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The fruits of CD40 research in basic and clinical medicine will soon be harvested

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The CD40 ligand/CD40 pathway is widely recognized for its prominent role in immune regulation and homeostasis. CD40, a member of the tumor necrosis factor receptor family, is expressed by antigen-presenting cells, as well as non-immune cells and tumors. The engagement of the CD40 and CD40 ligands, which are transiently expressed on T cells and other non-immune cells under inflammatory conditions, regulates a wide spectrum of molecular and cellular processes, including the initiation and progression of cellular and humoral adaptive immunity. Based on recent research findings, the engagement of the CD40 with a deregulated amount of CD40 ligand has been implicated in a number of inflammatory diseases. We will discuss the involvement of the CD40 ligand/CD40 interaction in the pathophysiology of inflammatory diseases, including autoimmune diseases, atherothrombosis, cancer, and respiratory diseases.

Keywords: CD40, Immunity, B cells, Alveolar macrophages

It is a great honor to have an opportunity to write my article for the centenary issue of the Nagoya J Med Sci. I also appreciate everyone who nominated me, especially Prof Toyokuni, Editor-in-Chief. When I began my CD40 research in 1992 as a graduate student, my theme was to establish CD40-deficient mice. Since the CD40 knock-out mouse has many unique phenotypes, we published our first report in Immunity,[1] which has been cited around 1,000 times. When I was invited to write a review article in the Nagoya J Med Sci in 2011,[2] I wrote a manuscript based on the latest information, including the findings of our several published papers. I prospected the future of CD40 research at the end of that review, concluding that a blockade of the CD40L-CD40 interaction should provide promising and novel therapeutic methods.

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I supposed at least two intriguing issues for investigating CD40 function. One is to elucidate the mechanism for promoting somatic hypermutation of the immunoglobulin by CD40 signaling to enhance affinity for antigen. Based on the findings from the intensive research in this field, the in vitro system will be established for fine-tuning on antigen specificity of an antibody produced from hybridoma cell lines. Another is a clinical application to activate or inactivate the immune system by agonists or antagonists of the CD40L/CD40 pathway, respectively, under disease conditions such as transplantation, autoimmune disorders, and cancer. Unfortunately, there is still no clinically available therapy, although it has been 11 years since my review article was published. However, over 100 clinical trials were observed by searching with the word "CD40" on the clinical trial registration webpage (https://clinicaltrials.gov/) run by the United States National Library of Medicine. While all clinical trials using an anti-CD40L monoclonal antibody (mAb) in conditions ranging from transplantation to lupus nephritis and immune thrombocytopenic purpura were halted because of severe thromboembolic side effects,[3] therapeutic approach targeting CD40 rather than CD40L has been developed as a safer and promising alternative to allow an interruption of the CD40/CD40L interaction.

Ongoing clinical trials using an anti-CD40 mAb bleselumab have shown its acceptable efficacy and safety in preventing acute rejection in kidney transplantation.[3,4] Moreover, interruption of the CD40/CD40L interaction inhibits the proliferation and activation of B cells in autoimmune disorders. Subsequently, autoantibody production is down-regulated, achieving a therapeutic effect. Clinical trials using an anti-CD40 mAb and an anti-CD40L antibody lacking a functional Fc region, dapirolizumab, are ongoing. Dapirolizumab inhibits CD40L-dependent immune responses without thrombotic complications and improves the clinical response in patients with systemic lupus erythematosus.

While most cancer immunotherapy has focused on blockage of immune checkpoints, including the treatment with anti-CTLA4 and/or anti-PD1 mAbs, immune stimulation is considered an alternative approach that involves activation of anti-tumor immune pathways such as promotion of the T-cell priming against tumor antigens by an agonist of a stimulatory receptor on antigen-presenting cells, such as an anti-CD40 antibody. Immune potentiating of the CD40L/CD40 pathway using agonist anti-CD40 mAbs alone has demonstrated moderate clinical activity, providing opportunities to use in synergistic combination with other cancer therapy, such as vaccines, chemotherapy, and treatment with immune checkpoint inhibitors.[5] Due to the recently developed antibody-based technologies, bispecific antibodies, including anti-CD40 or anti-CD40L mAbs, offer new treatment potential for cancer therapy. Therefore, we will see novel therapies targeting the CD40L/CD40 pathway in the near future.

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