Matrix Metalloproteinase 8: Could it Benefit the CAR-T Cell Therapy of Solid Tumors?- a- Commentary on Therapeutic Potential

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Introduction

Since the first experiences with genetically modified T cells in the 1980s, the concept of adoptive T cell immunotherapy has been evolved extensively [1, 2]. The introduction of chimeric antigen receptor (CAR), an artificially designed receptor on T cells against desired tumor antigens, has propelled the adoptive T cell therapy toward fair outcomes. A CAR is usually consisted up of an extracellular single chain fragment of variable (scFv) obtained from an antibody, a hinge, a transmembrane region and intracellular signaling domains [3]. This chimeric receptor provides the possibility for T cells to be activated MHC independently [4]. Therefore, can overcome the MHC down regulation and diminished antigen presentation observed in several malignancies [5]. The majority of CAR-T cell trials have been conducted on B cell and T cell malignancy platforms. Especially, anti-CD19 redirected CAR-T cells caused great success rate which was complete remission of 69–90% of patients with pediatric acute lymphoblastic lymphoma [6–10]. Developing generations and multi-receptor approaches of CAR-T cells are all planned to maximize the efficacy and decline the side effects [11].

CAR-T Cells in Solid Tumors

CAR-T cell therapy has been accompanied by fair outcomes in the case of B cell and T cell lymphomas, acute

myeloid lymphoma (AML), Hodgkin lymphoma and multiple myeloma [12–15]. Due to overexpression of CD19 in B cell malignancies, this tumor associated antigen has been a target of choice for CAR-T cell therapy of B cell lymphomas. So that, CD19 targeted CAR-T cells have attained the most successful outcomes with CAR-T cell therapy until now [14, 16].

Numerous CAR-T cells redirected against a variety of solid tumors have been applied in clinical trials. Although these trials have been reviewed elsewhere [5], Table 1 represents some of them in brief.

In contrast to hematological malignancies, CAR-T cell therapy of solid tumors is encountered to some obstacles. Lack of exclusive antigens restrains the establishment of highly specific CAR-T cells. A CAR-T cell with low specificity can cause severe off target effects and restrain the clinical application. On the other hand, the immunosuppressive microenvironment of solid tumors impairs the effector function of recruited CAR-T cells [17].

Apart from aforementioned problems, insufficient homing of effector cells into solid tumors is a critical obstacle [18]. Infiltration of effector T cells in inadequate numbers propels the desired immune-effector functions to be overwhelmed by the immunosuppressive milieu. Low population of effector T cells in a tumor cannot overcome the high amplitude of malignant cells residing in a compact mass of tumor [19]. In addition, lack of appropriate chemokine receptors on CAR-T cells hinders their sufficient chemotaxis toward chemokine gradients [5].

Moreover, stiff extracellular matrix (ECM) and collagen fibers produced by cancerous cells and cancer associated fibroblasts impede the homing of immune-effector cells into tumors. Disability of T cells to pass through the collagen barriers and unsuccessful infiltration has been shown in breast, lung and pancreas carcinomas [20–22]. Collagen fibers can also support tumor growth and invasiveness through augmentation of prolactin and integrin signaling pathways [23, 24].

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Table 1 Some of the clinical trials registered for CAR-T cell therapy on solid tumors

Antigen	Cancer types	Status	Phase	Clinical trial identifier
HER2	Breast cancer	Recruiting	1&2	NCT02547961
	Glioblastoma	Recruiting	1	NCT02442297
	HER2+ cancers	Recruiting	1	NCT02713984
Mesothelin	Metastatic HER2- breast cancer	Recruiting	1	NCT02792114
	Malignant pleural disease	Recruiting	1	NCT02414269
	Pancreatic cancer	Recruiting	1	NCT02706782
GD2	Neuroblastoma	Ongoing	1	NCT01822652
EGFR	Advanced glioma	Recruiting	1	NCT02331693
EGFRvIII	Recurrent glioblastoma multiforme	Recruiting	1	NCT02844062
GPC3	Advanced HCC	Recruiting	1&2	NCT02715362
CEA	CEA+ cancers	Recruiting	1	NCT02349724
EpCAM	Nasopharyngeal carcinoma and breast cancer	Recruiting	1	NCT02915445
	Stomach neoplasms	Recruiting	1&2	NCT02725125
	Liver Neoplasms	Recruiting	1&2	NCT02729493
MUC1	MUC1+ solid tumors	Recruiting	1&2	NCT02617134
PSMA	Prostate cancer	Recruiting	1	NCT01140373
EphA2	EphA2 malignant glioma	Recruiting	1&2	NCT02575261
FAP	FAP malignant pleural mesothelioma	Recruiting	1	NCT01722149
cMet	Triple negative breast cancer	Ongoing	1	NCT01837602
CD171	Neuroblastoma; ganglioneuroblastoma	Recruiting	1	NCT02311621

Strategies to Improve T Cell Tumor Homing

So far, multiple strategies have been applied to overcome the poor infiltration of T cells into solid tumors. Tumor modification prior to CAR-T cell therapy by an Ad5Δ24 oncolytic virus has been performed successfully for chemokine expression in malignant islets [25]. Chemotherapies can also exert a relative increase in local chemokine concentrations of various tumors [26]. Another approach is to overexpress specific chemokine receptors on CAR-T cells. The positive effect of

CXCR2, CCR4 and CCR2b overexpression on the tumor trafficking of CAR-T cells have been documented [27–29]. Boosting integrin function is another strategy for improving T cell homing into tumor [30].

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are Zn dependent endopeptidase proteases, capable of proteolysis of almost all

Fig. 1 Schematic illustration of the behavior of CAR-T cells (a) and (hypothetically) MMP8 overexpressing CAR-T cells (b) upon arrival to solid tumor islets. As a commentary, MMP8 can destruct the collagen fibers encompassing the tumor and enhance the homing of CAR-T cells

ECM components [31]. Based on the type of dominant substrate, MMPs are classified into sub-categories such as gelatinases, collagenases, stromelysins, MT-MMPs and others [32]. MMPs are involved in a myriad of physiologic functions such as organ development and tissue remodeling. Some MMPs play pathogenic roles in inflammatory disorders and cancer [33, 34]. The pathogenic roles of MMP2, MMP3, and MMP9 in pre-metastatic niche formation has been verified in numerous neoplasms [33, 35]. Unlike numerous MMPs with pro-metastatic activity, MMP8, also known as collagenase-2 [32], exhibits unique features. So that, the anti-cancer and anti-metastasis activities have been attributed to MMP8 in melanoma and breast adenocarcinoma. Also, the MMP8 expression was associated with good prognosis and survival in the mentioned cancers [36].

Evidence on the Anti-Tumor Activity of MMP8

An animal model of aggressive mammary carcinoma was exploited by Decock et al. [37] to evaluate the effect of MMP8 heterozygosity and knockout on tumor formation in polyoma virus middle T oncogene-driven (MMTV-PyMT) mouse. This study demonstrated an accelerated tumor formation, higher average volume and tumor vascularity in MMP8 heterozygote and knockout animals. It has been explored that MMP8 protects the animals against metastasis through modulation of tumor cell adhesion. Indeed, MMP8 overexpressing tumor cells have an increased attachment to ECM components [36]. As another mechanism of action, it has been shown that MMP8 can cleave decorin, a small proteoglycan in ECM. The cleaved decorin possesses an ability to sequester TGF- β 1. Therefore the tumor progression caused by TGF- β signaling could be hindered upon decorin activation [38]. The mentioned mechanisms are the probable underlings for the reported positive correlations of MMP8 expression to good prognosis and low metastasis rate.

Discussion

Despite the collagenase nature of MMP8 [32], it has been extensively supported by the literature for its anti-tumor and anti-metastatic activities [36–38]. Although some hurdles of solid tumor CAR-T cell therapy such as immunosuppressive microenvironment has been overcome by the introduction of anti-PD-1 blocking antibody and PD-1 knockout CAR-T cells [39, 40], the expected success rates still remain to be achieved.

Regarding the lower efficacies of CAR-T cell therapy in solid tumors compared to hematological malignancies, it seems that the missed key in developing well-suited CAR-T cells for solid tumors is a neglect to special physical properties of solid tumors. Hypothetically, MMP8 can

provide the possibility for CAR-T cells to pass through the stiff ECM and collagen barriers posed by solid tumors (Fig. 1). Modification of CAR-T cells to overexpress MMP8 along with other modifications such as chemokine receptor overexpression and inhibitory receptor blockage seems to increase the efficiency of solid tumor CAR-T cell therapy and help to approximate its outcomes to those obtained for hematological malignancies.

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