PhD defence Francesca Falconi

Assessing the antibody responses against dengue virus in the context of emerging arboviruses. From basic immunology to new diagnostics.

02 jun 202216:00 - 18:00
ITM - Antwerpen

Dit is de omschrijving

Attendance

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Supervisors

- Prof. Dr. Kevin Ariën (ITM)
- Dr. Michael Talledo (Institute of Tropical Medicine Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Peru)

Summary

Dengue virus (DENV) is the causative agent of dengue fever (DF), the most prevalent arthropod-borne viral disease worldwide. DF presents with non-specific symptoms similar to other febrile diseases that overlap geographically. Therefore, diagnosis cannot be made on clinical and epidemiological data alone and thus require laboratory techniques for case confirmation.

Antibody-based assays are simple, affordable, applicable at the point of care and offer a wide diagnostic window. However, the high genetic similarity of DENV serotypes and also with other flaviviruses such as Zika, results in cross-reactive (CR) antibodies complicating serological diagnostics.

Consequently, the search for and selection of appropriate biomaterials that enable capturing of highly specific anti-DENV antibodies is crucial to improve dengue diagnosis. The main objective of this PhD thesis was to (1) delineate the dynamics of the antibody responses against DENV at epitope level, (2) to identify regions able to capture DENV-specific Abs, and (3) investigate the value of these biomaterials for diagnostic purposes.

The characterization of the temporal evolution of the IgG and IgM response following dengue infection was done using a high-density peptide microarray spanning the entire proteomes and diversity of DENV1-4, Zika (ZIKV) and yellow fever virus (YFV). Sera from a cohort of dengue infected individuals from Peru, as representatives for secondary infections, and overseas travelers, as representatives for primary infections, were used. We found that reactive linear epitopes were located across the proteome both in structural proteins and in non-structural proteins and were targeted by either IgM and/or IgG antibodies. Subsequent analysis of the antibody response against the peptide libraries from DENV, ZIKV and YFV and the further alignment of the highly immunoreactive regions onto the DENV proteome allowed the identification of 15 and 12 DENV-type-specific epitopes and 13 and 12 flavivirus-CR epitopes, targeted by IgM and IgG antibodies, respectively.

The diagnostic potential of 20 peptides was further assessed using a bead-based multiplex peptide immunoassay on a large panel of carefully selected human serum samples. Individual peptides offered satisfactory diagnostic performance, but the combination of multiple peptides and using a machine learning algorithm substantially improved the sensitivity and specificity of the assay. In summary, this work has mapped in great detail the immunodominant linear epitopes across the DENV polyprotein and provided proof-of-concept that this approach offers clear potential for the development of highly accurate next-generation dengue serological tests.