A SINGLE SPARK CAN START A PRAIRIE FIRE – RE-THINK THE COMBINATION STRATEGY AND CLINICAL SETTING OF IL-12 WITH ANTI-PD-1

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Background Immune-checkpoint inhibitors have become the standard therapy in many types of cancers. The combination of anti-PD-1 and anti-CTLA4 demonstrated better anti-tumor response, but toxicity is a concern. Cytokines including IL-2, IL-12, IL-15, IL-21 that target immune cells have been developed to enhance immune response against tumors. IL-12, a multifunctional and potency cytokine, regulates both innate and adaptive immunity. IL-12 is considered to: (1) promote the proliferation and survival of T cell; (2) upregulate the chemokine and adhesion molecule to facilitate lymphocyte trafficking; (3) and trigger the T cell:DC crosstalk in combination with aPD1 treatment which might could potentely enhance antitumor immunity. Therefore, this study aims to explore the synergistic anti-tumor immune response of IL-12 and anti-PD-1.

Methods Demonstrate the combination tumor growth inhibition effect in 11 (MBT-2, MC38, CT-26, B16F10, 4T1, RENCA, B16F10, Hepa1-6, EMT-6, LL/2, J558) syngeneic mice tumor bearing model. Dose dependent effect, dosing sequential effect, and immunophenotyping in tumor microenvironment (TME) is conducted in CT26 and MC38 tumor bearing model. Mixed lymphocyte reaction (MLR) assay of Keytruda and human recombinant IL-12 (rHu-IL12) combination is conducted for in vitro lymphocyte proliferation and activation assessment.

Results MBT-2, MC38, EMT-6, Hepa 1-6, and J558 is moderate to high responding to mIL-12 monotherapy (TGI 30 ~ 90%); CT-26 and 4T1 is slight responding to mIL-12 monotherapy (TGI 10 ~ 20%); LL/2, RENCA and B16F10 is non-responding to mIL-12 monotherapy. Anti-PD-1 combine with mIL-12 has permissive effect in MC38 (TGI 70% vs. 70% vs. 95%) and J558 (TGI 10% vs. 30% vs. 30%); has synergetic effect in CT26 (TGI 20% vs. 25% vs. 60%); and indifference in B16F10 and 4T1. Immunohistochemical and flow cytometric analyses confirmed that CD8+ T cells accumulate at the tumor margin and infiltrate the tumor mass in response to the combination therapy, resulting in favorable effector and regulatory T-cell ratios (12.33% : 4.64% to 18.40% : 2.03%), M1/ M2 ratios (0.07%:0.08% vs. 0.1%:0.01%). In the MLR assay, rHu-IL12 could enhance the T cell proliferation combined with Keytruda; the T cell activation biomarker (CD25, CD69, HLA-DR) is also induced higher in rHu-IL12 combination group.

Conclusions Systemic mIL-12 administration could show the robust tumor growth inhibition effect under specific TME setting, and reshape the tumor microenvironment even at extremely low concentration (20~50ng/mice). It gives us a hint to re-think the clinical setting and combination strategy of rHu-IL12 with anti-PD-1.