

# OX40 (CD134) and OX40 ligand, important immune checkpoints in cancer

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**Abstract:** Immunotherapy has shown promising results in cancer treatment. Research shows that most patients might be resistant to these therapies. So, new immune therapies are needed. OX40 (CD134) and OX40 ligand (OX40L), costimulatory molecules, express on different types of immune cells. The interaction between OX40 and OX40L (OX40/OX40L) induces the expansion and proliferation of T cells and decreases the immunosuppression of regulatory T (Treg) cells to enhance the immune response to the specific antigen. For the important role OX40 takes in the process of immunity, many clinical trials are focusing on OX40 to find out whether it may have active effects in clinical cancer treatment. The results of clinical trials are still not enough. So, we reviewed the OX40 and its ligand (OX40L) function in cancer, clinical trials with OX40/OX40L and the correlation between OX40/OX40L and other immune checkpoints to add more ideas to tumor feasible treatment.

**Keywords:** cancer, immune checkpoints, OX40/OX40L, immunotherapy

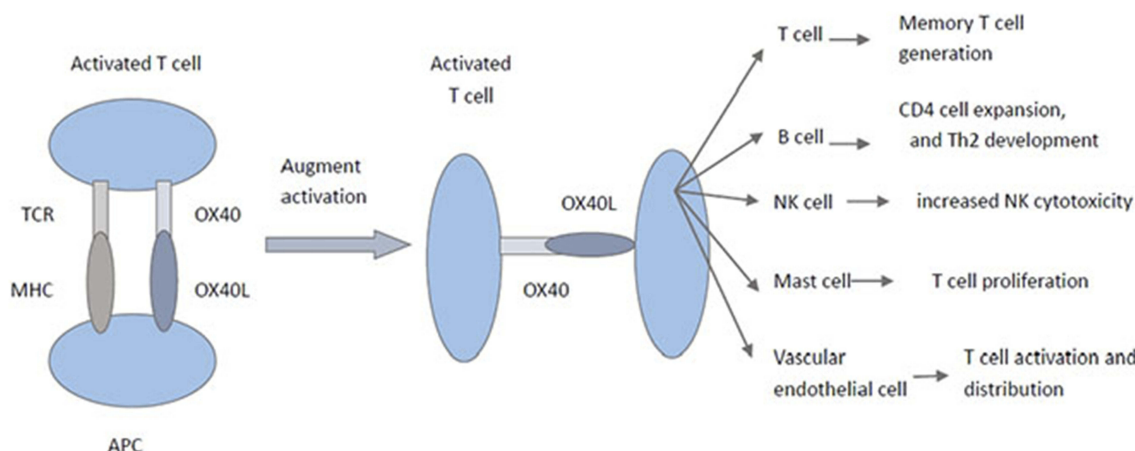
Immunotherapy has shown promising results in cancer treatment,<sup>1</sup> cancer immune checkpoint blockades also have got good results.<sup>2-5</sup> It was demonstrated that combining cancer vaccines or checkpoint inhibitors with different immunotherapeutic agents could augment the anti-tumor effects and get better results in cancer patients.<sup>6,7</sup>

Tumor necrosis factor receptor superfamily member 4 (OX40) (CD134) and OX40 ligand (OX40L) (CD134L) (CD252) are on chromosome 1. The OX40 and OX40L could be expressed by endothelial cells, mast cells, activated natural killer (NK) cells, dendritic cells (DCs), B cells, microglial cells, activated T cells and Foxp3<sup>+</sup> regulatory T cells.<sup>8-10</sup> OX40L could initiate OX40 signals in activated T cells. OX40L on T cells could provide signals via the interactions between T cells and upregulate the anti-apoptotic protein on T cells to enhance T cell survival, cytokine production and induce the CD4 memory T cell expansion.<sup>11-16</sup> The co-stimulation in B cells through the OX40/OX40L pathway contributed to CD4 cell generation, survival and T helper 2 (Th2) development.<sup>17</sup> OX40/OX40L could promote NK cell activation, cytokine production and cytotoxicity and enhance targeted cells lysis.<sup>18,19</sup> Mast cell via the OX40/OX40L pathway could induce T cell proliferation.<sup>20,21</sup> OX40 on Treg cells played an important role in Treg cell development and homeostasis.<sup>22,23</sup> We made a figure to clarify the function of OX40-OX40L pathway (Figure 1).

## OX40/OX40L and diseases

Many diseases were associated with OX40/OX40L, so many researchers focused on it to find new way of treatment. The activation of OX40 promoted the generation

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**Figure 1** OX40–OX40L interaction model.

**Abbreviations:** Th2, T helper 2; NK, natural killer; TCR, T cell receptor; MHC, major histocompatibility complex; APC, antigen presenting cell.

and expansion of activated T cells and memory T cells, thus aggravating autoimmune diseases like Graves' disease, autoimmune arthritis and uveitis.<sup>24–27</sup> OX40 was critically important in sustaining the anti-viral immune response during the viral infection.<sup>19,28–30</sup> OX40–OX40L signaling increased the adaptive immune response to an allograft by promoting effector and memory T cell survival. And blockade of OX40–OX40L interaction could decrease the T cells infiltration in the targeted organs to prevent allograft rejection.<sup>31–34</sup> OX40L could promote the inflammatory cells infiltration into lesional tissues, leading to the pathological fibrosis in skin and internal organs. And blocking OX40–OX40L regressed the fibrosis.<sup>35,36</sup> OX40–OX40L interaction on immune cells might contribute to idiopathic inflammatory myopathies through different pathways in the inflamed muscle.<sup>37</sup> OX40/OX40L pathway was involved in the pathological process of Crohn's disease (CD). And blockade anti-OX40 might be beneficial for the treatment by controlling the T cell-mediated inflammatory *in vivo*.<sup>38,39</sup> Data implicated that OX40/OX40L participated in pathophysiology of acute myeloid leukemia and also enhanced NK cell cytotoxicity.<sup>18</sup>

## OX40/OX40L and cancer

OX40 was expressed on the tumor-infiltrating lymphocytes (TIL) in head and neck squamous cell carcinoma, ovarian cancer, gastric cancer, cutaneous squamous cell carcinoma, breast cancer and colorectal cancer.<sup>40–45</sup> Agonistic anti-OX40 antibodies had anti-tumor effects.<sup>46–52</sup> OX40 triggering regressed Treg cells, allowing DCs to reach the draining lymph nodes and prime the specific CD8 lymphocytes

response to the tumor.<sup>48,53</sup> Many research focused on the anti-tumor immunotherapy, based on activating costimulatory molecules OX40 and OX40L. Here, we showed some of them (Table 1).

## Clinical trials of OX40/OX40L

Based on the role of OX40 and OX40L in the immune system, more and more research focused on its therapeutic effects. Many companies detected the immune checkpoints OX40 and OX40L, searching for the new approaches to treat tumors and autoimmune diseases, many of which are now making great advance in clinical development (Table 2). The results of clinical trials showed the OX40, as a potent immune-stimulating target, played an important role in anti-tumor therapy. The agonist anti-OX40 increased CD4 FoxP3<sup>+</sup> and CD8 T cells proliferation and the response to the tumor-specific antigen, enhancing both humoral and cellular immunity in cancer treatment.<sup>49</sup>

## Correlation of OX40/OX40L and other immune checkpoints

The results of studies suggested that some diseases were not sensitive to antibody therapy alone. So, it was necessary to study on the relationship between checkpoints to work out more effective treatment. CTLA-4, a molecule on T cells, inhibited the proliferation of T cells and cytokine production, thus limiting the lymphocyte immune reaction.<sup>68–72</sup> Anti-CTLA-4 blockade induced the depletion of Treg cells within tumor and activation of Teff cells.<sup>71,73–76</sup> Combining agonist anti-OX40 and antagonist anti-CTLA-4 further enhanced CD4 and CD8

**Table I** OX40/OX40L and cancer

Disease	Finding	References
Cancer	Anti-OX40L delayed the tumor progression and even eradicated tumors.	54
Breast cancer	Activation of OX40 receptor+ CD4+ T cells could stimulate the anti-tumor immune response in mammary cancer.	55
Colon cancer	High levels of OX40 positive lymphocytes were correlated with better survival in colon cancers.	56
Cancer	OX40L fusion protein could inhibit the tumor by direct intra-tumor injection.	9
Cancer	OX40L-transduced tumor cells could elicit tumor-specific Th1 immune responses, generate anti-tumor immunity and inhibit the tumor growth in vivo.	57
Cancer	OX40 agnostic therapy contributed to anti-tumor CD8 effector T (Teff) cells priming and enhanced CD8 T cell response to the antigen tumor derived.	58–60
Cancer	Intra peritoneal injection of OX40L-immunoglobulin fusion protein could inhibit tumor growth.	61
Cancer	OX40L on DCs could induce anti-tumor immunity via binding OX40 on CD4+ T cells and NK T cells.	62
Advanced cancer	Agonistic anti-OX40 increased circulating T cells, B cells and intratumoral Tregs, enhancing tumor-specific immune responses.	49
Cancer	Agonist anti-OX40 therapy combined with cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) blockade augmented antigen-specific CD8 T cells and limited the Th2 cells polarization, eliciting potent anti-tumor immunity.	63,64
Cancer	OX40 agonistic and IDO (indoleamine-(2,3)-dioxygenase) inhibitor produced a synergistic effect on the tumor immune response.	65
Glioma	Agonist anti-OX40 immunotherapy was active against intracranial glioma.	66
Metastatic ovarian cancer	Combining anti-OX40 and anti-CD73 immunostimulants increased cytotoxic T cell infiltration and decreased tumor promoting immune cells.	67

**Abbreviations:** NK, natural killer; DCs, dendritic cells; Th2, T helper 2.

T cells responses to antigen, indicating they had synergistic effects in improving tumor regression.<sup>77–79</sup> And the cytokine of Th1 and Th2 CD4 T cells increased significantly.<sup>64</sup> Whether the combination therapy altered the suppressive function of Treg cells remained deeper exploration.<sup>63,64</sup> The combination was still more than the sum of its part.<sup>80</sup>

Programmed death-1 (PD-1) is a molecule that suppresses the immune reaction, inducing T cell exhaustion and apoptosis. Programmed death-ligand 1 (PD-L1), expressed on tumor cells or other tumor-related immune cells, could suppress anti-tumor immune response.<sup>81–84</sup> The function of PD-1 and PD-L1 was affected by the complex immunoregulation. PD-1 blockade had already been used in cancer treatment and got a satisfying result.<sup>82,84</sup> It was reported that PD-1 inhibitor added at the initiation of the cancer treatment could reduce the effects of OX40 agonist antibody, for it might cause the antigen-specific CD8+ T cell diminishment.<sup>85</sup> And timing of PD-1 blockade using might determine whether it was effective immunotherapy when combined with OX40 therapy.<sup>81</sup> In most cases, OX40 agonist and PD-1 blockade had a synergistic effect in disease treatment. OX40,

combined with CD27 mediated co-stimulation, could synergize with PD-L1 inhibitor by activating CD8+ T cells.<sup>86</sup> Combining OX40 stimulation and PD-L1 blockade could synergistically augment hepatitis B virus (HBV)-specific CD4 T cell responses by promoting Th cells to secrete IFN- $\gamma$  and IL-21 in patients with HBV infection.<sup>87</sup> In some poorly immunogenic tumors, combining PD-1 blockade and OX40 stimulation had an anti-tumor effect by inducing cytotoxic T lymphocyte, increasing the Teff cells and decreasing the immunosuppressive cells, while individual did not.<sup>41</sup>

4-1BB (CD137), member of the TNFR family enhanced T cell proliferation, effector function and cytokines production, and induced maturation of DC, thus increasing the immune reaction.<sup>88–93</sup> Agonistic anti-4-1BB increased the TIL within tumor and upregulated the expression of 4-1BB on the immune cells, augmenting anti-tumor reaction.<sup>90,94,95</sup> The costimulatory pathway of OX40–OX40L and 4-1BB–4-1BBL functioned independently to enhance immune cells response.<sup>88</sup> The combination of OX40 agonist and 4-1BB agonist induced profound expansion of CD8 T cell.<sup>96,97</sup> But the response of CD4 T cell to the dual costimulation seemed to be additive instead of synergistic.<sup>98</sup> On the whole, the combination therapy

Table 2 Clinical trials with anti-OX40

Year	Drug	Phase	Company	Type	Objective	Clinical trial.gov identifier
2012	OX40 mAb	I	Providence Health & Services	Anti-OX40	OX40 in patients with advanced cancer	NCT01644968
2014	Anti-OX40	II	Ludwig Institute for Cancer Research	Anti-OX40	Combining a mouse monoclonal anti-OX40 and Ipilimumab in metastatic melanoma patients	NCT01689870
2014	MED16469	I	Providence Health & Services	Anti-OX40	MED16469 applied pre-surgical resection patients with oral, head and neck squamous-cell carcinoma	NCT02274155
2014	PF-04518600	I	Pfizer	OX40 Agonist	PF-04518600 and PF-05082566 in selected partially advanced or metastatic cancers	NCT02315066
2015	MOXR0916	I	Genentech, Inc.	Anti-OX40	MOXR0916 and atezolizumab (anti-PD-L1) in locally advanced or metastatic tumors	NCT02410512
2015	MED16469	I	Providence Health & Services	Anti-OX40	MED16469 in patients with metastatic colorectal cancer	NCT02559024
2017	PF-04518600	II	University of Southern California	Anti-OX40	PF-04518600 in combination with axitinib versus axitinib in metastatic renal cell carcinoma and exposed to immune checkpoint inhibitor	NCT03092856
2017	MED10562	I	Providence Health & Services	Anti-OX40	MED10562 administered pre-surgical resection in melanoma or squamous cell carcinoma	NCT03336606
2018	BMS 986178	I	Ronald Levy	Anti-OX40	Intratumoral injection of SD-101 and BMS-986178 combined with local radiation in patients with low-grade B cell lymphomas	NCT03410901

could synergistically inhibit cancer by producing more enhanced signals.<sup>98,99</sup>

## Summary

Immune checkpoints play vital roles in cancer treatment. It was proved that the agonist anti-OX40/OX40L could enhance anti-tumor response by promoting the function of immune cells. More and more researchers focused on OX40/OX40L in cancer immunotherapy. But until now, the effects of OX40/OX40L treatment are still limited. Researchers are devoted to combine OX40/OX40L with other immune checkpoints in cancer treatment, which had also made some achievements, but the mechanisms of the synergy between OX40/OX40L and other immune checkpoints still need to be further studied.

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## Disclosure

The authors report no conflicts of interest in this work.

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