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# OGR1-a Novel Modulator Target of Tumor Immunotherapy

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## Commentary

Tumors mainly utilize glucose to promote aerobic glycolysis for their survival (Warburg effect). The highly glycolytic environment is not suitable for the survival and function of effector T cells, and leads to the decline of antitumor immunity. A recent study by Cao et al. published in *Cancer Gene Therapy* showed the importance of OGR1 in modulating acidic microenvironment and enhances the function of effector $CD8^+$ T cells. These researchers have found a new target to change the function of $CD8^+$T cell in acidic microenvironment of tumor, which may provide a new strategy for improving cancer immunotherapy.

## OGR1 Structure and Function in Human Diseases

Ovarian cancer G-protein-coupled receptor 1 (OGR1) is also called GPR68, an acid-sensitive receptor that responds to extracellular acidity and regulates important physiological functions, including tumor metastasis, immunity, inflammation, pH homeostasis [1-7]. OGR1 is widely expressed in a large number of cells and tissues, especially including immune cells, spleen, testis, brain, etc. [8,9]. The structure of many GPCRs usually includes one extracellular N-terminal motif, followed by seven transmembrane motifs α-Helix (I–VII), with three intracellular and three extracellular rings, and an intracellular C-terminal domain. However, so far, the crystal or low-temperature electron microscope structure of OGR1 has not been analyzed. OGR1 has been receiving increasing attention in recent years and represents a potential therapeutic target for drug design and development. Relevant many studies have also reported the different allosteric activation modes of OGR1, one through interaction with divalent metal ions at the extracellular surface [10], and another way, some benzodiazepines can activate OGR1, it mainly acts as allosteric regulator and extracellular acidic pH. However, lorazepam can also activate OGR1 at high extracellular pH 8.0 [11]. Yu et al. research teams have produced an improved OGR1 positive allosteric modulator through the study of structure-activity relationship, which is used to study the physiological and pathophysiological effects of OGR1 *in vitro* and *in vivo* [12]. Cheryl de Vallièrea et al. evaluated the effects of a novel OGR1 inhibitor in murine models of colitis [13]. Interestingly, OGR1 also plays the role of mechanical transmission of pressure signals, which can sense the blood flow shear stress in the artery and regulate vascular physiology [14]. The expression of OGR1 in hematopoietic cells is up-regulated with age, which leads to the increase of the number of B lymphocytes in the process of hematopoietic regeneration [15].

## The Role of OGR1 in Cancer

The physiological pH of blood and tissue is about pH 7.4, but in the tumor microenvironment the pH can range from 5.5 to 7.0 [16-18]. However, the complex tumor microenvironment is composed of many types of cells. In addition to malignant cells, the tumor microenvironment is composed of macrophages, cancer-related fibroblasts, endothelial cells and other immune cells. Many factors, including insufficient blood perfusion (and hypoxia), inflammation and glycolytic cell metabolism,

can lead to acidic tumor microenvironment [19,20]. OGR1 is expressed in different cell types in tumor microenvironment and plays an important role in tumorigenesis and progression. Pancreatic ductal adenocarcinoma cells induce the expression of OGR1 in cancer associated fibroblasts. OGR1 can sense the acidic microenvironment, increase the production of fibrosis markers and IL-6, and promote the proliferation of pancreatic ductal adenocarcinoma cells. OGR1 expressed by cancer associated fibroblasts is a mediator of low pH promoting tumor microenvironment, especially the interaction between pancreatic ductal adenocarcinoma cells and cancer associated fibroblasts. It provides a new target for the treatment of pancreatic cancer [5].

## The Effects of OGR1 on Immune Modulation

In a previous study, Yan et al. used through genetically engineered mice that the expression of OGR1 in bone marrow-derived $CD11b^+$ $Gr1^+$ double positive cells is necessary for prostate cancer tumor cells to induce immunosuppression [6]. Adoptive therapy using engineered human immune effector cells and checkpoint blocking therapy have completely changed the traditional way of tumor treatment [21,22]. Effective anti-tumor immune therapy in solid tumors relies on the presence of effector T cells [23,24]. However, direct *in vivo* evidence of the interaction of OGR1 with T cells in the acidic tumor microenvironment has not been reported. Recently, Cao et al. highlights the inhibition of OGR1 enhances infiltration of T lymphocytes into the tumor parenchyma and T cell antitumor immunity, which results in attenuated tumor growth [25]. Cao et al. utilize a tumor-transplant model of the mouse melanoma cell line B16-F10 to show that tumor growth is significantly delayed in $OGR1^{-/-}$ mice relative to WT mice. However, the inhibition of OGR1 in B16-F10 cells did not affect the growth of tumor. These findings suggest that OGR1 plays a role in regulating tumor growth, and the contribution of OGR1 activity *in vivo* comes from host cells rather than tumor cells themselves. OGR1 functions in anti-tumor immunity through the following mechanisms: OGR1 inhibition (1) triggers a strong immune response signaling and (2) results in a significant increase in the number of T-cell infiltration. Therefore, infiltration of T cells is a prognostic hallmark for positive clinical outcomes and indispensable for a desired therapeutic effect of immune checkpoint inhibitors. Next, the researchers focused on the effect of OGR1 on T cells. OGR1 inhibition reactivates T cells and enhances $CD8^+$ T-cell effector functions at acidic pH. As a molecule that inhibits the function of T cells, OGR1 help to modulate the T cell activity, such as up regulation of type I interferon. Type I IFN-mediated immune activation is one of the essential parts in the regulation of T cell-infiltration to guide tumor from 'cold' to 'hot'. OGR1 determines whether it may be a drug target, and adoptive transfer with the $Ogr1^{-/-}$ T cell impeded tumor growth in $rag2^{-/-}$ tumor bearing mice, the results showed that OGR1 knockout in T cells significantly promoted its anti-tumor effect. Overall, the effects of OGR1 on the tumor acidic microenvironment remain to be clarified and could certainly have implications for the development of synergistic combinations in antitumor immunity therapy.

## Future Directions

Drug resistance to immune checkpoint inhibitors hinders their clinical success. Therefore, it has become a driving force to find new targets to restore the function of tumor specific T cells. The GPR171 pathway suppresses T cell activation and blockade of GPR171 signaling by an antagonist promotes antitumor T cell immunity and improves immune checkpoint blockade therapies [26]. OGR1 plays an important role in sensing the functional characteristics of effector T cells in tumor acidic microenvironment. Therefore, the sensing and inhibitory functions of Ogr1 on T-cell immunity prompted us to look at the anti-tumor effect in $Ogr1^{-/-}$ mice combined with PD1 inhibitor. Unpublished data shows that the combination of PD-1 inhibitors in $OGR1^{-/-}$ mice showed stronger antitumor effects than PD-1 inhibitors alone. Targeting Ogr1: a promising adjuvant strategy in cancer immunotherapy. OGR1 inhibitor strategy still needs to overcome its potential toxicity in order to become the target of cancer treatment in the future. Future studies will design specific inhibitors for OGR1, and the combination of PD1 inhibitors will be better transformed into clinical practice.

## Statements

The author has no conflict of interest to disclose.

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