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Review

Rationale for anti-OX40 cancer immunotherapy

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Abstract Immune checkpoint blockade with antagonistic monoclonal antibodies (mAbs) targeting B7 immunoglobulin superfamily molecules (CTLA-4, PD-1, and PD-L1) generate long lasting anti-tumour immune responses translating into clinical benefit across many cancer types. However, many patients are primarily resistant to immune checkpoint blockade –based monotherapy and many others will eventually relapse. Therefore, new immunostimulatory targets are needed to overcome primary and secondary resistance to immunotherapy. Besides the B7 co-inhibitory receptors, the tumour necrosis factor receptor superfamily contains many other immune checkpoints, which could become the next generation immunomodulators. Among them stands OX40 (CD134), a co-stimulatory molecule that can be expressed by activated immune cells. Several anti-OX40 agonistic monoclonal antibodies are currently tested in early phase cancer clinical trials. Accumulating preclinical evidence supports their clinical development. However, conflicting results and controversies between *in vitro* and *in vivo* data point to the need for comprehensive ancillary studies to be performed in upcoming clinical trials to better understand the mechanism of action of anti-OX40 mAbs-based therapy.

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1. Introduction

Long term protective anti-tumour responses obtained upon immune checkpoint blockade therapy with anti-CTLA4 and anti-PD1/PD-L1 monoclonal antibodies (mAbs) have demonstrated the importance of the immune system in the fight against cancer [1]. Moreover, the anti-CTLA4 and anti-PD1 mAbs combination therapy developed in metastatic melanoma further demonstrated that primary resistance to these drugs is lower when they are used in combination [2–4]. Indeed, multiple pathways can be involved to prevent the immune destruction of tumour cells, which are considered as a recognition of 'self' by the immune system, leading to peripheral tolerance. Therefore, new immunomodulatory mAbs are now needed in the clinic to overcome primary and secondary resistance to the first generation immune checkpoint blockers. The costimulatory molecule OX40 (CD134) belongs to the next generation of immune therapeutic target currently tested in early phase clinical trials in oncology. Here we will review the rationale, which has supported the development of drugs targeting OX40 and discuss our current understanding of their mechanism of action.

2. Molecular and cellular biology of OX40

Adaptive immunity relies on the specific recognition of antigens (mostly peptides) presented by major histocompatibility (MHC) molecules expressed at the surface of antigen presenting cells (APCs) to the T-cell receptor (TCR). This is the first step required for T-cell activation. However, for a full blown T-cell triggering, the first MHC/TCR signal requires the involvement of co-stimulatory molecules of the B7 family (that can be further dampened by signalling through co-inhibitory receptors expressed on T-cells (such as CTLA4 or PD1)). OX40 is a member of the tumour necrosis factor receptor superfamily (TNFRSF), subserving co-stimulatory functions. It is a 50 kD glycoprotein that has a cytoplasmic tail, a transmembrane domain and an extracellular region (Fig. 1). It has only one known ligand called OX40L (CD252), which is classically expressed on activated APCs. Upon OX40 costimulation of T-cells, intra-cytoplasmic pathways associated to T-cell signalling are activated such as nuclear factor (NF)-kappaB and Nuclear factor of activated T-cells (NFAT) which can enhance the expression of molecules such as survivin, cyclin A, cyclin-dependent kinases, Bcl-2 anti-apoptotic molecules, cytokines, and cytokine receptors (reviewed in [5]).

3. Impact of OX40 signalling on immune cells

The expression of OX40 on the surface of mouse T-cells typically occurs between 24 h and 96 h after cognate antigen recognition. Engagement of the OX40 receptor on T-cells (*in vitro*), using anti-OX40 agonistic antibodies, directly promotes an increase in survival of different effector T-cell subsets, [6–10].

Moreover, the immunosuppressive subset of CD4+ T-cells called regulatory T-cells (Tregs) also express high levels of OX40. Of note, murine Tregs seem to constitutively express OX40 whereas human Tregs would upregulate OX40 upon activation [11,12]. Apart from technical aspects (such as intracytoplasmic versus membrane expression), basal expression might represent a relevant parameter to consider when translating preclinical studies into human clinical trials.

Tregs can inhibit effector T-cells through the secretion of immunosuppressive cytokines such as transforming growth factor-beta (TGFβ) and interleukin-10

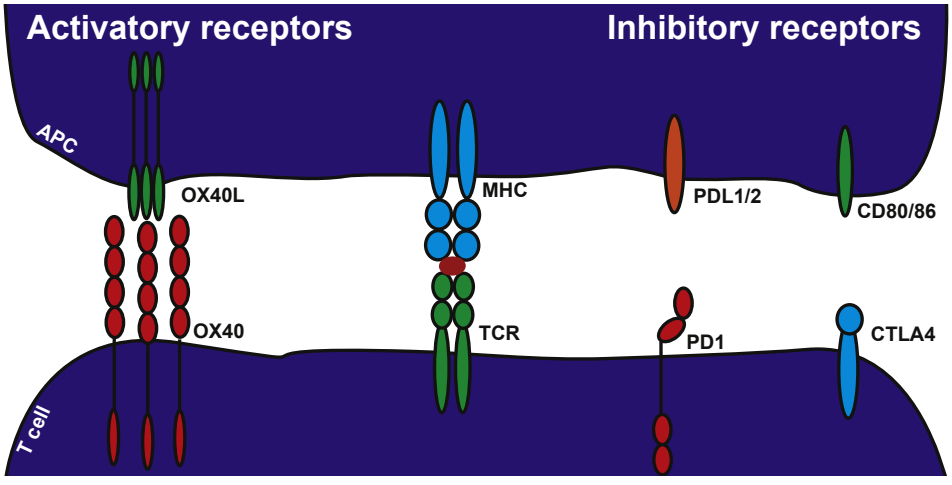

Fig. 1. Structure of OX40 compared to CTLA4 and PD-1. OX40 is expressed at the cell surface of a T-cell. OX40L is present at the cell surface of an antigen presenting cell. Three OX40 molecules bind to one OX40L molecule. CTLA4 and PD1 are inhibitory members of the B7 family and are mainly expressed by T-cells. They respectively bind to CD80/86 and to PDL1/PDL2 which are in general present on antigen presenting cells.