an early and critical role in the pathogenesis of severe dengue viral infection in human. Targeting iNKT cells and CD1d serve as a potential therapeutic strategy for severe dengue infection in the future.


Editor: Ernesto T. A. Marques, University of Pittsburgh, United States of America

Received: December 19, 2013; Accepted: May 7, 2014; Published: June 19, 2014

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Funding: This work was supported by Mahidol University (to PM), the Thailand Research Fund (MRG5480015 to PM), the Medical Research Council, UK, the Wellcome Trust, UK, the National Institute for Health Research Biomedical Research Centre, Funding Scheme, the Office of the Higher Education Commission and Mahidol University under the National Research Universities Initiative, and European Commission Seventh Framework Programme (FP7/2007-2013) for the DEFTFREE project under Grant Agreement n° 228 378. OS is a Wellcome Trust Senior Investigator. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: ponpan.post.harvard.edu (PM); jmongkoltsapaya@imperial.ac.uk (JM)
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- **Demographic and clinical data**
  - DF and DHF: not significantly different in age and gender
  - DV Serotype: DV1 > DV2 > DV3 > DV4
  - DHF compared to DF: platelet count↓, serum albumin↓, liver transaminases↑

- **The percentage of peripheral blood iNKT cells remain unchanged during the course of DV infection**

**Figure 1:** The frequency of peripheral blood iNKT cells during dengue infection with different disease severity.
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- Invariant NKT (iNKT) cells were activated during acute DV infection and the level of activation associated with dengue disease severity.

- Peripheral blood iNKT cells from acute DV infected patients had reduced α-GalCer mediated production of IFN-γ.

**Figure 2:** iNKT cells were activated during acute phase of dengue infection.

**Figure 3:** Cytokines production by iNKT cells from dengue infected patients with and without stimulation with α-GalCer.
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- Upregulation of CD1d expression on monocytes during acute DV infection

Figure 4: Upregulation of CD1d expression on monocytes during acute DV infection
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- Cytotoxic T cells were activated in relation to iNKT cell activation

Figure 5: Activation of conventional T cells during acute phase of dengue viral infection