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Multi-specific T Cell Engager And Multi-specific Natural Killer Engager, the Novel Immunotherapy Approaches for Cancer Treatment

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Abstract. T cell engagers and NK cell engagers are the specialized multi-specific antibodies for cancer treatment. They recruit the immune cells to attack cancer issues, simultaneously induce tumor cell lyse activity by targeting their surface antigens. This article discussed the mechanism and development of multi-specific T cell engager and multi-specific NK engagers, as well as their current applications in tumor treatment and outlook on the future development. It might serve as a useful review for understanding the immune therapeutic approaches and shedding light on the development of more promising approaches for cancer therapy.

Keywords: Immunotherapy, Multi-specific T cell engager, Multi-specific Natural Killer engager

1. Introduction

Cancers currently remain the most dangerous disease. Reports from World Health Organization(WHO) have shown that nearly 20 million people diagnostic positive and approximately 9.7 million people death caused by cancer in 2022 [1]. The total global death due to cancer is expected to increase from 18% to 25% till 2050 [2]. Due to the seriousness of cancer, the development of cancer treatment methods has become one of the top priorities for human health. In the past decades, tumor treatments have developed rapidly, like the chemotherapy and radiation therapy, etc. Nevertheless, none of these traditional therapies achieved the ideal therapeutic efficacy and safety during clinical trials and treatments [3]. Utilizing tumor immune escaping theory, cancer immune-therapeutic approaches have been developed in the past decades. Due to their improved safety and efficiency, immunotherapy has emerged as a groundbreaking approach for cancer treatment [4]. Among different immunotherapeutic approaches, Bi-specific T cell engager(BiTE) and Bi-specific Natural killer engager(BiKE) antibodies are two of the most potential cancer treatment approaches. They are designed to re-recruit T cells and NK cells to trigger an immune response against tumor cells that escaped from the monitoring of our innate immune system [5]. This review discussed the current applications of BiTE & BiKE for cancer treatment.

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2. Novel Immunotherapy: BiTE

2.1. Development of bispecific antibody to BiTEs

In the past decades, the development of therapeutic antibodies enabled the breakthrough in tumor treatment. Inspired by the advances in immune oncology(IO), numerous types of monoclonal antibodies (mAb) have been developed for cancer treatment [6-7]. However, the mono specificity of mAb is the major limitation for its application in IO-based treatment. Current application is limited to immune checkpoint inhibitor and adoptive cell therapies. T cell being the robust defender of immune system have been increasingly considered as the potent weapon against the cancer. However, due to the lack of Fc receptors on T cells, the induction of tumor killing activity via T cell cannot be achieved by mAb [8]. Recently breakthrough in bispecifc antibodies enables the development of BiTE [9]. The first-in-class BiTE, Blinatumomab, consists of two variable chains which recognize CD19 of B cell and CD3 of T cell [10]. The killing of tumor over-expressing CD19 is achieved by the recruitment of and activation of T cell via the CD3 binding arm. This BiTE not only showed high response rates in refractory or relapsed patient population, but also cause acutely adverse event involved pyrexia, neurological, etc. [11]. The discovery of various tumor-enriched antigens in the past decades leads to a spike in the number of BiTE for cancer treatment moving to preclinic and clinic trials [12]. For example, Tarlatamab(DLL3-targeted BiTE) against to Small-Cell Lung Cancer, a Pronectin^{TM}-based BiTE(pAXL×CD3ε) makes a great progress in preclinical models of human soft tissue and bone sarcomas, and Teclistamab-cqyv(CD3-BCMA) caters to multiple myeloma(MM) [13-15].

2.2. Structure of BiTE

Antibody is composed of several structurally independent submits with defined functions. The two variable regions (VH, VL) are involved in target recognition and Fc regions regulates corresponding downstream immune responses [16,17]. A bispecific antibody can be engineered to recognize two different targets by grafting their sequences in the variable regions into the two binding arms of an antibody. A BiTE that consists of two binding arms is able to simultaneously recognize TAA and T cell receptors such as CD3 and CD28. Via these two binding arms, BiTE can recruit T cells, redirect T cells to target tumor antigens and induce the proliferation of T cell [18,19], figure1(a).

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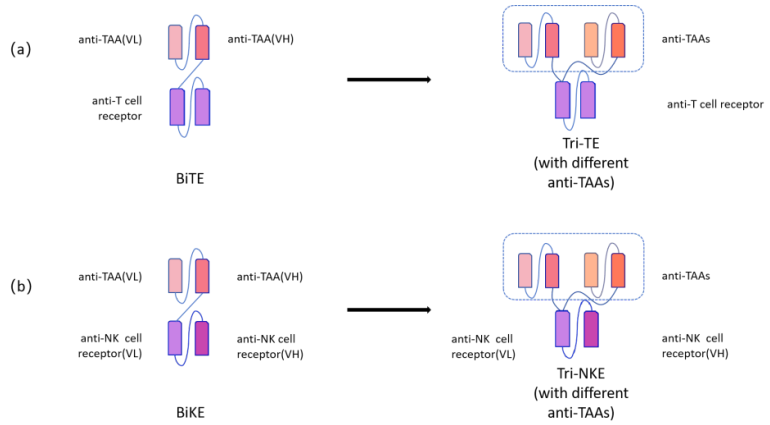

Figure 1. The structure of BiTE(a) and BiKE(b): Bispecific antibodies with binding domains for TAA and T cell/NK cell receptors could recruit T cell or NK cell to eliminate cancers by targeting TAA. Tri-TE and Tri-NKE contain an additional binding domain for TAA and might recognize a broader range of cancer cells

2.2.1. T cell receptors

The most popular receptor to be used for T cell engager(TCE) design is CD3. The activation of CD3 can promote the maturation of T cells into CD4+T cells and CD8+T cells after binding to co-stimulatory receptors [20] and induce complement-dependent cytotoxicity (CDC) for tumor cell elimination [21], figure2. CD28 can also be used as the receptor for engaging T cells. CD28 interacts with B7 molecule(CD80/CD86) from dendritic cell(DC) and subsequently regulates immune responses and the extracellular elicitation of ADCC [22]. The crucial role of B7:CD28 signaling pathway in immunotherapies for cancer makes CD28 another promising receptor for T cell engagers [23].

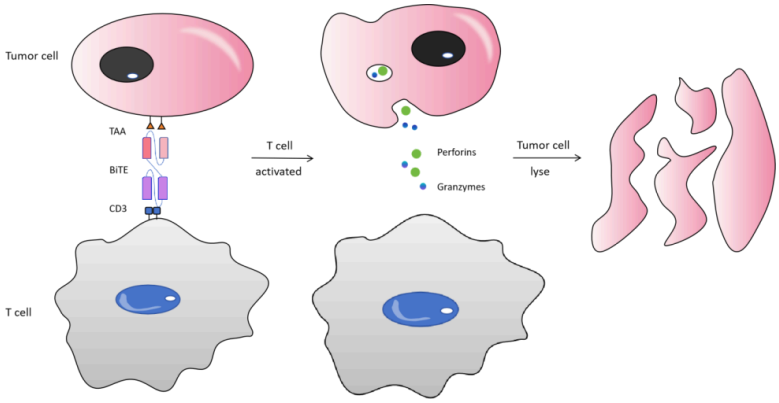

Figure 2. The mechanism of action for BiTE: BiTE targets tumor cell antigen and CD3 to induce T cell dependent killing of tumor cells. Perforins and granzymes released by activated T cells are internalized by tumor cells through endocytosis and lyses the tumor cells

2.2.2. Tumor antigens

There are numerous solid tumor associated antigens that can be used as targets for BiTE. One of the most remarkably targets is Human Epidermal Growth Receptor 2(HER2, gene ERBB2), which has predicted to be utilized in therapeutic target for breast or gastric cancer for decades [24-26].

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Meanwhile, HER3 is another the significant member in epidermal growth factor receptor(EGFR) family associated with cancer progression. The up-regulation of HER3 leads to resistance on epidermal growth factor receptor(EGFR) and HER2-targeted therapy. Other popular TAA targets for Antibody-drug conjugates (ADCs) like Trop2/TACSTD2, Folate Receptor-α(FLOR1), Nectin-4 EFNA4, cMET, B7-H3/CD276, NECTIN4, and PTK7, are also suitable to be used for the treatment of pancreatic, lung, breast, oesophageal, and head and neck cancers for BiTE [27].

2.2.3. Fragment- crystallizable (Fc) regions

The half-life span of an antibody, as well as its ability to activate immune systems, is determined by the Fc region. Two major classes of BiTE have been designed based on the presence and absence of the Fc region [22-23,28]. BiTEs without the Fc regions consist of two covalently linked variable regions. Due to its simple structure, they might be able to penetrate regions which are inaccessible to large molecules within solid tumor. Therefore, this type of BiTE might have better diffusivity within the high condensed tumor matrix and better killing efficacy against tumor [22]. However, due to the lack of the Fc region, this type of BiTE might have shorter half-life in vivo. On the contrary, BiTE with the Fc region can not only inherit the specificity and sensitivity of BiTE without Fc region, but also mediate the ADCC effect due to the presence of Fc region, further enhance the killing efficacy of cancer cells. At the same time, the existence of Fc region makes the whole molecule more stable and has a longer half-life [23].

2.3. Preclinic and clinic landscape of BiTE

A series of promising drug candidates utilizing the T cell engager mechanism have been developed by Amgen. AMG 757, a novel BiTE, has demonstrated the ability in killing small cell lung cancer(SCLC) cells by simultaneously targeting the Notch ligand Delta-like ligand 3(DLL3) and CD3 on T cell [29]. AMG 420, which recognizes B cell maturation antigens(BCMA) expressed on multiple myeloma cells, plasma cells, and mature B cells, had shown promising efficacy in preclinical and clinical studies [30]. In pancreatic adenocarcinoma and gastric cancer, Claudin 18(CLDN18) is a specifically expressed tumor cell antigen. AMG910 is designed to target CLDN18.2 for the treatment of pancreatic adenocarcinoma and gastric cancer [31]. Furthermore, DR30318, which targets CLDN18.2 and CD3, has about 3 weeks' more life span in vivo due to the addition of human serum albumin (HSA) fragment. Its subsequently in vitro and in vivo studies indicated a robust efficacy in suppressing tumor proliferation [32-33].

In addition to the examples above, numerous promising BiTEs for tumor treatment have entered clinic stages. For instance, AMG330(CD33/CD3 without Fc region), AMG673(CD33/CD3 with Fc region), JNJ-63709178(CD123/CD3), MCLA-117(CLEC12A/CD3) are utilized on Acute myeloid leukemia(AML) treatment. Meanwhile, Solitomab (EpCAM/CD3) has been tested against several types of solid tumors. AMG211(CEA/CD3), AMG596(EGFRvIII/CD3), BAT2010112(PSMA/CD3), BI764532(DLL3/CD3, which is similar to AMG757), Tebentafusp(HLA-A*02:01/CD3), SAR442257(CD3/CD28/CD38) are used for the treatment of gastrointestinal adenocarcinomas, glioblastoma, prostate cancer, neuroendocrine carcinomas, uveal melanoma, and non-hodgkin lymphoma, respectively [34]. Moreover, a bi-specific T cell engager Tb535H, which engages tumor-associated antigen 5T4, have shown progress in preclinic studies for multiple tumor models [35]. Furthermore, inspired by the idea of the BiTE, several tri-specific T cell engagers(TriTEs) have also been designed to target a broad range of tumor cells with variable TAA expression [19,36-37]. One

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of the examples is a novel tri-specific antibody(tsAb) architecture composed of CD19/CD22/CD3 that showed improved efficacy comparing to Blinatumomab (CD19/CD3) [38].

3. BiKE

3.1. Development and biology of BiKE

Inspired by the success of BiTE in cancer treatment, NK cell engager(NKE) is developed as an alternative approach under similar immunotherapeutic mechanism [39]. NK cells belong to group 1 innate lymphoid cell(ILC) family and are known for their vital role in native immune system as the first line defense. NK cells can mediate the cytotoxic activity without co-stimulatory signals. Upon activation, NK cells could release releasing interferon gamma(IFN-γ) and tumor necrosis factor alpha(TNF-α) and induce the lysis of malignant tumor cells [40]. Unlike BiTE, monoclonal antibody is able to recruit and activate NK cell via Fc binding to the Fc receptors, like CD16a, on the NK cells [36]. Afucosylation of a monoclonal antibody can enhance the binding affinity to CD16a thus expediting ADCC-dependent killing of tumor cells [41,42]. To further improve the killing efficacy for tumor cells, Bi-specific NK engager(BiKE) is designed based on the idea of BiTE. An additional binding arm targeting other NK cell stimulatory receptors can be employed (eg. NKp46, NKp30) and enhance the activity of NK cells. NKp46 is the most studied NK cell receptor for inducing ADCC effect. Therefore, an additional NKp46 binding domain within an antibody could occupate NKp46 caps with externalized calreticulin(ecto-CRT) in synapses between NK and ecto-CRT, further enhance the ADCC effect [43]. NKp30 is another promising NK cell receptor for BiKE-mediated ADCC. The activation of NKp30 accelerates the cytokines like interleukin-2 to release and enhance the NKp30-denpentent NK cells cytotoxicity [44,45]. NKp40 and NKp44 are currently also being tested as alternative activation receptors for NK cells engagers [46,47]. In addition, ligands that activate NK cells can also be used for NK cell engagement. For example, NKG2C and NKG2D are known for their essential roles in NK activation and promising alternative targets for engaging NK cells [46,48]. Furthermore, due to the inhibitory effect on NK cell-dependent cytotoxic process, HLA family inhibitors are promising binding domains for BiKE.

3.2. BiKEs' structure and its clinical landscape

The structures of BiKEs are similar with those of BiTE. BiKEs also consist of two binding arm target NK cell receptor and TAAs, with half-life expanding region additionally [figure1(b)]. For example, AFM13 is a BiKE without Fc domains and recognizes human CD16A on NK cells and CD30 expressed on Hodgkin Reed–Sternberg cells. In additions, other BiKEs, like AFM28 (CD123/CD16a), LAVA-051(CD1d/NKTTCR), IPH6101/SAR443579 (CD123/CD16/NKp46) and IPH6401/SAR445514 (BCMA/CD16/NKp46), have shown promising results in preclinic and clinic studies for hematological malignancies treatment [49]. Moreover, to further enhance the kill activity of NK cell, a fusion antibody composed of a single chain variable fragment(scFV) which targets CD16 as well as a scFV targets tumor antigen and a moiety of IL-15, had shown better tumor kill efficacy than IL-15 alone [50].

4. Conclusion and outlook

Immunotherapeutic approaches for cancer treatment have been developed rapidly and robustly in the past few decades. Both TCEs and NKEs have made outstanding contributions and shown great potential in the clinical treatments of both invasive and solid tumors at present. However, only

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limited numbers of TCEs have been approved so far [51-54]. Advancing new TCE and NKE based drug into clinic treatment remains challenging due to the limited accessibility of antibodies to the cell-surface TAAs in solid tumor issues [55], as well as the complications of cancer immune biology and resistance from tumor [56]. Therapeutic approaches combing drugs with different mechanism of actions might be a better cure for cancer [57].

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