Effect of BTK Inhibitors on Differentiation of Human

Monocyte-derived Dendritic Cells

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Dendritic cells (DCs) are primary antigen-presenting cells (APCs), which process tumor antigen and present it on the cell surface to the T cells of the adaptive immune system. However, immature DCs facilitate tolerance toward cancer cells. Bruton’s tyrosine kinase (BTK) is highly expressed in B cells, monocytes, macrophages and dendritic cells and plays crucial roles in differentiation and activation of myeloid cells. Dendritic cells in Btk⁻/⁻ mice were reported to have more mature phenotype and stronger in vitro and in vivo T cell stimulatory ability than wild-type DCs. However, the functions of BTK in human DC differencation and maturation were not well characterized. In this study, we revealed the effect of BTK inhibition with ibrutinib, an FDA approved drug for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), in human monocyte derived dendritic cells (moDCs). We show that BTK was expressed in monocytes and moDCs. BTK activity was regulated during moDCs differencation and BTK inhibitors blocked GM-CSF/IL4 induced activation of BTK. LPS instead of CD40L treatment increased BTK phosphorylation. It was noted that the percentage of CD11c⁺ MHC II⁻/⁻ subsets, which represented the immature DCs, was significantly reduced upon ibrutinib treatment during moDC differencation. Meanwhile, ibrutinib dose-dependently increased proportion of CD11c⁺ MHC II⁺ cells, which represent more mature DCs. We also tested BGB-3111, a more selective BTK inhibitor without ITK, TXK, EGFR, HER2 and JAK3 activity in the same assay. We observed increased MHC II level during differencation of human moDCs with BGB-3111 treatment. These results support combination strategies for BTK inhibitors with other cancer immunotherapy agents.