Precision Medicine for Kawasaki Disease

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ABSTRACT

Kawasaki disease (KD) is a multisystem inflammatory illness of infants and young children that could result in acute vasculitis. Death due to this systemic vasculitis syndrome most frequently results from thrombosed coronary artery aneurysms and coronary arteritis. Without treatment, 25% of children with KD develop coronary artery abnormalities. Current therapy for KD consists of intravenous immunoglobul within the first 10 days of fever onset; this treatment reduces the prevalence of coronary artery abnormalities to 5%. Advances in genetic and proteomic analysis have sparked a worldwide effort to identify genes and potential biomarkers associated with KD. In this review, we highlight important research advances that have been made in the epidemiology, etiology, genetic polymorphisms, diagnosis, and therapy of KD.

Keywords: Kawasaki disease, intravenous immunoglobulin, coronary artery abnormalities, vasculitis, genome-wide association study

1. INTRODUCTION

Kawasaki disease is an acute, systemic vasculitis syndrome. This disease affects primarily the medium-sized muscular arteries and most frequently occurs in infants and children under 5 years of age (1). The symptoms include prolonged fever that cannot be resolved by antibiotics, polymorphous skin rash, inflammation of the mouth, red eyes, and swollen hands and feet (2). Based on the epidemiological data (3-5), Kawasaki disease is most prevalent in Asian country, especially in Japan or in young children of Japanese ancestry. Specifically, the annual incidence of Kawasaki disease in Japan is 239 cases per 100,000 children under 5 years old (6, 7), which is approximately 14-fold higher than in the United States, where incidence is 17 cases per 100,000 children under 5 years old (8). Administrative data in the United States also point to a race-specific difference in KD incidence, with the highest incidence rates noted in Americans of Asian descent (9, 10). In addition, people of Korean descent have a high incidence of KD: 113 cases per 100,000 children under 5 years old (11), and the incidence in Taiwanese people is 69 KD cases per 100,000 children under age 5, which ranks third after the values in the Japanese and Koreans (3, 12). Coronary aneurysms, which develop in 15%–25% of untreated children, are major clinical problems in KD. Retrospective evidence also suggests that in KD, the coronary arteries function abnormally (13). However, the etiology of

KD and the formation of coronary aneurysms are poorly understood, although clinical and epidemiological features highly support that an infectious agent triggers the disease and that genetic predisposition may underlie its etiology.

2. ETIOLOGY

2.1 Superantigen Theory

Epidemiological features of KD suggest an infectious cause, including through well-defined epidemics with periodicity. However, to date, which pathogen is the major causative agent for Kawasaki disease is still unknown (14).

Although multiple suspected agents including many types of virus and bacteria have been proposed to be etiologically related to KD, but most findings were lack of a large scale subjects or independent cohorts for validation. One hypothesis holds that superantigens (SAgs) are the main cause of KD, based on the fact that SAgs are powerful T-lymphocyte activators (15, 16). An earlier report suggested a relationship between KD and the colonization of mucosal surfaces with toxic shock syndrome toxin-1-producing Staphylococcus aureus (17). In addition, reports of acute KD described selective expansion of T cells that expressed T-cell receptor (TCR) variable regions V 2 and/or V 8 (18-20) possibly suggesting the presence of a circulating SAg. Recent studies have gone on to suggest that the human leukocyte antigen (HLA) class II polymorphism may determine responses to bacterial SAgs (21-23), raising

the likelihood that HLA class II molecules play a critical role in T-lymphocyte activation by Sags via TCRs. Moreover, research has shown that certain SAgs are detected more frequently in patients with KD (15). However, the idea that the etiology of KD involves a SAg requires more strong evidence to validate this hypothesis.

2.2 Immune Responses

In the acute stage of KD, there is an increase in the levels of cytokines or chemokines; this implies that the activation of the innate immune response may be involved in the development of KD (24-26). Given the oligoclonal CD8 T-lymphocyte (27) and immunoglobulin (Ig) A and IgM B-lymphocyte (28, 29) responses that occur in KD, it is also possible that an antigen-driven adaptive immune response plays a role in the disease. Because an infiltration of oligoclonal IgA plasma cells have been found in vascular tissue obtained from patients with acute KD (30), KD could be hypothesized to be a immune-mediated disease. However, evidence of a primary autoimmune etiology has not been found for KD, and the low recurrence rate of the disease does not support its status as an autoimmune disease. Therefore, KD may be not originally develop only from the defect of immune system, and the precise role of the immune response in KD needs further investigation

2.3 Infectious Agents, Environmental Toxins, and Tropospheric Wind

Multiple infectious agents, such as bacteria, virus, and other micro-organisms, have been proposed as potential causes of KD. These agents can trigger immune responses through bacterial toxin mediated SAgs or allergens. Nevertheless, strong evidence is lacking that KD can be directly induced by a specific infectious agent. Despite this lack of evidence, most available epidemiological and immunological data implied that the causative KD incidence, namely California, Hawaii, and Japan, showed that a typical seasonal increase in KD cases correlated with the Asia–North Pacific wind pattern

From a practical point of view, these studies provided a potential way estimate KD activity even without knowing the causative pathogens. The ability to predict periods of increased disease activity in localized geographic regions may be helpful for doctors to identify KD patients. However, future investigations is still required to directly examine the capacity of suspected pathogen contained in those aerosol samples to mediate immune responses in the KD development.

3. GENETICS AND KAWASAKI DISEASE

Several lines of evidence support the genetic contribution to KD susceptibility and outcomes. Epidemiological studies have indicated that infection is a possible etiology for KD, and immune-associated loci have also been a focus of candidate-gene research for KD susceptibility determinants (39, 40). The high prevalence of KD in Asian (especially Japanese) strongly implies a genetic predisposition to developing KD, given that Japanese children with Western lifestyle still have the similar increased risk of developing the disease (41-43). The marked susceptibility of individuals of Northeast

Asia descent to KD, compared with the susceptibility of those of European descent, has been maintained following the migration of North Asians to countries where there is a low incidence of the disease (44). Moreover, siblings with KD have a 10-fold higher risk of developing KD than the general population does, and children whose parents had KD have a twofold increased incidence of developing the disease (40, 45-49). Based on a linkage analysis performed in Japanese KD sibling-pair samples, a functional polymorphism in the inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene was identified (39). These authors first demonstrated a functional single-nucleotide polymorphism (SNP) in the ITPKC gene associated with KD susceptibility and the development of coronary artery lesions. The polymorphism of rs28493229 located in the first intron of ITPKC gene that may alter gene expression level of ITPKC, which is a kinase that phosphorylates inositol 1,4,5-trisphosphate (IP3), which is an important factor for initiating calcium release from the endoplasmic reticulum. It is now possible to reassess genetic susceptibility to KD based on the advances in molecular genetics technology. Because KD is thought to be polygenic, with different genes affecting susceptibility in different ethnic groups, it would be helpful for understanding the genetic roles in KD through the genome-wide association study (GWAS) in different races. An earlier GWAS of Caucasian patients revealed variants located in multiple genes which are associated with inflammation or vascular pathology; NAALADL2 and ZFHX3 were the most significantly associated with these functions (50). On the basis of the first GWAS performed in a Han Chinese population (51), the most

strongly associated SNPs (p value around 1x10-6) detected in the joint analysis corresponded to three novel loci, including COPB2 (coatomer protein complex beta-2 subunit) gene, ERAP1 (endoplasmic reticulum amino peptidase 1) gene, and immunoglobulin heavy chain variable regions genes. These novel candidates identified in KD have been implicated in T cell receptor signaling, regulation of proinflammatory cytokines, and antibody-mediated immune responses. Although these GWASs identified a number of loci with plausible biological links to KD pathogenesis, their limited sample size prevented the identification of genetic variants surpassing the formal threshold for genome-wide significance ($p < 5.0 \times 10{-8}$).

To identify novel genetic factors that predispose an individual to KD, GWASs for KD in a Han Chinese (51, 52) and Japanese population (53) were recently conducted, and novel critical susceptibility loci located in the CD40, B-lymphocyte kinase (BLK), FCGR2A, as well as ITPKC gene regions were identified. These findings highlighted the importance of B-cell or T-cell activation by candidate genes to the pathogenesis of this inflammatory disease (Figure 1). Building on previous hypotheses and subsequent findings, future investigations are needed to clarify the interplay among those genetic susceptibility and infectious agents.

4. DIAGNOSIS AND THERAPY

The diagnosis of KD is made in the presence of at least 5 days of fever and four of the five principal clinical features, including changes in extremities, exanthema, conjunctival injection, lymphadenopathy, as well as changes in lips and oral cavity (54).

However, to date, a major clinical problem is that KD remains difficult to diagnose in the clinic because it has varied clinical manifestations and lacks specific laboratory tests (55). Based on an unbaised and highthroughput screeing for prot biomarkers, analysis from discovery and replication studies found that in KD, IFN- -inducible protein 10 (IP-10) levels had extremely high area under the receiver operating characteristic (ROC) curve values (26). This finding suggests that IP-10 could be used as a biomarker for differential diagnosis of KD, thereby allowing KD patients to receive timely treatment. Moreover, IP-10 levels could be used for

diagnosing KD at a very early stage (fever < 4 days) and monitoring the efficacy of intravenous immunoglobulin treatment. In the blinded validation study, levels of IP-10 have been proved to have great potential value in the clinic because of its discrimination power and extremely high sensitivity and specificity. Based on the stronge evidence from recent studies with three independent stages, levels of IP-10 appear to be one of the most significant biomarker for KD diagnosis because of its excellent performance. Therefore, IP-10 could be incorporated into a gold standard test for KD diagnosis, and combining with other potential biomarkers (eg., NT-proBNP, ESR, and KD-specifci unrine

targets) could be helpful for developing an ideal algorism for KD diagnosis (Figure 2) (56-59)

5. CONCLUSION

This is an exciting time in KD research because a practicable biomarker (eg., IP-10) with extremely high sensitivity and specificity has been identified (26), and the genetic contributions to KD are becoming clearer than ever (23, 39, 52, 53). Follow-up research based on these achievements could clarify the pathogenic mechanisms that lead to KD. Moreover, screening pertinent KD-related genes in independent cohorts and identifying the etiological agent(s) of KD would be the best single means of enabling the development of precision KD medicine including a diagnostic test, improving therapy, and ultimately, preventing the disease or its complications.

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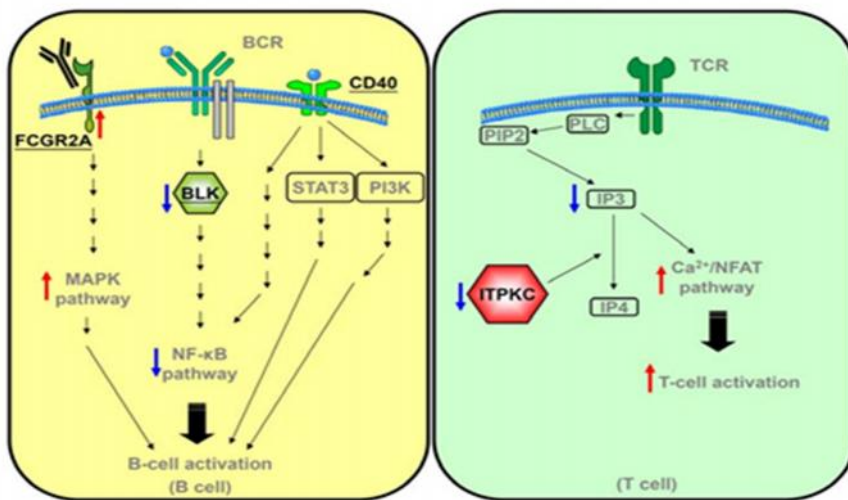Figure 1. FcrRII, IGHV, BLK, CD40 identified from GWAS are involved in the

Figure 1.

signaling cascade of B-cell mediated immune.

Figure 2. Combining with levels of IP-10 and other potential approaches, a successful diagnosis algorism could be developed in the near future.
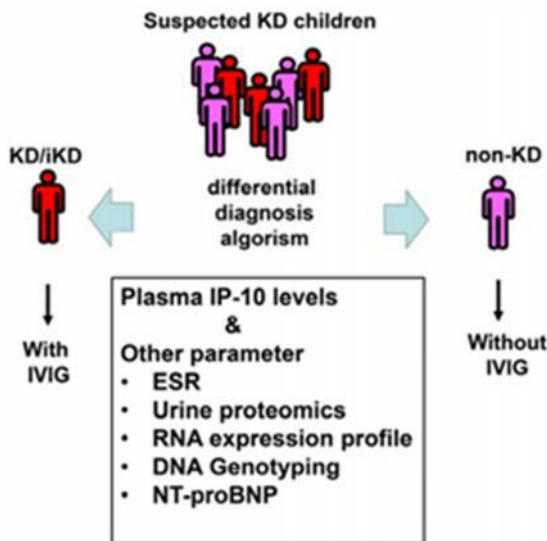

Figure 2.

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