Targeting the immune-suppressive tumor microenvironment to potentiate CAR T cell therapy

Tiffany C. Y. Tang1, Ning Xu1,2 and Alla Dolnikov1,2*
1Children's Cancer Institute, University of New South Wales, Sydney, Australia
2Kids Cancer Center, Sydney Children's Hospital, Sydney, Australia

Chimeric antigen receptor (CAR) T cell therapy

CAR T cell therapy is a promising new immunotherapy that reprograms patient T lymphocytes to specifically recognize and kill tumor cells. CAR T cell therapy has produced some dramatic responses in acute lymphoblastic leukemia and lymphomas, but responses have been less spectacular in solid tumors. To make CAR T cell therapy effective for solid tumors, CAR T cells must overcome an immune-suppressive tumor microenvironment (TME) that attenuates CAR T cell function. This review provides insights into mechanisms of CAR T cell therapy resistance with respect to the TME and offers strategies for improving CAR T cell therapy by targeting immune-suppressive factors in tumors.

Mechanisms and strategies to overcome immune suppression in the tumor microenvironment (TME)

Recent clinical studies have shown that CAR T cells can cure select patients with cancer, while others experience transient or no clinical benefit [4,5,10,15,24,25]. Short duration of remission in patients treated with CAR T cells can be associated with functional CAR T cell exhaustion in the immune-suppressive TME [6,7,26,27]. The immune-suppressive TME considerably reduces the efficacy of CAR T cell therapy against solid tumors such as prostate [28-30], ovarian [31-35], breast [36-39], pancreatic [40-44], and brain [45] cancers. Dismalowangioside (GD2)-targeting CARs incorporating CD28 and OX40 co-stimulatory domains showed efficient CAR T cell infiltration of neuroblastoma tumors; however, the suppression of tumor growth was marginal, suggesting that CAR T cell function is compromised by the immune-suppressive TME [46,47].

The immune-suppressive TME is enriched with regulatory immune cells such as regulatory T cells (Tregs) [48-55], myeloid-derived suppressor cells (MDSCs) [36,39,56,57], tumor-associated macrophages (TAMs) [58-60], and cancer-associated fibroblasts (CAFs) [35,61]. These regulatory immune cells inhibit CAR T cells by releasing suppressive factors such as TGF-β [28,30,58,62], IL-4 [43,63,64], IL-10 [40], prostaglandin E2 (PGE2) [65], and immune-suppressive metabolites such as kynurenine and adenosine via indolamine-2,3-dioxygenase (IDO) [59,66,67] and CD39/CD73.

Received: March 04, 2020; Accepted: March 26, 2020 Published: March 31, 2020

*Correspondence to: Alla Dolnikov, Children’s Cancer Institute, University of New South Wales, Sydney, Australia, E-mail: ADolnikov@ccia.org.au

Key words: cancer, CAR T cells, tumor microenvironment
respective [38,68-70]. Additionally, tumor cells often down-regulate T cell co-stimulatory ligands that would normally promote CAR T cell function, while up-regulating immune-suppressive ligands (MHC class II, galectin-9, PD-L1 and CD86) that activate immune checkpoints (LAG3, TIM-3, PD-1 and CTLA-4) in adoptively transferred T cells (Figure 1B) [71]. Chemoresistant and chemorefractory pediatric B-ALLs exhibit significant interpatient heterogeneity in the expression of 35 genes that encode T cell co-stimulatory and inhibitory ligands, and in vitro models showed association of CD86, CD70, ICOSL, OX40, and IL-10 with CAR T cell expansion and exhaustion [26]. B-ALLs exhibit low expression of PD-L1 and CD80/CD86, which activates the PD-1 and CTLA-4 checkpoints in CAR T cells [26]. Unlike B-ALLs, T cell acute lymphoblastic leukemia (T-ALL) cells express high levels of PD-L1 and often CD80/CD86, and so can be considered as more immune-suppressive than B-ALL in this respect [26]. B-ALLs from some patients, however, express MHC class II and galectin-9 (Ga9) that bind to the LAG3 and TIM-3 receptors on CAR T cells to promote CAR T cell exhaustion and apoptosis [71].

CARs with multiple co-stimulatory domains and/or genome-edited checkpoint receptors have been engineered to mitigate the immune-suppressive TME [70,72-83]. New approaches also combine CAR T cell therapy with chemotherapeutic drugs, epigenetic modulators, or targeted drugs that attenuate immune suppression in the TME in addition to direct anti-tumor activity [32,36,45,47,48,50,67,84-89]. Some epigenetic drugs up-regulate the tumor's antigen expression for targeting by CAR T cells, up-regulate T cell co-stimulatory ligands, or induce type I interferon responses in tumor cells against pro-viruses integrated into target cell genomes [90]. The hypomethylating agent 5-azacitidine (AZA) sensitizes leukemia and lymphoma cells to CAR T cell therapy by modulating the TME in leukemia and inducing OX40L to promote CAR T cell function [20,86]. Other epigenetic modulators down-regulate the immune-suppressive ligands that activate specific immune checkpoints in CAR T cells. JQ1, a potent small-molecule bromodomain and extra terminal domain (BET) inhibitor, down-regulates PD-L1 expression in neuroblastoma and sensitizes neuroblastoma cells to CAR T cell therapy [47,85]. JQ1 also promotes CAR T cell activity by up-regulating interferon regulatory factor 7 (IRF7) signalling to activate type I interferon responses [47,85].

Combining CAR T cells with specific targeted drugs have been shown to promote CAR T cell function [67,84,87,89]. Ibrutinib is a small-molecule drug that binds permanently to Bruton's tyrosine kinase and is used to treat chronic lymphocytic leukemia (CLL). CLL patients showed prolonged remission after combined treatment with ibrutinib and CAR19 T cells [84,87,89]. Ibrutinib induced mobilization of the disease into blood or bone marrow, where it is highly responsive to CAR T therapy [84,87,89]. Lenalidomide, another targeted drug for treating multiple myeloma (MM), delayed the onset of CAR T cell functional exhaustion in the immune-suppressive TME by potentiating CAR T cells that target B cell maturation antigens in MM [67].

Another promising strategy involves using checkpoint inhibitors to rejuvenate exhausted CAR T cells [70,75-83]. Up-regulation of specific checkpoint ligands such as PD-L1 in inflamed TME induces premature CAR T cell exhaustion. PD-1 checkpoint blockade with PD-1 and/or PD-L1 antagonistic antibodies [91-94] acts to rescue CAR T cells from exhaustion and improve their cytolytic activity in melanoma [77,95-97]. PD-1 checkpoint inhibitors induced remission in B-ALL patients who relapsed following CAR T cell therapy [98], but did not promote CAR T cell efficacy in recent neuroblastoma clinical studies [99], suggesting that additional factors in the TME may be involved in CAR T cell exhaustion in neuroblastoma patients.

Agents targeting Tregs, MDSCs, TAMs, and CAFs in the TME are currently being investigated in the context of CAR T cell therapy against hematological and solid tumors [100-107]. Macrophage colony stimulating factor 1 (CSF1) and granulocyte macrophage colony stimulating factor (GM-CSF) antagonists were shown to inhibit TAMs and MDSCs and promote CAR T cell function [100-102].
Conclusion

CAR T cell therapy has been a major breakthrough in cancer treatment. Despite encouraging clinical results in certain hematological malignancies, high resistance to CAR T cell therapies has often been reported in patients with solid tumors. Multiple mechanisms contributing to CAR T resistance have led to the design of complex therapeutic strategies to avoid immune suppression in the TME of solid tumors and to increase tumor cell susceptibility to CAR T cell attack. Resistance mechanisms need to be examined in different contexts in order to design effective therapeutic combinations and improve the efficacy of CAR T cell therapy.

Acknowledgments

This work was funded by Kids Cancer Project grants. The authors thank Dr Kenneth Micklethwaite from Westmead Institute of Medical Research, Sydney, for providing constructive discussion of the manuscript.

Author contributions

All authors participated in the preparation, writing and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

References

23. ClinicalTrials.gov (2020) Anti-CD19 CAR in PiggyBac Transposon-Engineered T Cells for Relapsed/Refractory B-cell Lymphoma or B-cell Acute Lymphoblastic Leukemia (Registry ID: NCT04028920). Yaman’s Affiliated Hospital of Kunming Medical University.


