Differential Regulation of Human T cells by TGR-1202, A Novel PI3Kδ Inhibitor

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ABSTRACT

1. Apoptotic signals. The p110 delta (p110δ) expressing isoform of PI3K is restricted to hematopoietic cell types; therefore the role of PI3K signaling is widely acknowledged as a key component of cell survival in many hematological disorders. Further characterization of effects on the T cell compartment are ongoing.

2. Production, FoxP3 mRNA expression, and maintains Treg percentage and expression of immune checkpoint molecules, greater retention of immune checkpoint blockade and suppressive phenotype. Treating Tregs by decreased expression of co-inhibitory molecules CTLA-4 and PD-1 on the Tregs. Interestingly, TGR-1202 significantly reduced mRNA expression of T-bet (Th1), GATA-3 (Th2) and FoxP3 (Treg), however FoxP3 levels were consistently higher in TGR-1202 treated vs. untreated Tregs.

3. TGR-1202 exhibits less effect on reduction of checkpoint molecules compared to other PI3K inhibitors (i.e. PD-1 and CTLA-4 expression). TGR-1202 is a novel, orally available PI3Kδ inhibitor in clinical development that selectively targets PI3Kδ with a high level of specificity.

BACKGROUND

The role of PI3K signaling is widely acknowledged as a key component of cell survival in many hematological malignancies. The PI3K pathway regulates cell survival, proliferation, and apoptosis, among other functions. Following BCR stimulation, Fyn is activated and recruits PI3K, which initiates intracellular signaling that leads to Akt activation and cell proliferation. However, despite the critical role, PI3K signaling is also involved in CLL therapy resistance. In CLL patients, PI3K substrates, like Akt and ERK, are overactivated, resulting in increased cell survival and proliferation. Akt inhibition in CLL cells leads to decreased cell survival and increased apoptosis. This study seeks to identify a novel, selective PI3Kδ inhibitor that results in decreased cell survival and increased apoptosis in CLL cells.

OBJECTIVE

To determine whether a novel, orally available PI3Kδ inhibitor, TGR-1202, differentially regulates regulatory T cells (Tregs) compared to other PI3Kδ inhibitors, in a panel of human T cell subsets.

MATERIALS AND METHODS

Fifty CR-1 T cells were isolated from peripheral blood mononuclear cells (PBMCs) of healthy donors. TCR-stimulated T cells were cultured for 24 h with each drug and FoxP3 mRNA expression was determined by qRT-PCR (n=10).

RESULTS

1. TGR-1202 reduces regulatory T cell number and diminishes function to a lesser degree compared to other PI3Kδ inhibitors

2. TGR-1202 decreases effector T cell number and diminishes function to a lesser degree compared to other PI3Kδ inhibitors

3. TGR-1202 reduces T cell proliferation to a lesser degree compared to other PI3Kδ inhibitors

4. TGR-1202 reduces T cell survival to a lesser degree compared to other PI3Kδ inhibitors

CONCLUSIONS

TGR-1202 exhibits differential effects on regulatory T cells compared to other PI3Kδ inhibitors. TGR-1202 differentially regulates T cell proliferation, survival, and function to a lesser degree compared to other PI3Kδ inhibitors. This study highlights the potential for TGR-1202 to be a selective PI3Kδ inhibitor with differential effects on T cells.

REFERENCES


CONFICT OF INTEREST

TG Therapeutics, Inc., Employment and equity ownership.