Journal for ImmunoTherapy of Cancer

High antigen density of BCMA: friend or foe to CAR T cells?

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To cite: Gaballa MR, Maus MV. High antigen density of BCMA: friend or foe to CAR T cells? *Journal for ImmunoTherapy of Cancer* 2022;**10**:e005822. doi:10.1136/jitc-2022-005822

Accepted 20 August 2022

► http://dx.doi.org/10.1136/jitc-2022-005403

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The therapeutic landscape of multiple myeloma (MM) has been rapidly evolving with the development of newer modalities such as chimeric antigen receptor T-cell (CAR-T) therapies. Currently, there are two CAR-T cell products approved by the U.S. Food and Drug Administration for MM, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel). Both products target B cell maturation antigen, or BCMA, on the surface of MM cells and showed impressive results in pivotal clinical trials, with overall response rates of 73% and 97%, respectively.[1 2] Nonetheless, to date, MM remains largely incurable, with post BCMA-directed therapy relapse posing a major hurdle.

In this issue, Li *et al*[3] describe a novel mechanism of relapse post BCMA-directed CAR-T therapy, which appeared paradoxical at first: namely, a case with excess surface BCMA expression on MM cells. This started as a case report of a patient with refractory MM who received CT103A, a fully human, BCMA-targeting investigational CAR-T product. The disease was characterized by very high levels of BCMA antigen expression on the surface of the MM cells, along with unexpectedly low levels of soluble BCMA. The patient received a target cell dose of 6×10^6/kg of CAR+T cells, but unfortunately, she had an unfavorable course complicated by grade 4 cytokine release syndrome (CRS) and early relapse after a short-lived partial response. She ultimately died of concomitant disease and severe CRS despite intensive management.

The poor outcome initially seemed counterintuitive to what one would expect with high levels of surface BCMA expression by MM, so the authors went on to study the possible underlying mechanisms. Whole genome sequencing revealed a single-base missense mutation and deletion of the Psenen alleles. They demonstrated that Psenen gene alterations led to reduction of gamma-secretase, which in-turn augmented surface-bound BCMA antigen expression, abrogating steady-state cleavage of BCMA. The Psenen-coding protein PEN2 is a component of gamma-secretase, which was downregulated in Psenen gene knockout (KO) cells, and resulted in elevation of membrane-bound BCMA expression and improved MM plasma cell survival. This effect was reversible upon restoring Psenen expression, suggesting that Psenen has an important role in augmenting MM cell survival through its effect on gamma-secretase and surface BCMA expression. To further investigate this, the investigators then constructed a mutated cell line (m-PEN2) with single-base mutations in KO cells. Cells with m-PEN2 showed augmented surface BCMA expression and lower soluble BCMA compared with the non-mutated cells, proving that Psenen gene alterations can lead to loss of gamma-secretase, elevation of membrane-bound BCMA expression, and reduction of soluble BCMA (figure 1).

This study gleans important insights on the relationship between high BCMA antigen density and outcomes after CAR-T cell therapy. As shown by the correlative studies, high antigen density was available for targeting by CAR-T cells; this may have played a role in the clinical development of severe CRS. Nonetheless, the patient had an early relapse, possibly explained by increased signaling of membrane-bound BCMA expression leading to enhanced MM cell survival that was not overcome by the higher BCMA antigen density available for targeting by the CAR-T cells. This is the first case that describes higher levels of membrane-bound BCMA expression as a factor implicated in severe CRS and early relapse after CAR-T therapy.

This study sheds light on BCMA biology and its interaction with CAR T cells; evidently, target-related resistance can result from either overexpression or underexpression of surface BCMA. Until now, most of the literature has focused on reduced antigen expression as a mechanism of resistance to CAR T

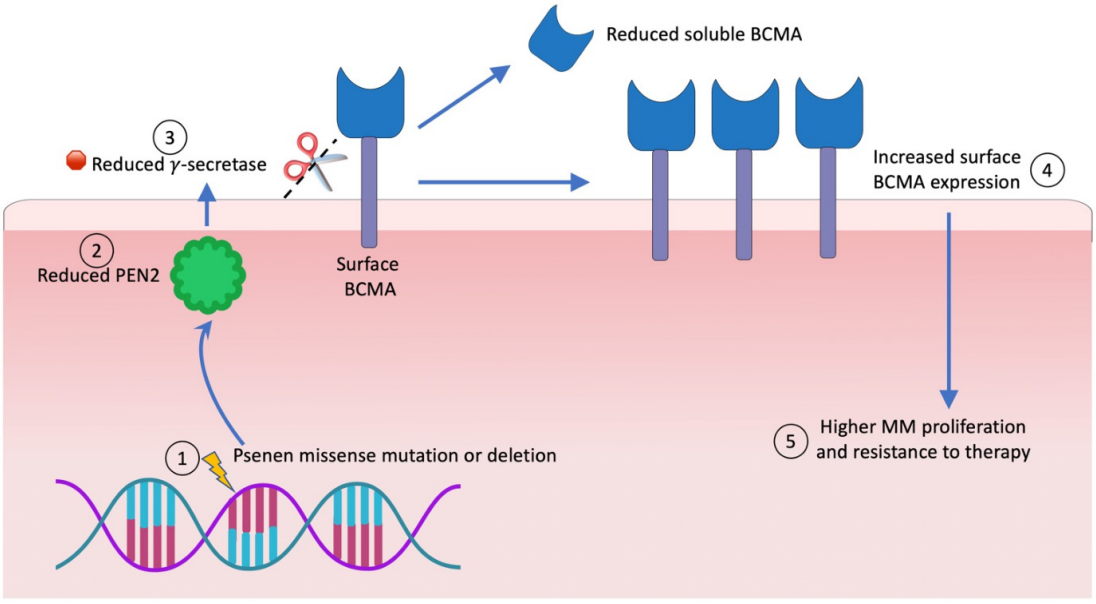

Figure 1 Role of Psenen gene alterations and downstream effects leading to enhanced MM cell survival. BCMA, B cell maturation antigen; MM, multiple myeloma.

cells, including reduced BCMA in MM. Indeed, MM is known to have numerous subclones, which could result in the emergence of clones with negative or low expression of BCMA.[4] In addition, acquired biallelic loss of BCMA after CAR-T therapy has been described by Samur *et al*,[5] where ineffective BCMA-directed CAR-T was caused by deletion of one allele and mutation in the second allele creating an early stop codon, with subsequent diminished expression of BCMA. The study highlighted that MM cells have the capacity to acquire alternative BCMA-independent survival mechanisms. Furthermore, a recent study showed that the tumor microenvironment can play a critical immunosuppressive role through cancer-associated fibroblasts (CAFs).[6] Preclinical models showed that CAFs inhibit CAR-T antitumor effects and promote MM progression. CAFs also express FAP and SLAM-F7, and animal models showed that CAR-T cells targeting both MM and CAFs led to improved efficacy.[6]

In conclusion, this study highlights that BCMA overexpression may be associated with poor outcomes after CAR-T therapy, either through the development of severe and possibly fatal CRS or early relapse. It also highlights that Psenen mutations can be the underlying culprit, which together with prior reports describing acquired biallelic loss of BCMA, adds to the body of evidence that genetic alterations in target expression seem to be a critical player promoting early relapse or resistance. Furthermore, this study suggests that in patients with very high levels of membrane-bound BCMA expression, consideration should be made for early and aggressive anti-CRS therapy.

Contributors MRG and MVM wrote the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MVM serves on the Board of Directors of 2Seventy Bio.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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