ABSTRACT

Modulation of plasmacytoid dendritic cell function: role of immunoreceptors TIM-3 and BDCA-2

Plasmacytoid dendritic cells (pDCs) are key players in the antiviral response as well as in linking innate and adaptive immune response. They express endosomal toll-like receptors 7 and 9, which can detect ssRNA and unmethylated CpG DNA, respectively. Due to the constitutive expression of the transcription factor IRF7, pDCs are able to rapidly produce massive quantities of type I (α, β, ω) and type III (λ1, λ2, λ3, λ4) interferons (IFN-I and IFN-III) as well as pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α. After maturation, they also function as antigen-presenting cells. Despite intense research, the mechanisms of IFN and pro-inflammatory cytokines production and regulation are still poorly understood. Using the pDC cell line GEN2.2 and also primary human pDCs, we shed light on the role of kinases MEK and SYK in IFN-I production and regulation. We found that SYK is not only involved in the regulatory receptor (RR)-mediated BCR-like pathway that represents the negative regulation of IFN-I and IFN-III secretion but also in the positive TLR7/9-mediated signal transduction pathway that leads to IFN-I production, representing the immunogenic function. We also found that MEK plays a crucial role in RRs inhibitory pathway. Further research on pharmacological targeting of SYK and MEK could serve to alleviate the symptoms of diseases caused by the dysregulation of IFN-I production, such as systemic lupus erythematosus (SLE), or conversely, to intensify suppression of viral infections, namely during an acute state of infection when the immune system is not activated enough, a typical situation in HCV, HBV or HIV infections.

In parallel, we studied dynamics of the immunomodulatory phenotypic markers (CD4, BDCA-2, HLA-DR, CD32 and TIM-3) in pDCs of a cohort of 21 treatment-naïve HIV-infected patients and during the first 9 months of the antiretroviral treatment (ART). We found that the expression of these markers was significantly disrupted in treatment-naïve HIV-infected patients in comparison to the controls (healthy donors, HDs). After the 9-month follow-up under ART, the immunogenic phenotype of HIV-infected patients was only partially restored. Importantly, we found a correlation between the levels of expression of TIM-3 in pDCs and the level of decrease of HIV-1 RNA in plasma during the first months on ART. This discovery opens the door to consider TIM-3 as a putative biomarker for antiretroviral treatment efficiency in HIV-infected patients.