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och
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**EXPLORING THE COMPLEXITY OF FUNCTIONAL
HIV-1 SPECIFIC T CELL RESPONSES AND GLOBAL
VIRUS-HOST GENETIC VARIABILITY**

AKADEMISK AVHANDLING

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ABSTRACT

HIV has become one of the biggest health problems up to date. After 30 years of tremendous effort, the development of an HIV vaccine is still far from achieved. One of the main issues is the high mutation rate of the virus which results in the selection of mutated variants. This gives the virus the ability to escape from selective pressures, such as the immune system. Also the correlates for an effective immune response against HIV remain uncertain.

T cells have been proven to play a key role in controlling the virus in HIV infected individuals. T cells recognize small fragments of HIV as antigenic peptides bound and presented on HLA molecules. The HLA molecules are the most polymorphic proteins in the entire human genome. As the HLA-peptide interaction is highly specific, HIV infected individuals will present different peptides from the HIV proteins dependent on their HLA repertoire. In this thesis we explore the complexity of functional HIV-specific T cell responses and global virus-host genetic variability in different study cohorts.

Individuals with frequent exposure to HIV without establishment of infection have been well studied in the hope of finding the secret of their reduced susceptibility. However, no one has studied if exposure to HIV through oral sex can induce T cell responses. Through access to samples from healthy HIV negative individuals living in a relationship with an HIV infected partner we show that oral exposure is enough to mount a systemic HIV specific CD4+ and CD8+ T cell response.

To cope with the enormous variability of HIV sequences and HLA alleles we combined the use of bioinformatic tools with molecular biology, and immunological assays. We successfully identified several highly immunogenic peptides that were recognized in a diverse study population infected with several HIV subtypes. Responses against these peptides were further investigated to address the effects of HIV point mutations on T cell recognition. We show that recognition of the HLA-peptide complex by the T cell receptor is highly sensitive and that one single point mutation will reduce the chance of inducing a response by 40%.

Despite the high mutation rate of HIV, there are some regions that are more conserved within the HIV genome. Mutations in these regions have the potential of reducing viral fitness, why viral variant carrying such mutations may be less pathogenic. We hypothesized that the character of the HIV peptide (*i.e.* variable or conserved) targeted by CD8+ T cells would influence the quality and quantity of T cell responses, and affect disease progression. We show that patients targeting a conserved peptide in early HIV infection maintain their responses for up to four years, while patients targeting a variable peptide lose their responses over time. Importantly, patients targeting a conserved peptide had a lower viral load and a slower CD4+ T cell decline. The identification of virological and immunological characteristics that influences disease outcome is highly relevant for the development of a therapeutic vaccine.

These studies are based on the access to exclusive patient material through excellent collaborations, and combination of bioinformatics and immunological assays. This thesis has brought new knowledge to the field, but also addressed the complexity of HIV specific T cell responses.