Background

Repeated T cell stimulation that occurs in both chronic viral infections and the tumor microenvironment progressively degrades functionality in a process referred to as T cell exhaustion or T cell dysfunction. Developing in vitro assays to model drug responses to compounds that potentially reverse/inhibit this process is urgently needed to propel next generation cancer therapeutics. Exhausted T cells in cancer display dramatically upregulated surface expression of key co-inhibitory receptors such as PD-1, have reduced effector cytokine secretion and have an altered epigenetic landscape. Nuclear architecture and chromatin accessibility impacts activation and exhaustion of T cells. Particularly, mSWI/SNF ATPase-specific inhibitors and degraders have recently been shown to attenuate T cell exhaustion and increase memory T cell phenotypes, where inhibition of SMARCA4/2 ATPase activity resulted in significant lowering of PD-1+/TIM-3+ double positive exhausted T cell populations, increasing progenitor exhausted cells (PD-1+/TIM-3-), lowering terminally exhausted CD39+ population and enhancing associated with lowered apoptosis in treated cells. Here, we employed our previously reported in vitro T cell exhaustion model, to test a novel inhibitor of SMARCA4/2 ATPase activity, FHT-1015.

Methods

To model chronic T cell stimulation in vitro, we repeatedly stimulated human PBMCs from 4 donors with CD3/CD28 Dynabeads. FHT-1015 was included or not included with each Dynabead treatment. Following stimulation, supernatant was harvested for IL-2, TNF-alpha and IFN-gamma cytokine analysis and T cells were collected for flow cytometry (PD-1, TIM-3, LAG-3, CD38, CD39, CD4, CD8, CD3, Live/Dead).

Results

Treatment of exhausted T cells, in our model, with FHT-1015, resulted in selective and consistent of key co-inhibitory receptor surface expression; TI. However, PD-1 surface expression was unchanged while that of CD38 was elevated. Cytokine secretion of IL-2, TNF-alpha and IFN-gamma were all reduced with FHT-1015 treatment. This selective impact of FHT-1015 in modulating T cell exhaustion pathways validates the use of this assay to screen small molecules drugs in reversing T cell exhaustion.

Conclusions

In conclusion, our in vitro T cell exhaustion assay allows identification of immunomodulatory drug candidates that have the potential to regulate the T cell exhaustion developmental continuum and T cell functionality after terminal differentiation.

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