STAT1 and Type I IFN signaling pathway regulates dendritic cell development during steady state and inflammation

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During infections and inflammation, pDCs are the most potent type I interferon (IFN-I)-producing cells. However, the developmental origin of pDCs and the signals dictating pDC generation remain incompletely understood. Previously we reported a synergistic role for IFN-I and Flt3 ligand (FL) in pDC development from common lymphoid progenitors (CLPs) at steady state. Here, we demonstrated that the administration of R848, a TLR7 agonist, dramatically altered the developmental process by enhancing cDC production at the expense of pDC in vitro and in vivo. The ratio of cDC1 to cDC2 also decreased upon TLR stimulation. More importantly, ex vivo DC development from CLPs of mice previously treated with R848 also favored cDC generation even though R848 is omitted in the culture conditions, suggesting that TLR signaling reprograms DC development from the progenitors. Fate mapping experiments using IL-7R-driven reporter mice also supported that CLPs contributed to increased cDC population during inflammation. Mechanistically, both primary and secondary signaling events downstream of TLR7 are involved. One of the secondary signaling events was IFN-I induced upon stimulation, which partially regulated TLR-dependent enhancement of cDC generation. While STAT1 is a canonical signal mediator of IFN-I, it was also activated directly by R848 through phosphorylation at S727. Both STAT1KO and S727A mutation in STAT1 blocked the effect of R848 on DC development. In sum, these findings reveal that DC developmental process from their progenitors is very dynamic during steady state and inflammation. Moreover, we define a novel function of STAT1 and IFN-I signaling pathway in TLR-mediated reprogramming of DC development. (NHRI-EX108-10632SI)

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