Review Article

OX40L-OX40 Interactions: A Possible Target for Gastrointestinal Autoimmune Diseases

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Abstract

Gastrointestinal (GI) autoimmune diseases have a high incidence in developed countries, such as Canada and the US. Some common GI autoimmune diseases include ulcerative colitis and Crohn’s Disease. These conditions are not only unpleasant for the patient, but also present a heavy burden on the healthcare system. OX40L, a member of the tumor necrosis family, has been identified as a key player in the pathological inflammatory response, which characterizes GI autoimmune diseases. OX40L is expressed in many cell types, including antigen presenting cells (APCs), T-cells, vascular endothelial cells, mast cells, and natural killer cells. The importance of OX40L-OX40 interactions in inflammatory autoimmune diseases is becoming more evident through different animal models, ranging from nematode models to mouse models. This literature review attempts to summarize the current literature regarding the role of OX40L-OX40 interactions in GI autoimmune inflammatory diseases and comment on its potential for treatment. Various databases, including OVID MedLine and PubMed were used to retrieve articles regarding the role of OX40L-OX40 interactions in the pathogenesis of autoimmune diseases. These articles were then reviewed and summarized in a comprehensive manner. OX40L-OX40 interactions have a strong potential for becoming a treatment target; however, there are still many gaps in the present knowledge, which need to be addressed before more definitive treatments can emerge. It is also suggested that upstream events leading to OX40L activation, such as thymic stromal lymphopoietin (TSLP)-activated dendritic cells, be explored as treatment targets as well. OX40L-OX40 interaction is a possible venue for treatment of GI diseases; however, the underlying mechanisms of actions and the downstream effects of OX40L knock down need to be investigated.

Keywords: Gastrointestinal autoimmune diseases, IBD animal model, OX40L, Thymic stromal lymphopoietin, Treatment

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Introduction

Gastrointestinal (GI) autoimmune diseases are characterized by the uninhibited immune response in the GI tract. These diseases are characterized by an increased number of mononuclear cells in the intestinal epithelium, which can lead to destruction of intestinal crypts.[1] Some common GI autoimmune diseases are Crohn’s disease and ulcerative colitis, commonly known as inflammatory bowel disease (IBD). IBD describes the inflammation and ulceration of the small and large intestines.[2] Recently published data show that the incidence of IBD is the highest in Canada, and direct costs alone in the healthcare system amount to $1.8 billion.[3] As such, it becomes even more important to find a treatment for the disease. However, the etiology of this inflammatory disease is still not clear—researchers have yet to answer what prompts the imbalance between tolerance and immune response leading to IBD.[2,4] Lately, OX40-OX40L interactions have come to light as potential treatment targets.

OX40L is part of the tumor necrosis family, expressed on antigen presenting cells (APCs) (dendritic cells, macrophages, and B-cells), vascular endothelial cells, mast cells, natural killer cells, and on some T-cells. Normal T-cells express OX40L after repetitive antigenic stimulation.[5] The interaction of OX40 and OX40L plays a crucial role in clonal expansion of antigen-specific T-cells.[6] OX40L is also important in determining the amount of memory T-cells remaining after the immune response.[5-7]
Roles of OX40-OX40L interactions in GI autoimmune diseases

OX40L-OX40 interaction has been implicated in various inflammatory autoimmune diseases through many different animal models. However, it is important to recognize that OX40L-OX40 interactions are important for normal immune response as well. Activation of OX40L produces anti-apoptotic proteins that aid in the survival and proliferation of T-memory cells. Co-stimulatory signals delivered through OX40 have been implicated in selectively promoting the differentiation of T-helper (Th)-2 cells, and help prolong antigen-specific proliferative response. OX40-deficient mice are shown to have impaired T-cell proliferation, even though the initial naïve T-cell response remains unimpaired. These mice have also exhibited lower levels of anti-apoptotic protein: Bcl-2 and Bcl-xL. This implies that OX40’s role is mainly in sustaining the immune response, and that OX40 indeed has a non-pathological role as well. However, in normal mice, OX40-positive cells are observed only in lymphoid tissues, including Peyer’s patches of the gut.

In pathological condition, as demonstrated by mice with hapten-induced colitis or interleukin (IL)-2 knockout mice with spontaneous colitis, OX40-positive cells are found in the lamina propria. When OX40 takes on a pathogenic role, it reactivates pre-existing self-reactive T-cells through constitutive activity. OX40 also starts to repress regulatory T-cells (T regs), which is responsible for toning down the immune response, contributing to the balance between tolerance and immunity. Experiments conducted have shown that when anergic self-reactive T-cells are introduced in a host along with OX40 agonist, the self-reactive T-cells are activated from their anergic state, resulting in autoimmunity. This statement is further supported by the administration of anti-OX40L monoclonal antibody, which reduced the clinical and histopathological disease. In vivo treatment with anti-OX40L antibodies decreased T-cell infiltration in the colon and suppressed the production of primary inflammatory cytokines: Interferon (IFN)-γ, IL-2, and tumor necrosis factor (TNF)-α in the lamina propria. Combining this treatment with anti-TNF-α antibodies further improved the therapeutic effect by further reducing IFN-γ, IL-2, and TNF-α production. In addition to animal models, many association studies have been done with IBD patients that have shown higher expression of OX40. This supports that OX40 indeed has a role in IBD.

Signal transduction pathway

OX40 signals are known to be transmitted through TNF receptor-associated factors (TRAFs). OX40 binds to TRAF2, TRAF3, and TRAF5. TRAF2 and TRAF5 activate the nuclear factor kappa-B (NF-κB) signalling pathway through IκB kinase pathway – though this has yet to be proven. This pathway is regulated by activation of TRAF3. Recent studies have shown that TRAF2 is critical to OX40 signalling pathway, as TRAF2-deficient mice did not have the same degree of effector and memory T-cell generation as the wild-type. The role of TRAF3 and TRAF5 is still unclear and needs to be investigated further.

OX40 also induces the expression of anti-apoptotic Bcl-2 family members: Bcl-2, Bcl-xL, and Bcl-1, which directly correlates with activity of NF-κB1 as well. This gives strong proof that NF-κB pathway as known to researchers now is involved in OX40 signalling pathway. Overall, the Bcl-2 family ensures that the CD4 T-cells do not undergo apoptosis after the immediate immune response, proven by studies showing that Bcl-2-deficient mice failed to maintain high levels of CD4 T-cells 4-8 days after activation.

OX40 signalling also maintains the active form of protein kinase B. Protein kinase B leads to the expression of survivin, which is a member of the inhibitor of apoptosis (IAP) family and regulates the division of T-cells. Expression of survivin leads to the downstream phosphorylation of PI-3 kinase (PI3K). PI3K connects this pathway to several cyclin-dependant kinases, such as cyclin A, which are involved in cell cycle progression. Through a pathway, which may be linked to PI3K, OX40 also increases the influx of Ca²⁺ in CD4 T-cells, leading to dephosphorylation and nuclear entry of transcription factors known as nuclear factor of activated T-cells (NFATs), which regulate the production of cell cytokines.

OX40 activation also downregulates cytotoxic T-lymphocyte antigen 4 (CTLA-4), Foxp3, and interleukin (IL)-4. The decreased levels of these molecules, which are inhibitory in nature, lead to a strong response from T-cells helping them survive and proliferate. It is believed that OX40 interaction also leads to elongation of mRNA half-life, thus allowing more cytokines to be expressed.

Treatment potential of OX40-OX40L axis

Considering the role that OX40 plays in the inflammatory immune response, it has the potential to treat some debilitating diseases. However, when using OX40 or OX40L as a possible treatment target, it is important to realize that at this point, researchers do not know what makes OX40 signalling ‘turn’ pathogenic? One answer, though not complete, is provided by TSLP, which is produced by mucosal epithelial cells or skin cells in response to allergens. TSLP leads to the maturation of
dendritic cells (DCs).[22, 23] However, unlike regular DCs, these TSLP-activated DCs express OX40L, which leads to the differentiation of naïve T-cells into inflammatory Th2 cells, and these do not produce IL-10, but produce TNF-α instead.[22,23] Papers indicate that both TSLP and OX40 can induce inflammatory diseases in recombination activating gene-2 (RAG-2)–deficient mice, indicating that the two molecules may share a common signalling pathway.[5,21] Since TSLP-activated DCs will produce inflammatory response, TSLP can be viewed as a target for treatment that will implicitly remove inflammatory OX40 signalling.

Potential roadblocks in using OX40L–OX40 axis

Considering the above, even though OX40 and OX40L may seem to be a tempting target for curing all kinds of inflammatory disease, it is important to remember that OX40 has a normal role in the human body as well. OX40-deficient mice did not show any severe side effects; however, there were defects in T-cell proliferation and cellular immunity.[10] These side effects cannot be risked when considering possible clinical applications of the OX40L–OX40 axis. Another question that arises is how OX40 or TSLP can be knocked down in humans. Gene therapy or neutralizing antibodies usually produce a strong immune reaction from the host. Furthermore, there are many things that are still unclear in the OX40L–OX40 signalling pathway. For example, the extent of involvement of NF-κB and PI3K, which are molecules important for many other cell functions as well. Tampering with their signalling cascade can lead to other unforeseen side effects. Another thing that is unclear is whether OX40’s inhibition or OX40L’s inhibition that will lead to desired results. A study found that using OX40L antibodies did not inhibit IBD, whereas using OX40 antibodies did.[6] Overall, changing OX40L–OX40 interactions may be tempting; however, the target of this change needs to be investigated.

Conclusion

Overall, OX40L–OX40 interaction is a potential target for autoimmune diseases. OX40 signalling is pro-inflammatory, priming Th2 to produce TNF-α. However, even though the side effects in the OX40 deficient mice are little, there is no guarantee that side effects will not be present in humans. Hence, changing OX40L–OX40 signalling may result in a myriad of side effects through the complicated cellular pathways, demanding that caution be taken before doing any clinical trials.

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