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CD80-Fc fusion protein as a potential cancer immunotherapy strategy

Songna Wang[1,2], Pinliang Hu[3], Jiajun Fan[2], Jing Zou[3], Weidong Hong[3], Xuan Huang[1,2], Danjie Pan[1,2], Huaning Chen[1,2], Yi Zhun Zhu[1] and Li Ye[1,2,*]

[1]School of Pharmacy and State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau, 999078, China , [2]Minhang Hospital & Department of Biological Medicines at School of Pharmacy, Fudan University, Shanghai 201100, China , and [3]Research & Development Department, Beijing Beyond Biotechnology Co., Ltd, Room 308, C Building, NO. 18 Xihuannanlu Street, BDA, Beijing, 100176, China

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ABSTRACT

The activation of T lymphocytes is a crucial component of the immune response, and the presence of CD80, a membrane antigen, is necessary for T-cell activation. CD80 is usually expressed on antigen-presenting cells (APCs), which can interact with cluster of differentiation 28 (CD28) or programmed cell death ligand 1 (PD-L1) to promote T-cell proliferation, differentiation and function by activating costimulatory signal or blocking inhibitory signal. Simultaneously, CD80 on the APCs also interacts with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on the surface of T cells to suppress the response of specific effector T cells, particularly in the context of persistent antigenic stimulation. Due to the pivotal role of CD80 in the immune response, the CD80-Fc fusion protein has emerged as a promising approach for cancer immunotherapy. This review primarily focused on the crucial role of CD80 in the cancer immunotherapy. We also reviewed the current advancements in the research of CD80-Fc fusion proteins. Finally, we deliberated on the challenges encountered by CD80-Fc fusion proteins and proposed the potential strategies that could yield the benefits for patients.

KEYWORDS: CD80; CD28; immune checkpoints; T-cell activation; cancer immunotherapy

INTRODUCTION

The T-cell immune response is regulated by the complex interaction of numerous ligands and receptors [1, 2]. Initially, the specific antigenic peptide presented by the major histocompatibility complex (MHC) of antigen-presenting cells (APCs) is recognized by the T cell receptor (TCR) of T lymphocytes, which forms the TCR-antigenic peptide–MHC complex to initiate T-cell activation [3]. Although the MHC/TCR signal stimulates the T-cell response as the "first signal," it does not completely control the effective activation of T cells [4]. The MHC/TCR signal is regulated by both costimulatory and coinhibitory signals, which are also known as "second signals" and largely determine the outcome of adaptive T cell immunity [5–7]. In particular, the CD28/CD80 costimulatory signal plays an important role in this process. CD80 on the surface of APCs binds to CD28 on the surface of T cells to activate downstream signaling pathways such as PI3K/Akt, Ras/MAPK, nuclear factor kappa-B (NF-κB), JAK/STAT and induce cytokines release, which promotes the proliferation and activation of T cells [7, 8]. However, coinhibitory signals such as programmed cell death protein 1 (PD-1) and CTLA-4 inhibit the activation and functional activity of T cells by binding to their own ligands [9, 10]. Thus, the "second signals" are key regulators of T-cell immunity and important drug targets for recalibrating the immune response [10, 11]. During the tumor progression, T cells are activated and exert anti-tumor effects after recognition of tumor antigens. Due to the complexity of tumor immunity, it is difficult to activate and maintain an effective anti-tumor immune response by blocking only one or two inhibitory pathways. Clinical data show that most patients have a low response rate to PD-1/PD-L1 antibodies alone and may even develop drug resistance [12]. Therefore, new strategies are urgently needed to break the current bottleneck in the cancer immunotherapy.

Multiple lines of evidence suggest that CD28 costimulatory signal is a major downstream target of PD-1-mediated immunosuppression [13]. Anti-PD-1 antibodies alleviate the inhibition of CD28 signal by blocking PD-L1 and PD-1 interactions, which in turn reactivates the anti-tumor immune response [13]. It has been found that the use of CD80 blocking antibodies significantly reduces the efficacy of PD-1 antibodies [14]. Therefore, insufficient CD28/CD80 costimulatory signal is an important reason

*To whom correspondence should be addressed. Li Ye, School of Pharmacy and State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau, China. Tel: (853)8897-2831. Email: lye@must.edu.mo

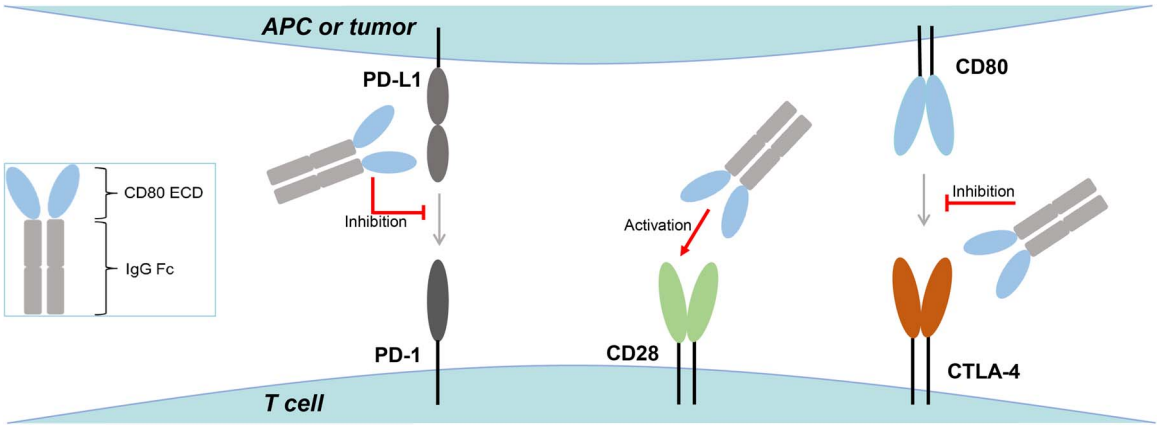

Figure 1. Mechanism of CD80-Fc fusion protein. CD80-Fc fusion protein consists of the ECD of CD80 and the structural domain of IgG Fc. Soluble CD80-Fc fusion protein binds to CD28 to generate T-cell costimulatory signal, whereas its binding to PD-L1 blocks inhibitory signals. Meanwhile, soluble CD80-Fc fusion protein also can bind to CTLA-4 to exert a CTLA-4-trap effect.

for the low response rate of PD-1 antibodies, and enhancing costimulatory signals while blocking inhibitory signals has the potential to be an effective cancer immunotherapy strategy. CD80-Fc fusion proteins can regulate T-cell activation by activating stimulatory signals and blocking inhibitory signals and are thus under intensive study to a great detail [15]. Soluble CD80-Fc fusion protein binds to CD28 to generate T-cell costimulatory signal, whereas its binding to PD-L1 blocks inhibitory signals [16]. Meanwhile, soluble CD80-Fc fusion protein also can bind to CTLA-4 to exert a CTLA-4-trap effect (Fig. 1). At present, a variety of CD80-Fc fusion proteins are under development, such as natural or mutant CD80-Fc fusion proteins and CD80 bifunctional fusion proteins. Although there are still no drugs related to CD80-Fc fusion proteins on the market, their potential in activating effective anti-tumor immune response is enormous. CD80-Fc fusion proteins are expected to become a new strategy for cancer immunotherapy and benefit more patients.

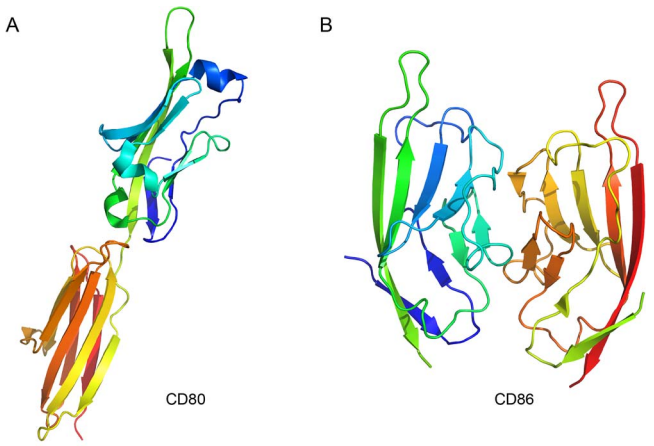

Figure 2. The structures of human CD80 and CD86. (A) The monomer structure of CD80 (PDB: 1DR9) [20] (B) The structure of CD86 (PDB: 1I85) [67].

STRUCTURE AND FUNCTION OF CD80

The structure of CD80

CD80, also known as B7-1, is a costimulatory molecule that belongs to the immunoglobulin superfamily (IgSF) [17]. The mature CD80 molecule contains 262 amino acids, which is mainly composed of the extracellular domain (ECD), the transmembrane domain and the intracellular domain [4]. The ECD of CD80 contains two immunoglobulin-like structural domains (IgV and IgC), of which the IgV region is the main binding domain of CD28, CTLA-4 and PD-L1 [18, 19]. In addition, there is a signal peptide sequence at the N-terminus of the CD80 molecule, which acts mainly to target CD80 to the cell membrane [4].

The monomer of CD80 is a relatively elongated molecule with a size of $23 \times 30 \times 90$ Å^3 [20]. It mainly includes a short linker region and two anti-parallel IgSF structural domains (Fig. 2A). CD80 is usually present as a dimer on the cell surface and is mainly expressed on a variety of immune cells, including dendritic cells (DCs), macrophages, B cells and T cells [4]. It has been reported that the expression of CD80 *in vivo* is regulated by cell–cell interactions and cytokines. For example, signals delivered by the cytoplasmic tails of MHCII molecules can induce the expression of CD80 on B cells [21, 22]. Interferon-γ (IFN-γ) can increase the expression of CD80 in peripheral blood monocytes and decrease its expression in peritoneal macrophages [23].

The function of CD80

As a costimulatory molecule, CD80 plays an important role in the T-cell activation (Fig 3). During the immune response, T-cell activation signal is initially provided by the binding of TCR on the T cells to MHC molecules on the surface of APCs, but this signal is not sufficient to fully activate T cells [24]. The primary costimulatory receptor in naive T cells is CD28, which is constitutively expressed on the cell surface and acts as the primary auxiliary signal augmenting the MHC/TCR signal. Upon antigen stimulation, APCs will upregulate the expression level of CD80.

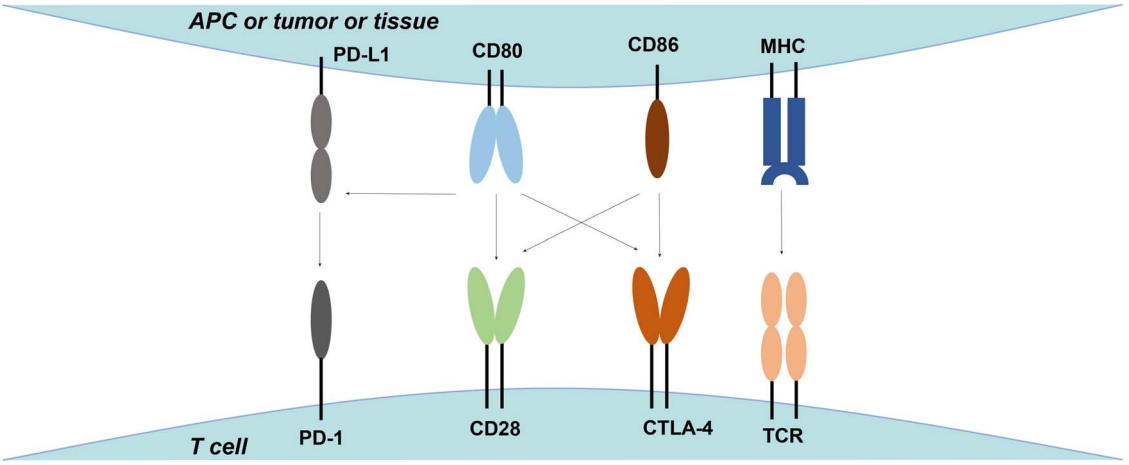

Figure 3. The interactions of CD80 with various molecules. The costimulatory molecule CD80 can bind CD28, CTLA-4 and PD-L1 on the membrane of T cells. As another costimulatory molecule, CD86 can bind to CD28 and CTLA-4 but not to PD-L1.

MHC/TCR and CD28/CD80 signals activate the signaling pathways such as NF-κB, MAPK and calmodulin phosphatase. This is followed by inducing the secretion of various cytokines, such as interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), TNF-β and IFN-γ, which initiate and sustain T-cell activation [25, 26]. In addition, CD28/CD80 costimulatory signal stimulates glucose metabolism and ATP synthesis of T cells by activating the PI3K/Akt signaling pathway [27]. This provides energy to support T-cell proliferation and function. When T cells are activated by MHC/TCR and CD28/CD80 signals, CTLA-4, which exists as homodimers in intracellular vesicles, is induced to relocate to the cell surface [28]. CD28 and CTLA-4 are highly homologous and both have MYPPPY binding motifs (Fig. 4) [29]. CD28 has the same ligands as CTLA-4, and CTLA-4 has a higher affinity for the ligands. Some experiments have shown that the affinity of soluble ^{125}I-labeled CD80-Ig to immobilized CTLA-4-Ig ($K_D \sim 12$ nM) is 20-fold greater than that of immobilized CD28-Ig ($K_D \sim 200$ nM) under the same conditions (Table 1) [30, 31]. Thus, CTLA-4 competes with CD28 for CD80, reducing the second signal required for full T-cell activation. Simultaneously, the binding of CTLA-4 to CD80 inhibits phosphorylation of protein kinase B of the CD28 signaling pathway by activating phosphatase PP2A5 [32]. Then, the secretion of cytokines such as cyclin D3, IL-2, cyclin-dependent kinases 4 (CDK4) and CDK6 and the proliferation of T cells were inhibited [33]. Notably, CD86 (B7-2), as another costimulatory molecule, can also bind CD28 and CTLA-4 (Fig. 2B) [34]. It is completely different from CD80 in terms of amino acid sequence, cytoplasmic domains and expression [4]. In addition, an increasing number of studies have shown that CD80 and PD-L1 can interact in cis on DCs, thereby competitively blocking the binding of PD-L1 and PD-1 [35–38]. However, this cis-interaction does not affect the binding of CD80 to CD28, which is still able to transmit T-cell costimulatory signal and induce the immune responses [39]. At the same time, the cis-interaction between CD80 and PD-L1 can also prevent CD80 trans-endocytosis induced by CTLA-4

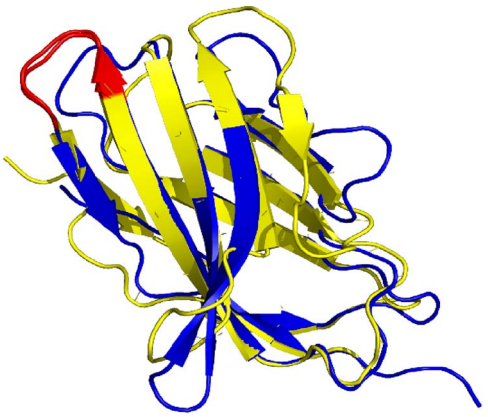

Figure 4. The alignment of CD28 and CTLA-4. The structures of CD28 (yellow) and CTLA-4 (blue) are obtained from CD28: Fab (PDB:1YJD) and CD80: CTLA-4 (PDB:1I8L) binding complexes, respectively. The red part represents the MYPPPY binding motif. The RMSD value is 0.973 nm.

Table 1. The affinity of CD80 with CTLA-4 and CD28

Affinity (K_D)	CTLA-4	CD28
CD80	~12 nM	~200 nM

[39]. Thus, the interaction of CD80 with PD-L1 on DCs is important for the activation of immune responses.

In conclusion, the structure and function of CD80 are crucial for the normal function of the immune system, and have a wide range of applications in fields such as immunology and oncology.

CD80 AND TUMOR

During the tumor progression, T cells are activated after recognizing tumor antigens and exert adaptive immune

effector functions. At the same time, tumors will evade the anti-tumor effect of the immune system through various pathways *in vivo*, including the regulation of costimulatory molecules and the inhibition of tumor-specific antigen expression [40–42]. CD80 is one of the important costimulatory molecules for immune cell activation. Studies have shown that CD80 is not only expressed on the surface of dedicated APCs, but also on a variety of tumor cells, which is one of the important ways for tumors to evade immune surveillance [43, 44].

The expression of CD80 is upregulated in a variety of tumors such as pancreatic cancer and nasopharyngeal carcinoma [45, 46]. On the one hand, high expression of CD80 inhibits the differentiation and maturation of Th1 cells through CTLA-4 inhibitory signal, reduces the secretion of oncogenic factors and promotes the proliferation and invasion of tumor cells [47]. On the other hand, elevated CD80 expression was associated with increased secretion of interleukin-10 (IL-10). IL-10 plays an immunosuppressive role by inhibiting helper T-cell factors, thereby promoting tumor growth and metastasis [45, 46]. In contrast, CD80 expression is significantly downregulated in certain tumors. Low expression of CD80 preferentially binds to CTLA-4 to inhibit T-cell activation, which promotes tumor evasion of immune surveillance. Studies have shown that CD80 expression is downregulated in gastric cancer compared with normal gastric mucosa, especially in poorly differentiated gastric cancer tissues [48]. Low expression of CD80 is closely associated with poorer overall survival and disease-free survival in gastric cancer patients [48]. Therefore, CD80 is considered an independent prognostic factor in gastric cancer patients. Similarly, the expression of CD80 was significantly reduced in papillary thyroid carcinoma and was associated with poor prognosis as well as lymph node metastasis [49]. In conclusion, these findings suggest that CD80 is involved in tumor evasion of immune surveillance and has the potential to be a valuable prognostic and therapeutic target for cancer.

CD80-FC FUSION PROTEINS AND CANCER IMMUNOTHERAPY

Given the significant role of CD28/CD80 costimulatory signaling in T-cell immune response, there have been multiple efforts to activate CD28 signaling. TGN1412, a CD28 superagonist with a high affinity for CD28, was initially developed by TeGenero [50]. However, all volunteers in the Phase I clinical trial suffered severe cytokine storms after being injected with TGN1412. This has also led to a deadlock in research on CD28. Over the past 2 years, several companies have restarted their research on CD28-stimulating antibody. CD28 bispecific antibodies (MUC16 × CD28, PSMA×CD28, EGFR×CD28, BCMA×CD28) of Regeneron Pharmaceuticals, triple-specific antibodies targeting CD3 and CD28 (CD3 × CD28 × CD38, Her-2 × CD3 × CD28) of Sanofi and CD28-based triple-specific antibody (CD19 × CD3 × CD28) of CytoCares have entered the clinical stage [51–54]. These antibodies have shown that the activation of CD28 signaling can enhance the anti-tumor immune effect of T cells. However, an appropriate reduction in antibody affinity against CD28 is necessary to control the risk of generating cytokine storms. As a natural ligand of CD28, CD80 can effectively activate costimulatory signals and induce T cell responses. Using CD80 fusion proteins to activate CD28 costimulatory signal may be safer than using CD28-stimulating antibodies. Simultaneously, CD80 fusion protein can bind to both CTLA-4 and PD-L1, thus promoting the effective T-cell activation by blocking dual immune checkpoints. Therefore, another potential strategy for activating CD28 is to develop CD80-Fc fusion proteins. The related drugs of CD80-Fc fusion proteins include FPT-155 developed by Five Prime Therapeutic, ALPN-202 developed by Alpine Immune Sciences and CD80/IL2 bifunctional fusion protein (GI-101) developed by GI Innovation in collaboration with Simcere (Table 2).

FPT-155

FPT-155 is a CD80-Fc fusion protein developed by Five Prime Therapeutics. It includes the ECD of CD80 and the structural domain of human IgG1 Fc (Fig. 5). FPT-155 can directly bind to CD28 to activate primitive and memory T cells. It can also induce T-cell costimulatory signal by binding to CTLA-4, which allows endogenous CD80 to interact with CD28 at the immune synapse (Fig. 5). *In vivo* studies in mice have shown that murine-derived FPT-155 (mFPT-155) has promising anti-tumor activity in a variety of tumor models, even in tumor models resistant to PD-1/PD-L1 antibodies. In particular, mFPT155 could induce complete tumor regression after a single dose at 0.2 mg/kg. The results also found that mFPT-155 preferentially induced activation of effector T cells in tumors, but did not induce non-specific T-cell activation.

FPT-155 is currently in clinical phase I (NCT04074759) with the primary objectives of evaluating its safety, tolerability, immunogenicity, pharmacokinetic (PK) parameters, pharmacodynamics (PD) parameters and clinical activity. Preliminary PK assessments indicated that the half-life of FPT-155 was approximately 1 week. The dose-escalation was currently well tolerated with no dose-limiting toxicity. After being treated with FTP155, no consistent treatment emergent elevation in cytokines including IL-6, IFN-γ, CXCL9, MCP-1 and CXCL10 was observed. There was also no dose response between FPT155 and cytokine elevation after treatment with a range of doses (0.07, 0.21, 0.7, 2.1, 7, 21 mg). More importantly, unlike the superagonist CD28 antibody TGN1412, FPT-155 requires co-engagement with the TCR for effective T-cell activation. This also suggests that FPT155 is not a CD28 agonist and does not cause a severe cytokine storm [50].

ALPN-202 (Davocepticept)

ALPN-202 developed by Alpine Immune Sciences is a CD80-Fc fusion protein consisting of a mutated CD80 IgV domain and a human IgG Fc structural domain [15] (Fig. 6). By selectively mutating the CD80 IgV domain, ALPN-202 enhances the affinity of CD80 against PD-L1 while retaining the ability to bind CTLA-4. The results of

Table 2. Projects related to the CD80-Fc fusion protein

Projects	FPT-155	ALPN-202	GI-101
Types	Natural CD80-Fc fusion protein	Mutant CD80-Fc fusion protein	Natural CD80-Fc/mutant IL-2 fusion protein
Targets	CTLA-4,CD28,PD-L1	CTLA-4,CD28,PD-L1	CTLA-4,CD28,PD-L1,IL-2R
Indications	Solid tumors	Solid tumors	Solid tumors
Clinical Trials	Clinical phase I(NCT04074759)	/	Clinical phase I/II (NCT04977453)
Company	Five Prime Therapeutic	Alpine Immune Sciences	GI Innovation/Simcere

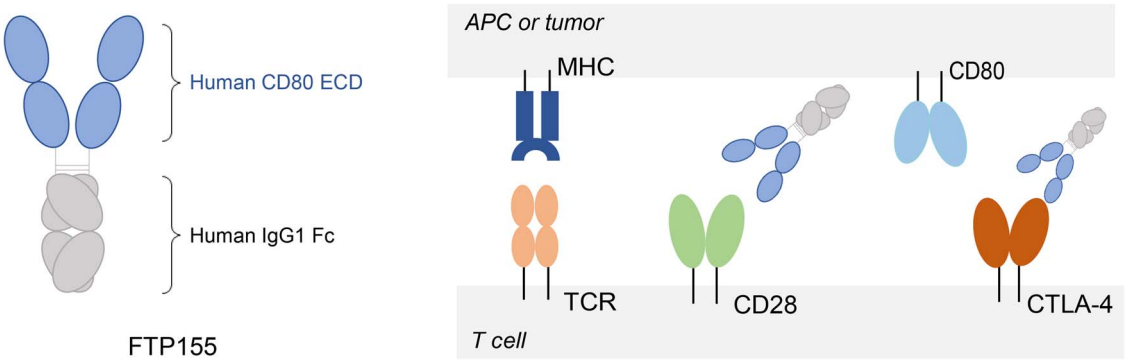

Figure 5. The structure and mechanism of action of FTP155.

molecular and cellular experiments showed that ALPN-202 had significantly higher affinity for PD-L1 and CD28 than WT CD80 ECD-Fc [15]. In the MC38 or human PD-L1 tumor models, ALPN-202 promoted effective dose-dependent anti-tumor activity through systemic or intratumoral delivery. Compared with anti-PD-L1 antagonist durvalumab, ALPN-202 significantly induced greater tumor inflammation signature and increased the clonability and abundance of T cells, which might translate into improved anti-tumor immunity. More importantly, CD28 costimulation by ALPN-202 requires TCR activation and co-binding with PD-L1, suggesting that ALPN-202 activity is costimulatory as opposed to overtly stimulatory. Cytokine release assays indicated that incubation of ALPN-202 with high-density PBMC cultures from multiple donors did not significantly induce cytokine release, including IL2, IL-6, IFN-γ and TNF-α, compared with the control group. The company previously conducted the NEON-1 study, a clinical phase I of ALPN-202 as monotherapy, designed to evaluate its efficacy and safety for the treatment of adult patients with advanced malignancies. Subsequent data showed that ALPN-202 treatment achieved a disease control rate of 60% in patients and was well tolerated.

Immune checkpoint inhibitors represented by PD-1/PD-L1 have been shown to be clinically active, but only a small proportion of cancer patients benefit from them [55]. It has been shown that insufficient CD28/CD80 costimulatory signaling is an important reason for the low response rate to PD-1 antibody immunotherapy. Therefore, the association of PD-1 antibodies with CD80-Fc fusion proteins has the potential to produce synergistic effects and exert more effective anti-tumor activity [14]. In MC38 and B16F10 tumor-bearing mouse models, the anti-tumor activity of ALPN-202 in combination with an anti-mouse PD-1 antibody was stronger than that of each of the two drugs alone [15]. Similarly, Alpine Immune Sciences previously conducted the NEON-2 study to evaluate ALPN-202 in combination with Keytruda for the treatment of patients with choroidal melanoma. Unfortunately, the company voluntarily suspended the registration of two clinical trials of ALPN-202 for the treatment of advanced malignancies. The reason for the termination was primarily grade 5 serious adverse events in the NEON-2 study, which resulted in two patient deaths. Both patients received one dose each of davoceticept and pembrolizumab. Current report indicated that the immediate cause of death was cardiogenic shock. Medical professionals suspected that this could be associated with immune-mediated myocarditis or an infection. Alpine Immune Sciences is also exploring safety issues, but has not determined a safe dose regimen for davoceticept in combination with pembrolizumab.

CD80 bifunctional fusion protein

The development of CD80 bifunctional fusion proteins has become a popular new strategy for cancer immunotherapy. GI-101 (SIM0323) adopts a novel design in which the ECD of CD80 and a mutant of IL-2 are placed at the N-terminal and C-terminal of IgG4 Fc segment, respectively (Fig. 7). The previous study has demonstrated that soluble CD80 acts as a CTLA-4-trap and blocks CTLA-4 mediated immunosuppression [35]. Thus, on the one hand, CD80 in the GI-101 binds to CTLA-4 of T regulatory cells (Tregs) with high affinity, which blocks inhibitory signal

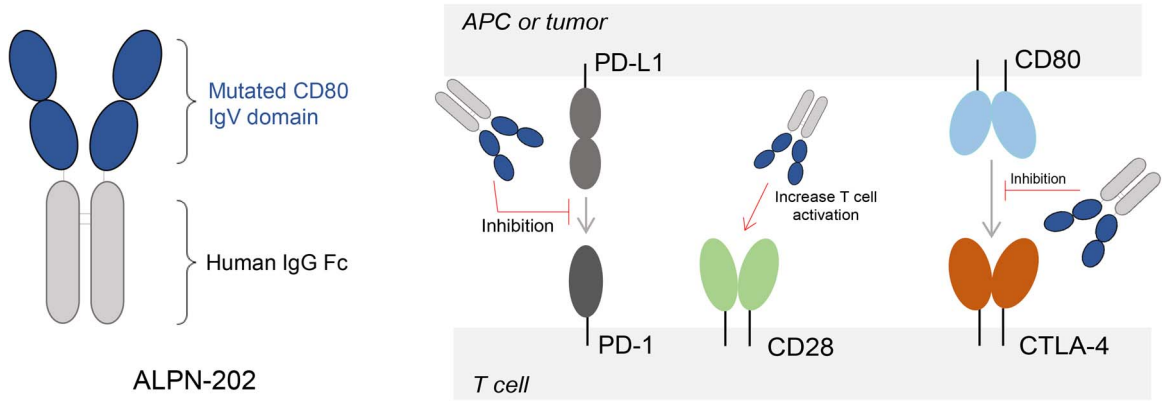

Figure 6. The structure and mechanism of action of ALPN-202.

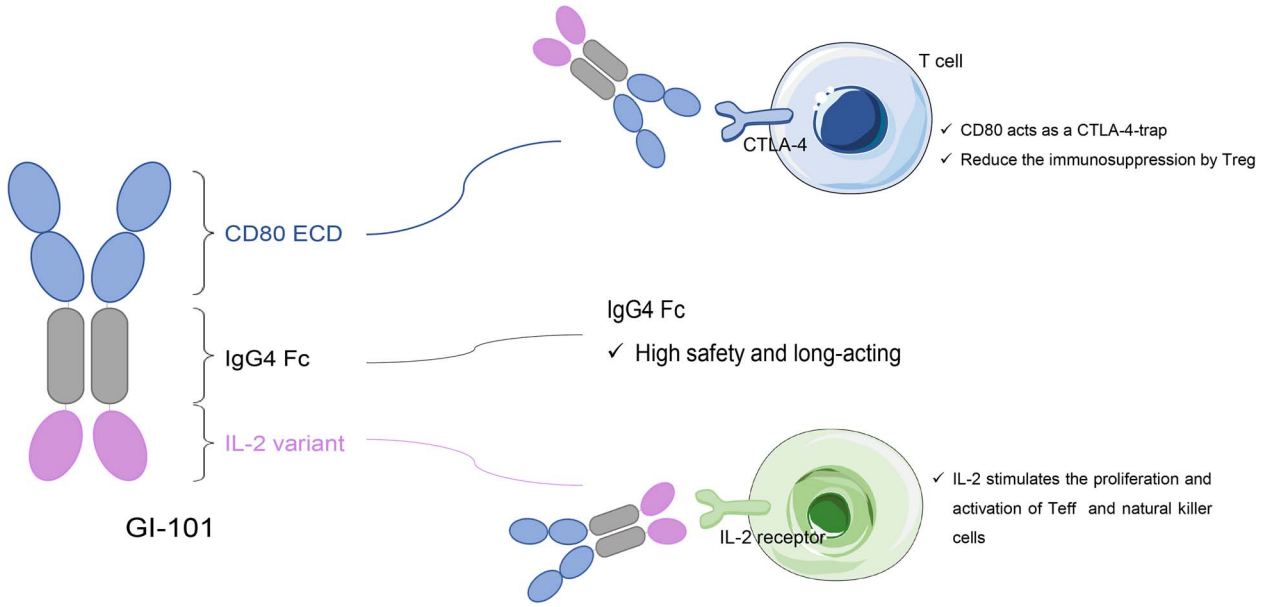

Figure 7. The structure and mechanism of action of GI-101.

and promotes T-cell proliferation, differentiation and function. On the other hand, IL-2 in the GI-101 can effectively stimulate the proliferation and activation of a variety of immune cells, including T cells, B cells and natural killer cells and then synergically activate the immune response *in vivo* [56]. Therefore, GI-101 is expected to effectively activate the anti-tumor immune response while relieving immunosuppression by binding CD80 and IL-2.

Currently, this bifunctional fusion protein has entered a clinical phase I/II for the treatment of advanced solid tumors as monotherapy or in combination with other drugs (NCT04977453), which aims to evaluate its safety, tolerability and anti-tumor effect.

CHALLENGES OF CD80-FC FUSION PROTEIN IN CANCER IMMUNOTHERAPY

CD80 has been shown to be abnormally expressed in a variety of tumor types and to positively and negatively regulate tumor immune responses through costimulatory and coinhibitory signals. The previous study indicated that soluble CD80-Fc fusion protein could promote T-cell activation by activating CD28/CD80 costimulatory signal and blocking PD-L1 and CTLA-4 coinhibitory signals [16]. It has stronger anti-tumor activity *in vivo* than PD-L1 antibody. In the study of CD28/CD80 costimulatory signal, the CD28 agonist antibody TGN1412 in the clinical phase I caused severe CRS within hours in all volunteers due to its TCR-independent super-agonist effect [50]. In contrast, although CD80-Fc fusion protein activates the CD28/CD80 costimulatory signal, its activation of T cells is dependent on the TCR signal. In the study of FPT155, researchers found that even at high concentrations, FPT155 did not induce spontaneous release of CRS-related cytokines. When anti-CD3 antibody was added, it could induce the production and release of cytokines. This demonstrates that CD80-Fc fusion protein is not CD28 super-agonist and has good safety.

However, CD80-Fc fusion proteins currently have no relevant drugs on the market, and their development still presents some problems and challenges. In our previous study, we found that the anti-tumor activity of CD80-Fc fusion protein mainly depended on the activation of peripheral naive T cells and their following infiltration in

tumor tissues, and that insufficient tumor immune infiltration limited its anti-tumor effect. As a major component of the tumor microenvironment (TME), immune infiltration has been shown to be associated with tumor progression and immunotherapeutic effects [57]. Therefore, how to enhance immune infiltration in the TME to further expand the efficacy of CD80-Fc fusion protein is a key problem to be addressed. Our previous study investigated the expression and role of discoidin domain receptor 1 (DDR1) in gastric cancer by bioinformatics analysis, and found that DDR1 was highly expressed in gastric cancer and closely associated with poor patient prognosis [58]. Meanwhile, the expression level of DDR1 was negatively correlated with the infiltration of most immune cells, such as $CD8^+$ T cells, macrophages and DCs [58]. Thus, we hypothesized that inhibition of DDR1 has the potential to further enhance the anti-tumor activity of CD80-Fc fusion protein. In addition, some current strategies to turn cold tumor to hot tumor have potential for improving the efficacy of CD80-Fc fusion protein, such as cytokines (IL-2 [59], IL-15 [60], TGF-β trap [61], VEGF inhibition [62], PDGF inhibition [63]), neoepitope cancer vaccine [64], therapeutic desialylation [65] and Toll-like receptors (TLR7 agonist [66]). In conclusion, insufficient immune infiltration is an important problem limiting the anti-tumor effect of CD80-Fc fusion protein, and new strategies to promote tumor immune infiltration are needed to further enhance the efficacy of CD80-Fc fusion protein.

SUMMARY

As an important costimulatory molecule, CD80 plays a positive coordinating role between T cells and APCs and promotes the activation, proliferation and differentiation of T cells in order to enhance the ability of the immune system to fight against pathogens [24]. Recent studies have shown that CD80 not only plays an important role in the immune response, but also participates in tumorigenesis and progression. Therefore, CD80 has begun to receive more and more attention in the field of cancer immunotherapy. Several studies have attempted to modulate the immune response in tumors by altering the expression or functional status of CD80. For example, some studies have found that increased CD80 expression enhances T-cell activation and immune response in PD-1/PD-L1 inhibitor therapy, while the efficacy of inhibitors is significantly reduced using CD80 blocking antibodies [14].

The activation and persistence of tumor immune responses involves the co-regulation of multiple signals, and it is difficult to rely on only one or two inhibitory pathways to achieve a durable anti-tumor effect. Although PD-1/PD-L1 antibodies are approved for the treatment of many solid tumors, only a small percentage of cancer patients can benefit from them. In contrast, CD80-Fc fusion protein has emerged as a promising strategy to improve the efficacy of immunotherapy due to its unique advantage of activating the CD28 costimulatory signal while blocking the CTLA-4 and PD-L1 inhibitory signals. Meanwhile, the activation of CD80-Fc fusion protein does not cause cytokine storm and has good safety. Overall, CD80-Fc fusion proteins have the potential to be an effective strategy for cancer immunotherapy. Future studies will further explore the possibility of their combination with other therapeutic agents to improve the therapeutic effect.

Key Points

This review focuses on the important role of CD80-Fc fusion protein in activating anti-tumor immunity. It has the potential to exert stronger efficacy than immune checkpoint inhibitors for multi-target activation of T cells. It is promising to be a new strategy for tumor immunotherapy to benefit more patients.

CRediT for author contributions

Songna Wang (Investigation-Lead, Writing—original draft-Lead, Writing—review & editing-Equal), Pinliang Hu (Investigation-Equal, Writing—review & editing-Equal), Jiajun Fan (Writing—original draft-Equal, Writing—review & editing-Equal), Jing Zou (Conceptualization-Equal, Investigation-Equal), Weidong Hong (Investigation-Equal, Writing—review & editing-Equal), Xuan Huang (Investigation-Equal, Writing—review & editing-Equal), Danjie Pan (Conceptualization-Equal, Investigation-Equal), Huaning Chen (Writing—original draft-Equal), Yi Zhun Zhu (Conceptualization-Equal, Writing—review & editing-Equal), Li Ye (Conceptualization-Equal, Writing—review & editing-Equal),

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Conflict of interest statement

Pinliang Hu, Jing Zou and Weidong Hong are employees of Beijing Beyond Biotechnology.

Data availability

All data generated or analyzed during this study are included in the article.

Ethics and Consent Statement

Not applicable.

Animal Research Statement

Not applicable.

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