Differential Regulation of T cells by PI3K delta inhibitors in a CLL Murine Model

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ABSTRACT

The purpose of this research was to evaluate the impact of PI3K inhibitors (Pi3k/Akt/mTOR pathway) on T cell regulation and function in a murine model of CLL. T cell subsets and cytokine expression were assessed in wild-type (WT) and CLL mice treated with the PI3K inhibitors idelalisib or duvelisib. CD4+ and CD8+ T cell subsets were analyzed in spleen and peripheral blood mononuclear cells (PBMCs) from WT and CLL mice treated with vehicle, idelalisib, duvelisib, or both drugs. Idelalisib and duvelisib were selected as PI3K inhibitors for their ability to inhibit PI3Kδ and PI3Kγ, respectively. The impact of PI3K inhibitors on T cell subsets and cytokine expression was assessed using flow cytometry and ELISA, respectively. In vivo, idelalisib and duvelisib inhibited PI3Kδ and PI3Kγ activity, respectively, with duvelisib having greater efficacy. In vitro, ID3K inhibitors led to a decrease in CD4+ and CD8+ T cell subsets in WT and CLL mice. However, treatment with ID3K inhibitors led to an increase in Treg cell subsets in WT and CLL mice. Furthermore, ID3K inhibitors led to a decrease in IL-2 and IFN-γ production in WT and CLL mice. These findings suggest that ID3K inhibitors may have potential therapeutic applications in CLL and other malignancies.

MATERIALS AND METHODS

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Graft-versus-host (GVH) disease was used in a murine model of CLL to evaluate the efficacy of PI3K inhibitors in vivo. Treg cells were isolated from WT and CLL mice and co-transplanted with tumor cells. The impact of PI3K inhibitors on Treg cell function was assessed using flow cytometry and ELISA. The impact of PI3K inhibitors on T cell subsets and cytokine expression was assessed using flow cytometry and ELISA, respectively.

CONCLUSIONS

Idelalisib and duvelisib have potential therapeutic applications in CLL and other malignancies.

REFERENCES


CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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