p38 MAPK is critical for nuclear translocation of IRF-7 during CpG–induced type I IFN expression in human plasmacytoid dendritic cells

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Abstract

Plasmacytoid dendritic cells (pDCs) are the major source of type I IFN (IFN-I) in response to viral and bacterial infection that are recognized through the Toll-like receptor 7 (TLR7) or TLR9 signaling pathway. TLR9 agonist, oligodeoxyribonucleotides containing unmethylated CpG motifs (CpG), stimulates pDC to produce IFN-I but the mechanism keeps incompletely defined. Here, we established a human pDC cell line with the gLuc under control of the IFNa4 promoter/enhancer, and utilized the high throughput assay to screen for protein kinase inhibitors to identify small molecules targeting IFN-I induction pathway in pDCs. We identified p38 MAPK inhibitors that show ability to inhibit IFN-I expression in pDCs without cytotoxicity upon CpG stimulation. p38 MAPK inhibitor inhibits IFN-I expression in a dose-dependent fashion in vitro and significantly suppressed IFN-I expression in humanized mice upon CpG treatment. There was a dramatic defect in the nuclear translocation of IFN regulatory factor 7 (IRF-7) in the presence of p38 MAPK inhibitor. Therefore, p38 MAPK enhances IRF-7 nuclear translocation and IFN-I expression in human pDCs. These findings identify p38 MAPK as a target for modulating pDC activity.

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