CSF as the main candidate mediators of this skewing of monocytes to an M2-like state. The use of specific neutralizing antibodies against each of these cytokines prevented the observed DC suppression to varying degrees. t-Distributed Stochastic Neighbor Embedding (t-SNE) identified specific shifts between monocyte subpopulations and modulated expression levels of associated surface markers. Neutralization of M-CSF reduced expression of BDCA3, PD-L2, and PD-L1, while increased CD16; whereas blocking TGF-beta led to a concerted reduction in CD14, CD163, PD-L1, and PD-L2 levels, but, unexpectedly, also of CD80.

In contrast, IL-10 neutralization resulted in a decrease of all M2-related markers, while CD80 levels were upregulated. Interestingly, while the SK-MEL-28 cell line did not secrete detectable levels of IL-10 in traditional monolayer cultures, RNA in situ hybridization revealed de novo expression in Mel-RhS in melanoma cells, as well as in keratinocytes and fibroblasts.

Conclusions We conclude that the 3D configuration of the Mel-RhS model results in cross-talk between tumor and stroma, which allows for the delineation of immune suppressive pathways in the melanoma TME. Ultimately, this model could be used as a novel in vitro tool for preclinical testing of immune modulatory therapeutic agents.


On Demand Talks: Combination Therapy

06 EXPRESSION OF ANTI-APOPTOTIC GENE CFLIP TO ENHANCE PERSISTENCE IN CAR T CELLS

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Background CAR T cell therapy has been successful for targeting blood cancers, but treatment of solid cancers has been limited due to the heterogenous nature of tumour-associated antigen expression on solid cancers, and the suppressive tumour microenvironment. 1 A major obstacle to CAR T cell therapy is activation-induced cell death (AICD) of the CAR T cells. 2 In this study, we expressed the anti-apoptotic cellular FLICE-like inhibitory protein (c-FLIP short; c-FLIPs) CAR T cells. 2 In this study, we expressed the anti-apoptotic cellular FLICE-like inhibitory protein (c-FLIP short; c-FLIPs) to a bispecific VHH approach to leverage the constitutive expression of V9V82-T cells with elevated levels of non-peptide phosphoantigens (pAg), induced by cell stress or malignancy. To date, V9V82-T cell based cancer immunotherapeutic approaches were well tolerated and in some cases capable of inducing relevant clinical responses. In an effort to improve the efficacy and consistency of V9V82-T cell based cancer immunotherapy, we designed a bispecific VHH that binds to both V9V82-T cells and EGFR expressed by tumor cells and results in the target-specific activation of V9V82-T cells and subsequent lysis of colorectal cancer cell lines and primary colorectal cancer samples both in vitro and in an in vivo mouse xenograft model. Of note, tumor cell lysis was independent of mutations in KRAS and BRAF that are known to impair the efficacy of clinically registered anti-EGFR monoclonal antibodies as well


07 A BISPECIFIC VHH APPROACH TO LEVERAGE THE POTENT AND WIDELY APPLICABLE TUMOR CYTOLYTIC CAPACITY OF V9V82-T CELLS

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V9V82-T cells include a unique and potent subset of T cells which play an important role in tumor defense. V9V82-T cells recognize and can lyse butyrophilin 3A1-expressing target cells with elevated levels of non-peptide phosphoantigens (pAg), induced by cell stress or malignancy. To date, V9V82-T cell based cancer immunotherapeutic approaches were well tolerated and in some cases capable of inducing relevant clinical responses. In an effort to improve the efficacy and consistency of V9V82-T cell based cancer immunotherapy, we designed a bispecific VHH that binds to both V9V82-T cells and EGFR expressed by tumor cells and results in the target-specific activation of V9V82-T cells and subsequent lysis of colorectal cancer cell lines and primary colorectal cancer samples both in vitro and in an in vivo mouse xenograft model. Of note, tumor cell lysis was independent of mutations in KRAS and BRAF that are known to impair the efficacy of clinically registered anti-EGFR monoclonal antibodies as well