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Emerging evidence of microbial infection in causing systematic immune vasculitis in Kawasaki disease

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Kawasaki disease (KD) is a systematic vasculitis that is often complicated by coronary artery lesions and is a leading cause of acquired heart disease in developed countries. Previous studies have suggested that genetic susceptibility, together with an inducing infectious agent, could be involved in KD pathogenesis; however, the precise causative agent of this disease remains unknown. Moreover, there are still debates concerning whether KD is an infectious disease or an autoimmune disease, although many studies have begun to show that various pathogens functioning as critical inducers could activate different kinds of immune cells, consequently leading to the dysfunction of endothelial cells and systematic vasculitis. Here in this review, we attempt to summarize all the available evidence concerning pathogen infections associated with KD pathogenesis. We also discuss the related mechanisms, present a future perspective, and identify the open questions that remain to be investigated, thereby providing a comprehensive description of pathogen infections and their correlations with the host immune system in leading to KD.

KEYWORDS

bacteria, fungi, Kawasaki disease, vasculitis, virus

1 Introduction

Pathogen infectious diseases have posed a great challenge to human health worldwide (Baldari et al., 2023). Currently, various pathogens have been suggested as critical triggers in inducing systematic vasculitis in children with Kawasaki disease (KD), which is a leading cause of acquired heart disease in developed countries (McCrindle et al., 2017). High-dose intravenous immunoglobulin (IVIG) infusion and aspirin can subdue KD symptoms and partially reduce the occurrence of coronary artery lesions (CALs); however, approximately 10%–20% of affected children develop recrudescence or persistent fever even after IVIG infusion, and those patients have a higher risk of CAL (Li et al., 2018; Nadig et al., 2023). Critically, if this disease is not untreated in a timely manner, sudden death may occur due to coronary artery aneurysms (Shulman and Rowley, 2015; McCrindle et al., 2017; Sosa et al., 2019). Although genetic background (Chang et al., 2014), urban industrialization, environmental factors (Chang et al., 2020; Corinaldesi

et al., 2020), and regional winds together with large-scale atmospheric circulation (Rodo et al., 2011, 2014), have been suggested to correlate with KD, these theories fail to explain the seasonal epidemics of this illness, and also fail to explain why Kawasaki disease does not broadly recur. Nevertheless, an increasing number of epidemiological and clinical data all point to KD having an infectious etiology. For example, epidemiological data from multiple centers worldwide demonstrate that KD has a significant seasonal epidemic (Valtuille et al., 2023), frequent occurrence, and low recurrence characteristics in young children (Nakamura et al., 2008, 2012; Burns et al., 2013; Lin et al., 2015; Ozeki et al., 2017, 2018; Kido et al., 2019; Kim et al., 2020; Xie et al., 2020). Notably, several studies have shown that both the immune repertoire (Kuo et al., 2019) and the heterogeneous host immune response including the autoantibody responses in KD children resemble those observed in patients with bacterial or viral infections (Lindquist and Hicar, 2019; Jackson et al., 2021; Ghosh et al., 2022), lending further support of an infectious disease cause of KD.

Additionally, serum KD-specific molecules which were mostly derived from biofilms possessed molecular structures common to MAMPs (microbe-associated molecular pattern) from *Bacillus cereus*, *B. subtilis*, *Yersinia pseudotuberculosis* (*Y. pstb*), and *Staphylococcus aureus* (Kusuda et al., 2014), implicating a possible relationship between MAMPs and the etiological mechanism of KD vasculitis. Recently, at least 14 types of viruses have been suggested to correlate with KD based on serological and polymerase chain reaction (PCR) analysis of clinical samples (Principi et al., 2013). However, another study showed that at least 15 types of viruses were related to KD because the isolation rates of various viruses in KD patients were significantly higher than those in the control group (Huang et al., 2015; Jackson et al., 2021). Viral infections can cause vascular damage either through direct invasion of the vascular endothelium or provoking a rapid cell-damaging event (Hara et al., 2021). This in turn results in a larger release of proinflammatory cellular components from damaged endothelial cells, pyroptosis, or proinflammatory cell death (Mohandas et al., 2023), hence making various kinds of innate immune cells infiltrate the coronary arteries of KD subjects (Kuijpers et al., 1999; Takahashi et al., 2010a). These data thus suggest that different kinds of microbes are implicated in the pathogenesis of KD, but which microbes are the key inducers and the underlying mechanisms remain unclear. In this review, to better understand the comprehensive profiles between microbial infection and KD pathogenesis, we summarized the major features of our current understanding with respect to various pathogens related to KD. We also discuss the state of this field in KD with respect to the relationship and/or mechanisms concerning the abnormal immune response triggered by various infectious agents, and the open questions that remain to be investigated.

Abbreviations: BCG, Bacillus Calmette-Guérin; CAA, Coronary artery aneurysm; CAWS, Candida albicans water soluble fraction; DAMP, Damaged-associated molecular patterns; ELISA, Enzyme-linked immunosorbent assay; KD, Kawasaki disease; LCWE, Lactobacillus casei cell wall extract; MAMP, Microbe associated molecular pattern; PAMP, Pathogen associated molecular pattern; PCR, Polymerase chain reaction; PRR, Pattern recognition receptor; SEB, Staphylococcal enterotoxin B; SEC, Staphylococcal enterotoxin C; SPE, Streptococcal pyrogenic exotoxins; TCR, T-cell receptor; TSS, Toxic shock syndrome; TSST-1, Toxic shock syndrome toxin-1.

2 Involvement of pathogens during KD pathogenesis

2.1 Viral infection and KD

2.1.1 DNA viruses

Several DNA viruses, including Epstein-Barr virus (EBV), human adenovirus, human parvovirus B19, torque teno virus, herpes family virus, varicella zoster virus, bocaparvo virus, and cytomegalovirus have been identified to be associated with KD pathogenesis.

2.1.1.1 Human adenovirus

Adenovirus type 2 was first isolated from a patient with fatal Kawasaki disease (Embil et al., 1985), while another case report showed that human adenovirus infection can be found in monozygotic twin boys who developed KD (Fukuda et al., 2017). Among the adenovirus-infected cohort, the overall incidence of KD was 5.29 times higher than that of the non-adenovirus-infected control subjects (adjusted HR 5.29, 95% CI: 2.48–11.3), as shown by a population-based cohort study (Huang et al., 2020), suggesting a correlation between adenovirus infection and KD pathogenesis. Notably, there are also studies showing a lack of association between adenovirus infection and KD, suggesting that more intense research is needed to explore the relationships between adenovirus infections and KD (Okano et al., 1990; Shike et al., 2005).

2.1.1.2 Human parvovirus B19

Human parvovirus B19 (HPV-B19) is a single-stranded DNA virus that may have a pathogenic role in the development of KD with other predisposing factors because it can cause symptoms resembling those observed in KD patients (Nigro et al., 1994; Holm et al., 1995). Importantly, HPV-B19 infection should be considered in the differential diagnosis of KD patients who show atypical clinical symptoms during the erythema infectiosum epidemic stage (Oura et al., 2022).

2.1.1.3 Torque teno virus

The torque teno virus (TTV), which is a single-stranded circular DNA virus, was first found in the lymph node of a KD patient (Katano et al., 2012). For instance, a high viral load of torque teno virus 7 (TTV7) was identified in KD patients (Thissen et al., 2018; Spezia et al., 2023a), and the viral load of TTV positively correlated with the level of total bilirubin and aspartate aminotransferase in KD patients (Spezia et al., 2023b), suggesting that TTV might play a critical role in the pathophysiology of patients with KD.

2.1.1.4 Herpes simplex virus

Herpes simplex virus (HSV) consists of multiple subtypes (Rowley et al., 2011), and its family members, including EBV, HHV-6 and varicella-zoster, were all found to be involved in KD. For instance, a previous study showed that the DNA sequence of EBV can be detected in KD patients (Kikuta et al., 1988), and there are many cases of KD-like lesions, specifically coronary artery aneurysms (CAAs), that were suggested to be caused by EBV infection (Kikuta et al., 1993; Rosenfeld et al., 2020; Xiao et al., 2020). However, EBV might not be the direct causative agent of KD, as shown by another study (Kikuta et al., 1990). Notably, a case of Kawasaki disease triggered by EBV virus infection was found to be complicated with familial Mediterranean fever (Maggio et al., 2019). Moreover, the prevalence

of EBV in KD children was significantly lower during the early stage (van Stijn et al., 2020), and deoxyuridine 5'-triphosphate nucleotide hydrolase (dUTPase), a pathogen nonstructural protein encoded by EBV, can stimulate monocyte-derived macrophages through Toll-like receptor 2-dependent signaling transduction (Ariza et al., 2009), suggesting that dUTPase could be used as a potential target for drug development against EBV infection and KD treatment.

In addition to EBV, certain KD patients also have concomitant varicella zoster virus or coxsackievirus A4 infection (Turkay et al., 2006; Toprak et al., 2015). Given that the features of HHV6-infected patients resemble those symptoms observed in KD children (Kakisaka et al., 2012; Alramadhan et al., 2020), HHV-6B was thus suggested to be a critical mediator during the pathogenesis of KD, and HHV-6B infection was also suggested to be responsible for the increased number of KD patients during the SARS-CoV-2 pandemic (Dursun and Temiz, 2020).

2.1.1.5 Bocavirus

Human bocavirus (HboV) is a single-stranded DNA etiologic agent that has been suggested as a cause of acute respiratory tract infection in children (Schildgen et al., 2008). This virus was first identified in nasopharyngeal, serum or stool samples, and was thus suggested to play a pathogenic role in some cases of Kawasaki disease (Catalano-Pons et al., 2007). Later, this work was verified by the results from another group showing that HboV can indeed be detected in nasopharyngeal secretions of KD patients, demonstrating a coincidental or possible etiological association between HboV infection and KD pathogenesis (Santos et al., 2011). Furthermore, a significant correlation between HboV infection and KD incidence was identified based on epidemiological data (Kim et al., 2014; Lim et al., 2021), whereas some investigators have proposed that there is little correlation between HboV infection and KD based on the serological test (Lehmann et al., 2009). Cytomegalovirus was also suggested to be involved in the development of atypical KD and coronary aneurysms (Catalano-Pons et al., 2005; Guc et al., 2008). Taken together, more intense researches are needed to elucidate the precise mechanism concerning DNA viruses associated with KD pathogenesis.

2.1.2 RNA viruses associated with KD

Apart from the DNA viruses mentioned above, a total of nine types of RNA viruses have been suggested to correlate with KD pathogenesis, including coxsackie virus, enterovirus, human coronavirus NL63 (HCoV-NL63), influenza virus, measles virus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), feline virus, influenza A virus H1N1 and human immunodeficiency virus, as discussed below.

2.1.2.1 Coxsackie virus

The coxsackie virus, which belongs to enteroviruses of small RNA viridine, has been identified as the main cause of viral myocarditis in humans since 1955 (Dalldorf, 1955). Both coxsackie virus B3 (CVB3) and coxsackie virus A4 were identified to correlate with KD (Rigante et al., 2012; Ueda et al., 2015), and this type of virus can induce neonatal symptoms similar to viral myocarditis observed in KD (Verma et al., 2009).

2.1.2.2 Enterovirus

It has been demonstrated that the KD incidence in the enterovirus (EV)-infected cohort was significantly higher than that in the

non-EV-infected cohort (Weng et al., 2018), thereby indicating a high correlation between EV infection and KD. In addition, a decreased incidence of severe enterovirus infection cases is simultaneously correlated with decreased KD hospitalizations during the SARS-CoV-2 epidemic (Guo et al., 2022), thus suggesting that enterovirus might function as a critical mediator during the pathogenesis of KD.

2.1.2.3 HCoV-NL63 virus

Although HCoV-NL63 was once identified in several KD patients (Dominguez et al., 2006), most data later do not support an association between HCoV-NL63 infection and KD (Baker et al., 2006; Chang et al., 2006; Lehmann et al., 2009). In fact, only 1 (2%) of 48 patients with KD was found to be positive for HCoV-NL63/NH (Shimizu et al., 2005), although HCoV-229E was also suggested to be involved in KD (Lehmann et al., 2009; Shirato et al., 2014).

2.1.2.4 Influenza virus

Influenza viruses have been revealed to positively correlate with the monthly KD incidence (Kim et al., 2014). For instance, influenza A H1N1/09 virus has been shown to be associated with the pathogenesis of KD by several groups (Joshi et al., 2011; Wang et al., 2019; Banday et al., 2021). Additionally, Parainfluenza type 3 virus (PIV-3) was also found to correlate with KD (Schnaar and Bell, 1982; Karron et al., 1993), suggesting that influenza virus infection has etiological importance in the development of KD. However, given that concomitant influenza infection affects the clinical manifestations of KD and impacts the laboratory test results of the disease (Huang et al., 2015), it remains to be determined regarding influenza infection and KD pathogenesis.

2.1.2.5 Measles virus

The measles virus (MeV), which is an enveloped RNA virus, frequently causes acute febrile illness accompanied by a rash (Takemoto et al., 2022). This virus can be isolated from KD children, and the symptoms caused by MeV infection partially resemble those observed in KD patients (Whitby et al., 1991; Kuijpers et al., 2000).

2.1.2.6 SARS-CoV-2

The RNA respiratory virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) can induce multisystem inflammatory syndrome in children (also called MIS-C), including multifocal endovascular dermatitis, thrombosis, and systemic thrombotic microangiopathy, which resemble certain features observed in KD (Ackermann et al., 2020; Consiglio et al., 2020; Loomba et al., 2020; Bukulmez, 2021; Cherqaoui et al., 2021; Sancho-Shimizu et al., 2021; Sokolovsky et al., 2021; Zhang et al., 2021).

Moreover, SARS-CoV-2 can be detected in certain KD patients, and a host of SARS-CoV-2-positive patients exhibit KD-like syndrome (Consiglio et al., 2020; Jones et al., 2020; Toubiana et al., 2020; Sharma et al., 2021). However, although high titers of anti-SARS-CoV-2 antibodies have been detected both in KD and multisystem inflammatory syndrome patients (Kabeerdoss et al., 2021), the two diseases are different because of the differential T-cell subsets, interleukin (IL)-17A, and biomarkers associated with arterial damage (Consiglio et al., 2020). On the other hand, global studies have reported that the incidence of KD declined during the COVID-19 pandemic, suggesting a potential KD pathogenesis involving transmission among children (Ae et al., 2022). However, several earlier studies showed that

the KD incidence has increased during the pandemic (Ouldali et al., 2020; Roe, 2020; Stower, 2020; Viner and Whittaker, 2020), supporting the hypothesis that KD might be caused by an unknown RNA virus that may function as the main trigger in inducing abnormal immune responses in genetically susceptible individuals.

2.1.2.7 Other types of RNA viruses

In addition to the RNA viruses mentioned above, several other types of RNA viruses were also found to be involved in KD. For example, both a novel feline virus (Moynahan, 1987) and the influenza A virus (Wang et al., 2019) were suggested to be related to KD symptoms. Notably, HIV patients also show symptoms similar to those observed in KD patients (Johnson et al., 2016). The intracytoplasmic inclusion bodies induced by viruses can be isolated from KD patients, suggesting that the infectious etiologic agent of KD might be associated with an unknown novel RNA virus (Rowley et al., 2011). In addition, dengue virus was also identified in the serum of certain KD patients in southern Thailand, and mosquitoes were hypothesized to work with the dengue virus to spread the KD pathogen, thus inducing cell proliferation and morphological changes in endothelial cells and coronary arteritis lesions in KD patients (Sopontammarak et al., 2008). Moreover, regions with the highest reported arboviral infections in Venezuela simultaneously have the highest incidence of KD (Paniz-Mondolfi et al., 2020), demonstrating the critical roles of viral infections in mediating the pathogenesis of KD.

2.2 Bacterial infection associated with KD

Regarding bacterial infection, the superantigens produced by gut bacteria may be involved in the onset of KD. Until recently, there were five *Streptococcus* spp. (*S. pneumoniae*, *pseudopneumoniae*, *oralis*, *gordonii*, and *sanguinis*) were found to increase during the acute phase in KD patients based on metagenomic sequencing, indicating that Streptococci are involved in the pathogenesis of KD disease (Kinumaki et al., 2015). Furthermore, the stool of KD patients contains higher numbers of gram-positive bacteria, including *Streptococcus*, *Staphylococcus*, *Eubacterium*, and *Peptostreptococcus* genera, Hsp60-producing gram-negative bacteria, and a lower number of lactobacilli, when compared with those from healthy control children (Yamashiro et al., 1996; Takeshita et al., 2002; Nagata et al., 2009). Specifically, three pathogens, *S. pyogenes* (Leahy et al., 2012), *S. mitis* Nm-65 (Tabata et al., 2021), and *S. sanguis* (Tsurumizu et al., 1991), have been identified in the pleural fluid, tooth surface or blood of KD patients. Additionally, serum IgM antibodies against superantigens of *S. aureus* and *S. pyogenes* have been identified in KD patients (Matsubara et al., 2006), and these two pathogens together can produce 19 different superantigens (Llewelyn and Cohen, 2002). Mechanistically, *S. aureus* isolated from the rectum or pharynx of KD patients can secrete toxic shock syndrome toxin 1 (TSST-1) and staphylococcal protein A, which in turn stimulate V β 2⁺ lymphocyte amplification and are thus involved in the abnormal immune responses of KD patients (Leung et al., 1993; Wann et al., 1999; Leung et al., 2002).

Regarding *Yersinia pseudotuberculosis* (Konishi et al., 1997), the *Propionibacterium acnes* strain and its products cytopathogenic proteins (CPPs; Kato et al., 1983; Tomita et al., 1987) can all be isolated from KD patients, suggesting a causative role of bacterial infection in mediating the pathogenesis of KD. Moreover, several recent studies suggest that

Y. pestis infection is closely related to KD pathogenesis (Kato et al., 2019; Kamura et al., 2020; Miyata et al., 2022; Ohnishi et al., 2022), and the antibody titers of *Y. pestis* were significantly elevated in both Chinese and Japanese KD patients (Chou et al., 2005; Tahara et al., 2006). In contrast, a recent study showed that the positive rate of *Y. pestis* infection is much lower in KD patients (Horinouchi et al., 2015; Hayashi et al., 2023), but when the population is exposed to a higher risk of *Y. pestis* infection, the incidence of KD is much higher (Vincent et al., 2007).

2.3 *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* hypothesis related to KD

In addition to the microbes mentioned above, *M. pneumoniae* infection was identified in an important proportion of KD patients (Umezawa et al., 1989; Ebrahim et al., 2011; Lee et al., 2011; Tang et al., 2016; Wang et al., 2021; Huang et al., 2022). For instance, the *M. pneumoniae* infection-positive rate in KD patients was significantly higher than that in non-KD patients during the SARS-CoV-2 epidemic (Ding et al., 2021), and certain KD patients were found to be coinfecting with *M. pneumoniae* and Epstein–Barr virus (Huang et al., 2012).

Additionally, the positive rate of serum *Chlamydia pneumoniae* IgM antibody in KD children was significantly higher than that in the control group (Numazaki and Chiba, 1996); however, another study showed that the link between *C. pneumoniae* infection and KD pathogenesis or coronary artery lesions remains to be clarified (Chua et al., 2000; Strigl et al., 2000), suggesting that more intense research is needed to confirm the correlations between *M. pneumoniae* or *C. pneumoniae* infection and KD pathogenesis.

2.4 Rickettsia infection and KD

Rickettsia-like organisms were also found in biopsies of the skin and lymph nodes of KD patients (Tasaka and Hamashima, 1978). However, in most cases, only *Coxiella burnetii* but not *Rickettsia conorii*, *R. typhi*, *Coxiella burnetii* or *Ehrlichia phagocytophila* was suggested to cause KD-like symptoms in young children (Kafetzis et al., 2001), suggesting its specific causative roles in KD pathogenesis.

2.5 Pathogen infection evidenced from experimental studies with a murine model

Given that the fungus *Candida albicans* can be isolated from KD patients, and its extract, the *Candida albicans* water soluble fraction (CAWS) intraperitoneally injected in mice could induce symptoms resembling those observed in KD patients (Murata, 1979; Martinez et al., 2012; Yoshikane et al., 2015; Stock et al., 2016; Noval Rivas and Arditi, 2020). Furthermore, β -glucan, which is the major component of CAWS, is also increased in KD patients (Ishibashi et al., 2014). Mechanistically, the mannoprotein- β -glucan complex of *C. albicans* can affect the functions of leukocytes, endothelial cells, and platelets *in vitro* (Kurihara et al., 2003). The systematic vasculitis induced by CAWS in mice can be alleviated after administration of human immunoglobulin or etanercept (Takahashi et al., 2010b; Ohashi et al.,

TABLE 1 Microbial etiology demonstrated as critical triggers of Kawasaki disease.

Pathogens	Related to KD	References
Virus		
<i>Epstein–barr Virus (EBV)</i>	EBV infection is associated with recurrence of KD	Kikuta et al. (1990)
	EBV infection is associated with the development of coronary aneurysms in KD	Kikuta et al. (1993)
	EBV infection was first demonstrated in KD cases by PCR	Rosenfeld et al. (2020)
<i>Adenovirus</i>	The cause of KD was not proved to be adenovirus by TaqMan PCR test	Shike et al. (2005)
	The specific immune response to HADV-3 plays a key role in the occurrence of KD	Fukuda et al. (2017)
<i>Human parvovirus B19 (HPV-B19)</i>	HPV-B19 can cause some symptoms resembles to those observed in KD	Nigro et al. (1994)
	Infection with HPV-B19 is closely associated with KD and collagen diseases	Holm et al. (1995) and Oura et al. (2022)
	HPV-B19 DNA was identified in the blood and pathological tissues of adult KD patients	Flossdorf et al. (2020)
<i>Torque Teno virus 7</i>	A low copy number torque teno virus 7 was detected in cervical lymph nodes of a KD case by using real-time PCR	Katano et al. (2012)
	TTV7 variants were detected by metagenomic sequencing and PCR method in two KD patients	Thissen et al. (2018)
<i>Herpes virus</i>	Patients with KD and HHV6 infection had similar skin changes at the BCG vaccination site	Kakisaka et al. (2012)
	The number of KD patients increased significantly due to HHV-6 infection during the SARS-CoV-2 epidemic	Dursun and Temiz (2020)
	A child with incomplete KD complicated with HHV-6B infection developed aseptic meningitis	Alramadhan et al. (2020)
<i>Varicella Zoster Virus</i>	A case of KD patient was found to infect with EB virus and varicella-zoster virus	Turkay et al. (2006)
	A case of KD patient was found to complicate with varicella-zoster virus infection	Toprak et al. (2015)
<i>Human boca virus (HboV)</i>	Certain KD patients were found to infect with HboV by using PCR method	Catalano-Pons et al. (2007)
	The serological data shows no association between HBoV infection and KD occurrence	Lehmann et al. (2009)
	Human boca virus DNA was identified in the nasopharyngeal secretions of a male child with KD	Santos et al. (2011)
	KD was significantly correlated with the monthly incidence of human boca virus	Kim et al. (2014)
<i>Cytomegalovirus</i>	Two infants with cytomegalovirus infection developed atypical KD and coronary aneurysm	Catalano-Pons et al. (2005)
	A case of atypical KD was found to infect with cytomegalovirus	Guc et al. (2008)
<i>Dengue virus</i>	The dengue virus titer is positive in certain KD children	Sopontammarak et al. (2008)
<i>Coxsackie virus</i>	The <i>coxsackie virus</i> infection was found in two cases of KD by using ELISA method, and the CVB3 antibody was detected by complement binding assay	Rigante et al. (2012)
	The antibody titer to coxsackie virus A4 was significantly higher than those in an adult KD case	Ueda et al. (2015)
<i>Enterovirus</i>	The cumulative incidence of KD in enterovirus-infected cohort was significantly higher than that in non-EV-infected cohort	Weng et al. (2018)
	The decrease in the number of KD hospitalizations was positively correlated with the decrease in the number of severe enterovirus infections	Guo et al. (2022)
HCoV-NL63	A lack of evidence proving human coronavirus NL63 infection associated with KD induction	Shimizu et al. (2005)
	The infection rate of HCoV-NL63 in KD patients is very low	Dominguez et al. (2006)
	Lack of association between infection with HCoV-NL63 virus and KD	Chang et al. (2006)
	Serological data showed no association with HCoV-NL63 infection in KD children	Lehmann et al. (2009)
	Serological data support that HCoV-NL63 is not involved in KD, but suggest that HCoV-229E may be involved in KD	Shirato et al. (2014)
<i>Parainfluenza type3 virus</i>	The parainfluenza type 3 virus infection was suggested to associate with KD occurrence	Schnaar and Bell (1982)
	The parainfluenza virus type 3 infection was found to associate with KD in one patient	Johnson and Azimi (1985)
<i>Measles-virus</i>	The measles-virus infection was suggested to associate with KD occurrence	Whitby et al. (1991)

(Continued)

TABLE 1 (Continued)

Pathogens	Related to KD	References
SARS-CoV-2	The KD incidence has increased during the SARS-CoV-2 pandemic	Ouldali et al. (2020), Sandhaus et al. (2020), and Stower (2020)
	The cases of SARS-CoV-2 infection children have a higher frequency of myocarditis or pericarditis than the classic KD	Ventura et al. (2020)
	The KD incidence is increased during the pandemic of SARS-CoV-2 or influenza A H1N1 in western counties	Kam et al. (2020)
	The SARS-CoV-2 cases show a highly active proinflammatory cytokine response similar to KD	Choi (2020)
	Asymptomatic children with SARS-CoV-2 infection shows a hyperinflammatory syndrome similar to KD shock syndrome	Rehman et al. (2020)
	Several concurrent incomplete KD cases with SARS-CoV-2 infection were identified	Rivera-Figueroa et al. (2020) and Raut et al. (2021)
<i>Feline virus</i>	KD was suggested to correlate with a new feline virus transmitted by fleas	Moynahan (1987)
<i>H1N1</i>	The H1N1 virus infection was identified in the cases of incomplete KD patients	Wang et al. (2019)
<i>Human immunodeficiency virus</i>	The inflammatory characteristics of pediatric KD resembles the symptoms of adult immunodeficiency virus syndrome	Johnson et al. (2016)
<i>Virus-like particles</i>	The virus-like particles were found in the circulating peripheral blood of KD patients	Lin et al. (1992)
	The accumulation of virus-like particles (VLP) in lung tissue of KD patients, and the intracytoplasmic inclusion bodies of skin cells in the ciliated bronchial wall of KD patients were suggested to be induced by virus-like particles	Rowley et al. (2011)
Bacteria		
<i>Staphylococcus aureus</i>	The amplification of T cells in KD patients may be caused by a new clone of TSST-producing <i>S. aureus</i>	Leung et al. (1993)
	High levels of extracellular SpA secreted locally by <i>S. aureus</i> in the gastrointestinal tract may lead to KD-like symptoms	Wann et al. (1999)
	The value of <i>S. aureus</i> in larynx and rectum mucosa was higher in KD patients	Abe et al. (2003)
	Staphylococcus superantigens is associated with KD pathogenesis	Matsubara and Fukaya (2007)
	Multiple superantigens are involved in KD by using serum IgG and IgM antibodies against all the superantigens	Matsubara et al. (2006)
<i>Yersinia pseudotuberculosis</i> (<i>Y. pstb</i>)	<i>Y. pseudotuberculosis</i> was isolated from the stool of a KD patient	Konishi et al. (1997)
	Some studies have shown that superantigen (YPM) is produced <i>in vivo</i> and plays an important role in the pathogenesis of pseudomonas tuberculosis infection	Abe et al. (1997)
	KD was significantly associated with myocarditis and the increase of yersinia antibody titer	Chou et al. (2005)
	The incidence of coronary artery lesions in <i>Y. pseudotuberculosis</i> positive group was significantly higher than that in <i>Yersinia</i> negative group in KD patients	Tahara et al. (2006)
	The KD incidence is higher when the population is exposed to the risk of <i>Y. pseudotuberculosis</i> infection	Vincent et al. (2007)
	Specific molecules in the serum samples of KD share a common molecular structure with the microbe associated molecular pattern (MAMP) of <i>Y. pseudotuberculosis</i>	Kusuda et al. (2014)
	KD Patients associated with <i>Y. pseudotuberculosis</i> infection had significantly more frequent cardiac sequelae (CS)	Horinouchi et al. (2015)
	A KD-like patient who was positive for yersinia tuberculosis was diagnosed with far east scarlet fever	Ocho et al. (2018)
	LOOP-mediated isothermal amplification method identifies <i>Y. pseudotuberculosis</i> infection in KD patient	Kato et al. (2019)
	The symptom caused by pseudomeric <i>mycobacterium tuberculosis</i> infection resembles o the features observed in KD	Kamura et al. (2020)
<i>Propionibacterium acnes</i>	The levels of anti-cytopathic protein (CPP) antibodies in serum of KD patients are increased during the acute phase	Tomita et al. (1987)
	The variant strain of <i>P. acnes</i> may have a causative role in KD and house-dust mites a role as vectors	Kato et al. (1983)
<i>Rickettsia-Lick organism</i>	The clostridium bursteni is associated with KD instead of other rickettsiae pathogen	Kafetzis et al. (2001)
<i>Streptococcus sanguis</i>	Streptococcus hemorrhage can be isolated from KD patients in acute stage	Tsurumizu et al. (1991)
<i>Bacillus cereus</i>	KD specific molecules in serum share a common molecular structure with the MAMP of <i>B. cereus</i> .	Kusuda et al. (2014)

(Continued)

TABLE 1 (Continued)

Pathogens	Related to KD	References
<i>Lactobacillus casei</i>	The asymmetric inflammatory coronary inflammation was detected in the LCWE-induced mouse model	Lehman et al. (1988)
	The macrophage dectin-1/Syk-mediated pathway is involved in LCWE-induced CALs and production of IL-6 and MCP-1	Lin et al. (2013)
	CD8 ⁺ T cells functionally contributed to the development of KD vasculitis in LCWE-induced mouse model	Noval Rivas et al. (2017)
	The endothelial progenitor cell Notch4 signaling pathway was identified in the LCWE-induced mouse model	Wang et al. (2016)
	The adrenergic stimulation after KD vasculitis can cause myocardial hypertrophy and bridging fibrosis in the LCWE-induced mouse model	Matundan et al. (2019)
	The electrophysiological abnormalities and cardiac neuronal remodeling were observed in the LCWE-induced mouse model	Abe et al. (2020)
	The coronary artery stenosis with severe coronary vasculitis and elastin degradation was detected in the LCWE-induced mouse model	Suganuma et al. (2020)
	Nonpathogenic LCWE-specific T-cell combinations are related to KD occurrence	Hsieh et al. (2021)
<i>Mycobacterium SSP</i>	Atypical mycobacterium infection enhances autoimmunity leading to coronary arteritis after vaccination with BCG	Nakamura et al. (2007)
	The development of tuberculid in the two infants might be associated with the remnant immune activation of KD	Yamada et al. (2016)
<i>Streptococcus</i>	Group A streptococcus was not detected in an adult Japanese female with KD	Hattori et al. (2005)
	The superantigens of <i>S. pyogenes</i> are involved in KD pathogenesis based on the IgM antibodies test	Matsubara et al. (2006)
	KD is associated with many streptococcal superantigens	Matsubara and Fukaya (2007)
	The first case of incomplete KD complicated with <i>S. pyogenes</i> pneumonia was reported	Leahy et al. (2012)
	The complete genome sequence of <i>Streptococcus</i> nM-65 can be isolated from KD patient	Tabata et al. (2021)
Fungi		
<i>Candida albicans</i>	The fungi <i>C. albicans</i> isolated from KD patients can produce coronary arteritis in mice	Murata (1979)
	CAWS strongly inhibits leukocyte function <i>in vitro</i>	Kurihara et al. (2003)
	The adeno-associated virus vector encoding IL-10 improves CAWS-induced cardiac dysfunction and lethality in mouse	Nakamura et al. (2018)
	The genetic background of CAWS immune response is related to the occurrence of coronary arteritis	Nagi-Miura et al. (2004)
	The genetic control of susceptibility to induction of vasculitis by the <i>Candida albicans</i> extract is dependent on the mouse strains, but is not linked to the histocompatibility-2 loci	Takahashi et al. (2004)
	Severe stenosis of the aorta and coronary arteries, and fibrinoid necrosis in the vessel walls were observed in the CAWS-induced DBA/2 mouse strain	Hirata et al. (2006)
	Most CAWS strains can induce vasculitis	Nagi-Miura et al. (2008)
	<i>Candida</i> cell wall mannan might contribute to coronary arteritis and acute shock, and that an alteration of mannan structure could be responsible for <i>Candida</i> pathogenicity	Tada et al. (2008)
	The human immunoglobulin suppresses development of murine systemic vasculitis induced by CAWS	Takahashi et al. (2010b)
	The important role of CCR2 involved in the pathogenesis of CAWS-induced mouse model	Martinez et al. (2012)
	Etanercept is effective in inhibiting CAWS-induced vasculitis and may be a new therapeutic drug for KD	Ohashi et al. (2013)
	The preformed toxins and the <i>Candida</i> species were identified as the dominant fungus leading to KD	Rodo et al. (2014)
	The α -mannan contained in <i>C. albicans</i> extract could induce coronary arteritis and acute shock	Tada et al. (2014)
	KD patients have a higher titer of β -glucan (BG) antibody against <i>Candida</i> cell wall	Ishibashi et al. (2014)
	Granulocyte/macrophage colony stimulating factor was found in the CAWS-induced cardiac inflammation site of KD mice	Stock et al. (2016)
	The CAWS-induced mouse model showed inflammatory cell infiltration, destruction of elastic lamellae, loss of medial smooth muscle cells and intimal thickening, whose features resembles the vascular lesions of KD patients	Yoshikane et al. (2015)
	The recognition of A-mannan by A-mannan receptor dectin-2 plays an important role in the pathogenesis of vasculitis in KD mice induced by <i>C. albicans</i> cell wall polysaccharide.	Oharaseki et al. (2020)
	The mannoprotein fractions of clinically isolated <i>Candida</i> species can induce vasculitis in mice	Tanaka et al. (2020)
The cell wall mannoprotein of <i>C. krusei</i> could induce coronary vasculitis in mouse model	Yanai et al. (2020)	

(Continued)

TABLE 1 (Continued)

Pathogens	Related to KD	References
Mycoplasma		
<i>Mycoplasma pneumoniae</i>	The pulmonary symptoms of KD were suggested to be associated with pneumococcal infection	Lee et al. (2011)
	Incomplete KD patients were found to be related with acute <i>M. pneumoniae</i> infection	Ebrahim et al. (2011)
	Many cases of KD simultaneously infected with Epstein–barr virus and <i>M. pneumoniae</i> were identified	Huang et al. (2012)
	MP infection occurs in the elderly population, and the respiratory tract involvement rate is higher in KD patients	Tang et al. (2016)
	The MP infection rate in KD patients was significantly higher than that those observed in non-KD patients	Ding et al. (2021)
	<i>M. pneumoniae</i> infection may be associated with a reduced incidence of small CAA in KD patients	Wang et al. (2021)
	The serological test for <i>M. pneumoniae</i> infection was positive in one case of acute KD patients	Huang et al. (2022)
	A lack of evidence showing association between <i>M. pneumoniae</i> infection and KD induction	Strigl et al. (2000)
Chlamydia		
	The positive rate of serum <i>C. pneumoniae</i> IgM antibody in KD was higher than those in control group	Numazaki and Chiba (1996)
	A deficiency evidence of <i>C. pneumoniae</i> infection associated with KD occurrence	Chua et al. (2000)

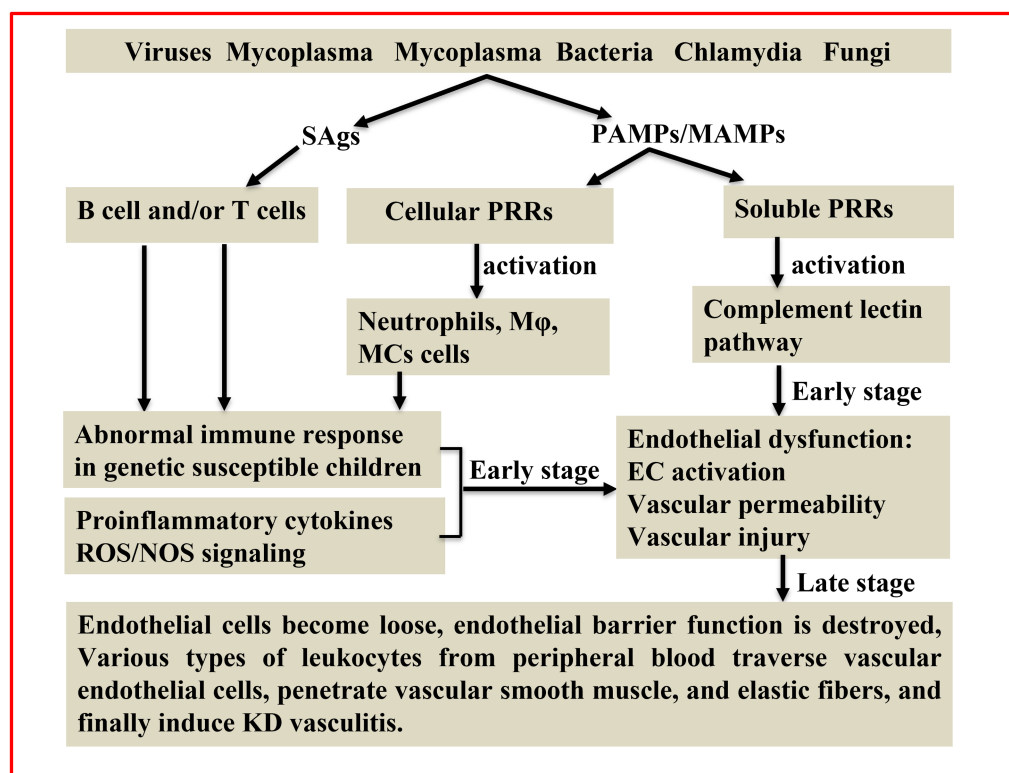


FIGURE 1

Schematic illustrating the pathogenic mechanisms of KD. The superantigens (SAGs) hypothesis and different infectious agents produce pathogen/microbe-associated molecular patterns (PAMPs/MAMPs) were all proposed to be involved in KD pathogenesis. SAGs non-specifically activate T cells and/or B cells. PAMPs/MAMPs also stimulate immune cells [e.g., macrophages (Mφ), dendritic cells (DCs), monocytes (MCs)] and endothelial cells (ECs) through cellular pattern recognition receptors (PRRs; e.g., TLRs, NOD1, and Dectin-1/-2). Additionally, PAMPs/MAMPs can activate the complement lectin pathway through soluble PRRs (e.g., ficolin-1 and mannose binding lectin-2). Activated complement pathways can induce inflammatory vascular damage through recruitment of innate inflammatory cells and direct injury to ECs. This cross-talk among different cells augments the production of proinflammatory cytokines/chemokines and reactive oxygen/nitrogen species (ROS/NOS), hence leading to a systemic inflammatory reaction in KD.

2013). Together, these findings imply that infectious agents might play critical roles in triggering this disease.

Another major KD-like murine coronary arteritis model involves induction by *L. casei* cell wall extract (LCWE), which is widely used to mimic systematic vasculitis in KD patients (Lehman et al., 1988;

Abe et al., 2020). In the LCWE-induced mouse model, the TLR2 and ILβ-dependent signaling pathways were suggested to play important roles during its pathogenesis (Rosenkranz et al., 2005; Lee et al., 2012; Matundan et al., 2019). Additionally, the dectin-1/Syk signaling pathway in macrophages (Lin et al., 2013) and the Notch4 signaling

pathway in endothelial progenitor cells are also involved in LCWE-induced coronary artery disease, thereby contributing to the development of KD pathogenesis (Wang et al., 2016). Moreover, LCWE was likewise suggested to function as immunogenic for proinflammatory T helper (Th) 1, Th17, and CD8⁺ T cells and inducible regulatory T cells (iTreg) (Noval Rivas et al., 2017; Hsieh et al., 2021). Taken together, the systematic vasculitis induced by CAWS or LCWE in mice resembles pathological features observed in KD patients, demonstrating the causative roles of etiological agent infection and related PAMP/MAMP signaling activation in inducing KD vasculitis (Table 1).

3 Summary and perspective

Taken together, various pathogens identified in KD were all suggested to be the critical triggers in causing systematic vasculitis, and these pathogens were demonstrated to work independently or synergistically to potentiate abnormal immune responses by inducing pyroptosis and/or proinflammatory cell death, hence leading to systematic vasculitis in KD (Figure 1). However, whether these pathogens are direct causes or merely the accompanying pathogens after KD induction remains elusive. Additionally, the causative agent of KD remains ambiguous, and several questions remain to be clarified. First, those pathogens suggested to be involved in the pathogenesis of KD largely rely on PCR and serological methods using a relatively small sample size. Second, the differences in timing of obtaining the blood sample and constraints of the study design used to measure pathogens in KD patients by different investigators could make pathogen identification inconsistent. Third, whether KD is caused by a single pathogen or is the combined result of more than one agent remains to be investigated. Consequently, the relationship between pathogen infection and KD vasculitis is far more complex than currently appreciated. Caution should be exercised in the clinic when considering the possible agents merely based on the symptom similarities between KD and other infectious diseases. Importantly, given that the recognition of the infectious origin of KD is a critical prerequisite to understanding its pathogenetic mechanism, more intense research using artificial intelligence, metagenomic sequencing and culturing specific pathogens isolated from KD patients from multiple centers and then verifying each of them in animal models could help uncover the underlying mechanisms of pathogen infections involved and thus facilitate the development of novel intervention strategies for Kawasaki disease.

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Author contributions

WW: Writing – original draft, Data curation. LZ: Conceptualization, Funding acquisition, Investigation, Writing – original draft. XL: Writing – original draft, Data curation, Project administration. ZL: Data curation, Resources, Writing – original draft. HL: Conceptualization, Investigation, Supervision, Writing – review & editing. GQ: Conceptualization, Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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