

Kinetic Analysis of Co-stimulatory and Co-inhibitory Molecules: A New Approach to the Treatment of Kawasaki Disease

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Kawasaki disease (KD) is a pediatric vasculitis characterized by fever, conjunctivitis, inflamed oral mucosae, redness and swelling of the hands and feet, nonspecific polymorphous erythema, and cervical lymph node swelling. In some cases, complex aneurysms of the coronary arteries develop. These symptoms are caused by systemic arteritis of small- to medium-sized blood vessels. KD is common in Japan, with an annual incidence of 218.6 per 100,000 children of 0–4 years of age in 2008. Recently, the prevalence of KD in children was estimated to be more than 1 in 150 in Japan. Although Kawasaki et al. first described this syndrome more than 40 years ago¹, its etiology remains unclear. *Streptococcus*, *Yersinia pseudotuberculosis*, Epstein-Barr virus, and *Mycoplasma* infections are associated with KD. In 2009, Nagata et al. reported 13 strains of gram-negative bacteria and 18 strains of gram-positive bacteria from the gut of patients with KD, which have superantigenic properties that may contribute to the development of KD by inducing production of heat shock protein (HSP) 60 and proinflammatory cytokines².

Japanese children have a KD rate 10 to 20 times greater than that of European and American children. The risk of KD is 10 times greater in children who have siblings with KD and 2 times greater if the parents have KD. Molecular genetic techniques have contributed greatly to clarifying the possible causes of KD. One novel risk gene is the inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene, which acts as a negative regulator of T-cell activation. A study of ITPKC single-nucleotide polymorphisms (SNPs) in a Japanese population revealed that the G→C allele was 1.89 times as frequent in patients with KD and 2.05 times as frequent in patients with coronary complications³.

In the 1970s, the percentage of patients with KD who had coronary aneurysms was approximately 40%. However, in patients receiving the standard treatment of 2 g/kg intravenous immunoglobulin (IVIG) and high-dose aspirin, the prevalence of coronary complications decreased to 3.7%, that of dilations decreased to 2.3%, and that of aneurysms decreased to 1%. Unfortunately, IVIG treatment is not effective in 15% of patients with KD. Furthermore, the percentage of patients with large aneurysms (0.35%) is not decreased by the standard treatment of IVIG plus aspirin. Current strategies for refractory cases include steroid pulse therapy, ulinastatin, cyclophosphamide, plasma exchange, and infliximab, which induce stronger suppression of an abnormal immune response than IVIG.

The immune system is divided into the innate and the acquired immune systems. Co-stimulatory and co-inhibitory molecules play important roles in the communication and coordination of these systems. T-cell receptors recognize antigen epitopes on major histocompatibility complex (MHC) class I molecules on the surfaces of antigen-presenting cells. Formation of these complexes, consisting of T-cell receptors, MHC class I molecules, and antigen epitopes induces an activation signal called “Signal 1” in T cells (**Fig. 1**). However, Signal 1 alone is insufficient for T-cell activation; in addition, complexes of co-stimulatory molecules and their T-cell receptors, such as CD28/CD80 and 4-1BB/4-1BBL, are also required for T-cell activation. On the other hand,

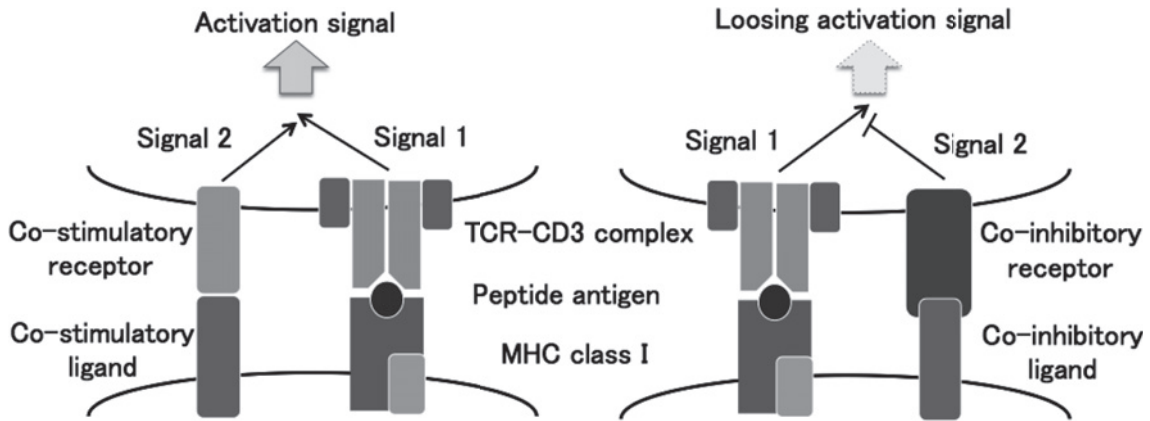


Fig. 1 T cell receives antigen information from the antigen-presenting cells through the complex of MHC class I, T-cell receptor, and CD3 (Signal 1). Co-stimulatory molecule complexes (Signal 2) are indispensable for T-cell activation. On the other hand, co-inhibitory molecules contribute to the suppression of T-cell activation via negative feedback.

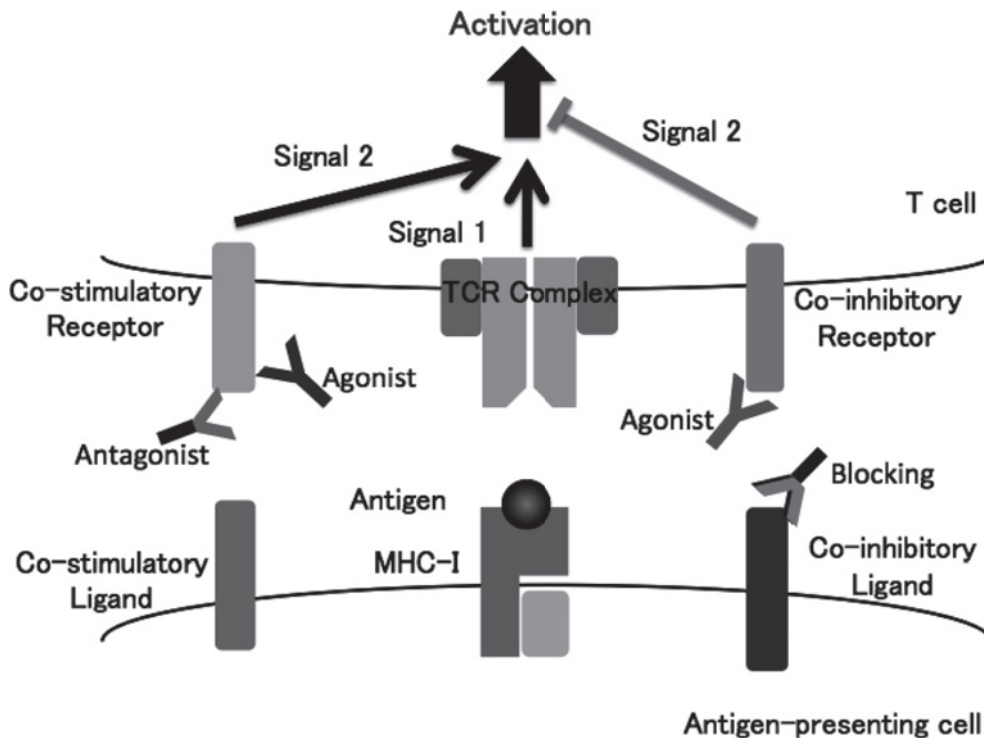


Fig. 2 The model of T-cell regulation by agonist and antagonist molecules. Agonists for the co-stimulatory receptors or antagonists for the co-inhibitory ligands contribute to T-cell activation. On the other hand, antagonists for the co-stimulatory receptors or agonists for the co-inhibitory ligands suppress T-cell activation.

complexes of co-inhibitory molecules and their specific T-cell receptors, such as PD-1/B7H1, provide negative feedback that suppresses Signal 1 and subsequent T-cell activation. These signals are referred to as Signal 2, and they modulate Signal 1 (Fig. 1). During the Immunotherapy Agent Workshop held at the US National Cancer Institute in 2007, 20 promising target molecules were selected for cancer immunotherapy from a list of 124 agents. Interestingly, 7 of these molecules, selected because they are believed to have substantial potential for cancer therapy, were co-stimulatory or co-inhibitory molecules. In addition, many other co-stimulatory and co-inhibitory molecules are the focus of basic *in vitro* and *in vivo* studies⁴ and clinical trials⁵.

In conclusion, co-stimulatory and co-inhibitory molecules are important therapeutic targets modulating the immune reactions in KD. We hypothesize that regulation of T-cell activation by agonistic or antagonistic antibodies, fusion proteins, or co-stimulatory and co-inhibitory molecules would help control KD and subsequently lead to a cure, without the risk of complications. However, few studies have examined the functions and kinetics of co-stimulatory and co-inhibitory molecules in patients with KD. In the near future, we plan to analyze the binding kinetics and T-cell activation potential of co-stimulatory and co-inhibitory molecules in patients with KD. Dysfunctional co-stimulatory or co-inhibitory molecules could be used as biomarkers to evaluate the severity of KD. In future, newly developed treatments (recombinant immunoglobulins or fusion proteins) based on co-stimulatory and co-inhibitory molecules may be used to prevent the formation of large aneurysms (**Fig. 2**). These more specific treatments (without IVIG) are expected to reduce opportunistic infections caused by general immunosuppressants in patients with KD and allow for normal vaccination schedules during childhood.

References

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