EXPLOITING ALTERNATIVE ANTIGEN PRESENTATION TO OVERCOME TUMOR ANTIGEN ESCAPE IN T-CELL RECEPTOR-BASED THERAPY

Jiao Huang, Min Liu, Cuiqiong Zhang, Kai Zhan, Hanli Sun, Zhiming Weng, Wanli Wu, Hongjun Zheng, Yingjie Huang, Shi Zhong*, Xiangxue Life Science Research Center, Xiangxue Pharmaceutical Co. Ltd., Guangzhou, Guangdong Province, China

Background T cell receptor engineered T (TCR-T) cell therapies have demonstrated promising efficacy in the treatment of solid tumors. However, a major challenge in their effectiveness arises from tumor antigen escape. One such mechanism involves deficiencies in the antigen presentation machinery (APM). The classical APM requires molecules like proteasome and the peptide transporter TAP. Alterations in these molecules have been observed in various tumor types and contribute to tumor antigen escape. Interestingly, the presentation of some peptide antigens have been shown to utilize an alternative pathway. We hypothesize that TCR-T cells specific for these particular peptide antigens can bypass defects in the classical APM and overcome tumor antigen escape.

Methods We have previously identified an HLA-A*24:02 restricted alpha-fetoprotein (AFP) peptide (AFP2-11).1 A TCR specific for AFP2-11 was isolated from peripheral blood mononuclear cells of a healthy donor. The TCR was affinity enhanced through phage display. The antitumor activity of the affinity enhanced TCR-T cells was evaluated using tumor cell lines and in vivo tumor models. The specificity of the affinity enhanced TCR was assessed using a panel of primary cells from various tissues and the X-scan method. To determine whether AFP2-11 requires the classical APM, we investigated AFP2-11 presentation on HLA-A*24:02 overexpression T2 cells (a TAP1 deficient cell line) and by knocking out TAP and other key molecules involved in the classical APM in HepG2 cells (an AFP and HLA-A*24:02 positive hepatocellular carcinoma cell line).

Results The affinity-enhanced AFP2-11 specific TCR demonstrated significantly enhanced antitumor activities in in vitro assays. Adoptive transfer of TCR-T cells led to inhibition of tumor growth in hepatocellular carcinoma (HCC) tumor models. The affinity-enhanced TCR maintained antigen specificity, as confirmed by cross-reactivity assays using a diverse panel of primary cells and the X-scan method. Furthermore, AFP2-11 specific TCR-transduced T cells effectively responded to AFP overexpressing T2 cells and TAP1-knocked-out HepG2 cells, indicating that AFP2-11 could still be presented on the cell surface despite defects in the classical APM.

Conclusions We have successfully developed an affinity-enhanced TCR specific for a peptide antigen utilizing the alternative presentation pathway. This TCR has the potential to overcome tumor antigen escape resulting from defects in APM. Our study holds significant implications for TCR-based therapy, suggesting a novel strategy for overcoming tumor escape.

REFERENCES

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0436