Abstract

Plasmacytoid dendritic cells (pDC) are a highly specialized subset of immune cells that sense viral nucleic acids by endosomal toll-like receptors 7 and 9 (TLR7/9). Activation of TLR7/9 leads to the production of type I interferons (IFN-I). Moreover, pDC contribute to the antiviral response by presenting viral antigens to T lymphocytes and link innate and adaptive immunity.

pDC need to be properly regulated in order to limit excessive production of IFN-I that is associated with autoimmune diseases. Therefore, pDC possess a battery of regulatory receptors (RR) that limit TLR7/9-mediated cytokine production. This thesis focuses on the mechanism of RR-mediated inhibition of IFN-I production in pDC and explores interactions between pDC and two enveloped viruses, that possess the ability to hijack RR in pDC: hepatitis B virus (HBV) and human immunodeficiency virus (HIV). We showed, that MEK-ERK signaling pathway plays an active role in RR-mediated inhibition of IFN-I in pDC. Our results indicate that in line with other studies of our group, pharmacological targeting of MEK1/2-ERK signaling could be a strategy to re-establish immunogenic activity of pDC. Then, we investigated whether antiretroviral therapy (ART) in a cohort of 21 treatment-naive chronic HIV-infected patients has restored the number and phenotype of pDC. We found that chronic HIV infection induces exhausted phenotype of pDC that is associated with the elevated expression of TIM-3 and TRAIL. The pDC frequency and phenotype was only partially restored after ART. Moreover, our results suggested that the level of TIM-3 could be used as a predictive marker of HIV RNA decline during ART. Finally, we demonstrated that pDC activated with various TLR7/9 synthetic ligands inhibit HBV replication in hepatoma cell lines and primary human hepatocytes. Our results indicated that targeting of various TLRs in other immune cells and not specifically pDC, could be a better strategy towards an HBV cure.

Collectively, this thesis presents and assesses novel results that uncover the interplay between positive and negative signals in pDC triggered by TLR7/9 and RR, and the effect of TLR7/9-activated pDC on the HBV lifecycle.

Key words: pDC, HBV, HIV, regulatory receptors, interferon