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A critical appraisal of the role of intracellular Ca^{2+}-signaling pathways in Kawasaki disease

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ABSTRACT

Kawasaki disease is a multi-systemic vasculitis that generally occurs in children and that can lead to coronary artery lesions. Recent studies showed that Kawasaki disease has an important genetic component. In this review, we discuss the single-nucleotide polymorphisms in the genes encoding proteins with a role in intracellular Ca^{2+} signaling: inositol 1,4,5-trisphosphate 3-kinase C, caspase-3, the store-operated Ca^{2+}-entry channel ORAI1, the type-3 inositol 1,4,5-trisphosphate receptor, the Na^+/Ca^{2+} exchanger 1, and phospholipase Cß4 and Cß1. An increase of the free cytosolic Ca^{2+} concentration is proposed to be a major factor in susceptibility to Kawasaki disease and disease outcome, but only for polymorphisms in the genes encoding the inositol 1,4,5-trisphosphate 3-kinase C and the Na^+/Ca^{2+} exchanger 1, the free cytosolic Ca^{2+} concentration was actually measured and shown to be increased. Excessive cytosolic Ca^{2+} signaling can result in hyperactive calcineurin in T cells with an overstimulated nuclear factor of activated T cells pathway, in hypersecretion of interleukin-1ß and tumor necrosis factor-α by monocytes/macrophages, in increased urotensin-2 signaling, and in an overactivation of vascular endothelial cells.

1. Introduction

Kawasaki disease (KD) was first described by the pediatrician Tomisaku Kawasaki in Japanese in 1967 and in English in 1974 [1,2]. KD occurs worldwide, but is especially frequent in Southeast Asia. The prevalence of KD in children younger than 5 years is the highest in Japan, followed by Korea and Taiwan. The incidence in Japan is 265/100,000 [3] and more than 1 in every 100 Japanese children will develop KD [4]. The incidence is 10–20 times higher than in Western countries. The incidence rate and the number of patients with KD are increasing steadily.

KD is an acute multi-systemic self-limited vasculitis of the small- and medium-sized arteries that predominantly occurs in infants and children under 5 years old. The disease is characterized in its acute phase by persistent high fever for at least 5 days and a multi-system inflammation with a polymorphous red skin rash, bilateral bulbar conjunctival congestion without discharge, diffuse oropharyngeal mucosal inflammation with a strawberry tongue and bright red fissured lips, bright red swollen hands and feet followed by desquamation beginning at the tips of the fingers and toes, and swollen cervical lymph nodes, which are characteristically located on one side [2,5]. The diagnosis is made according to clinical data, as no specific diagnostic laboratory tests are available [6]. KD then develops into a localized inflammation focused primarily at the coronary arteries, resulting in coronary artery dilatation, aneurysms, fistulas and stenosis, which in turn can lead to sudden death [5,7,8]. KD has replaced acute rheumatic fever as the leading cause of acquired pediatric heart disease in developed countries [4,9].

Many decades have passed since the discovery of this complex disease, but its exact etiology and pathophysiology remain unclear. The most recent hypothesis suggests that an environmental agent or a pathogenic microorganism triggers an abnormal innate and adaptive immune response in genetically susceptible individuals [8,10]. Although the seasonal pattern, the geographical localization and the symptomatology resembling common childhood infections suggest an infectious etiology, no causative infectious organism has been isolated so far from affected children [11,12]. KD depends on a heterogeneous interaction between various immune cells [13–15]. Macrophages and activated

Abbreviations: $[Ca^{2+}]_{cyt}$, free cytosolic Ca^{2+} concentration; CRAC, Ca^{2+}-release activated Ca^{2+} entry; EBV, Epstein-Barr virus; ER, endoplasmic reticulum; IP_3, inositol 1,4,5-trisphosphate; IP_4, inositol 1,3,4,5-tetrakisphosphate; IP_3R, IP_3 receptor; KD, Kawasaki disease; NCX, Na^+/Ca^{2+} exchanger; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding domain, leucine-rich-repeat-containing family, pyrin domain-containing 3; PMCA, plasma-membrane Ca^{2+}-ATPase; SERCA, sarco/endoplasmic-reticulum Ca^{2+}-ATPase; SNP, single-nucleotide polymorphism; SOCE, store-operated Ca^{2+} entry; STIM, stromal interaction molecule; TCR, T-cell receptor

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dendritic cells are present in close contact to T cells in the coronary arteritis lesions [16–18].

A single infusion of a high dose of intravenous immunoglobulins over a 12-hour period, combined with high doses of aspirin, is the standard treatment of KD [19–22]. The immunoglobulins decrease the rate of aneurysm formation from 25% to less than 5% [23,24]. Resistance to this therapy, defined as recrudescence of fever more than 36 h after intravenous immunoglobulin completion [25], continues to be a problem worldwide, and these patients need adjunctive therapies to reduce inflammation.

Abnormal cytosolic Ca^{2+} signaling plays a role in the development of multiple human diseases, including KD [26]. With the development of genome-wide association studies and linkage studies [27,28], glimpses of the genetic component of KD have been exposed. Some genetic aberrances occurring in KD patients are located in genes linked with Ca^{2+} signaling. In this review, we will provide a critical assessment of the role of Ca^{2+} signaling in the pathophysiology of KD. We will describe the relevant Ca^{2+}-signaling pathways in healthy cells, with a focus on T cells. We will then discuss the genetic susceptibility to KD involving Ca^{2+}-signaling pathways. We will end with some models of how dysfunctional Ca^{2+}-signaling pathways might cause KD and its complications.

2. Intracellular Ca^{2+} signaling in T cells

We will primarily discuss intracellular Ca^{2+} signaling in T cells, given the important role of this cell type in the pathogenesis of KD [16–18] and will mainly focus on those molecules of the Ca^{2+}-signaling toolkit that are thought to be important in the process.

Antigen binding to the T-cell receptor or ligation of chemokine receptors activates respectively phospholipase Cγ1 and phospholipase Cß [29]. These phospholipases hydrolyze phosphatidylinositol 4,5-bisphosphate in the plasma membrane to diacylglycerol and inositol 1,4,5-trisphosphate (IP_3). IP_3 diffuses in the cytosol and binds to and activates an IP_3 receptor (IP_3R). The IP_3Rs are Ca^{2+}-permeable ion channels localized predominantly in the endoplasmic-reticulum (ER) membrane and are encoded by a family of three genes (*ITPR1*, *ITPR2* and *ITPR3*). All three isoforms have been detected in T cells [30]. Their relative expression varies among T-cell subtypes and various physiological and pathological conditions. Binding of IP_3 to its receptor triggers the release of Ca^{2+} from the ER Ca^{2+} stores. This process only results in a short-lasting rise of the free cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$). A more long-lasting rise of the $[Ca^{2+}]_{cyt}$ requires the activation of a sustained influx of extracellular Ca^{2+} through activation of 'capacitative' or store-operated Ca^{2+} entry (SOCE). In T cells, the Ca^{2+}-release activated Ca^{2+} (CRAC) channels in the plasma membrane are the main SOCE channels. They can be formed by the 4-transmembrane domain-containing proteins ORAI1, ORAI2 and ORAI3, although quantitatively the latter two contribute much less to SOCE than the former. In T cells ORAI1 and ORAI2 are expressed at much higher levels than ORAI3 [31]. The depletion of the ER Ca^{2+} stores is the stimulus for the opening of the CRAC channels and the influx of extracellular Ca^{2+}. The reduction in the ER $[Ca^{2+}]$ is sensed by two transmembrane proteins located in the ER membrane, stromal interaction molecule (STIM) 1 and STIM2. Dissociation of Ca^{2+} from the luminal EF-hand domains of STIM1 and STIM2 results in conformational changes that enable them to bind to and open the ORAI channels in the plasma membrane [32,33]. Although both STIM1 and STIM2 promote SOCE into T cells [34], STIM2 activates Ca^{2+} influx upon smaller decreases in ER $[Ca^{2+}]$ and was proposed to be involved in a housekeeping feedback regulation to keep the basal $[Ca^{2+}]_{cyt}$ and the ER $[Ca^{2+}]$ within tight limits [35].

Two enzymatic pathways terminate IP_3 signaling. One involves hydrolysis of IP_3 by IP_3 5-phosphatase, which yields the inactive compound inositol 1,4-bisphosphate. Another enzymatic pathway involves IP_3 3-kinase which phosphorylates IP_3 to form inositol 1,3,4,5-tetrakisphosphate (IP_4), a compound that is unable to trigger intracellular Ca^{2+} mobilization. There are 3 isoforms of the latter enzyme encoded by 3 genes: *ITPKA*, *ITPKB* and *ITPKC* [36]. The C isoform was inducible in peripheral blood mononuclear cells and in leukemic cell lines by a phorbol ester and a Ca^{2+} ionophore [23]. The $[Ca^{2+}]_{cyt}$ returns to baseline due to both Ca^{2+} reuptake into the ER *via* the sarco/endoplasmic-reticulum Ca^{2+}-ATPase (SERCA) Ca^{2+} pumps and Ca^{2+} extrusion across the plasma membrane *via* the plasma-membrane Ca^{2+}-ATPase (PMCA) Ca^{2+} pumps [37]. The PMCA family comprises four members, two of which are expressed in T cells: PMCA1 and PMCA4 [38]. The Na^+/Ca^{2+} exchangers, of which 3 isoforms have been cloned in mammals (NCX1, NCX2 and NCX3) [39], seem to be unimportant for removing cytosolic Ca^{2+} from T cells [40,41].

Table 1
Susceptibility genes to KD having a link with intracellular Ca^{2+} signaling.

Candidate gene	Encoded protein	Function
ITPKC	IP_3 3-kinase C	Converts IP_3 into IP_4
CASP3	Caspase-3	Plays a central role in apoptosis Cleaves various proteins including NFAT1 and the type-1 IP_3R
ORAI1	SOCE channel ORAI1	Sets up influx of extracellular Ca^{2+} in conditions of a decreased $[Ca^{2+}]$ in the ER
ITPR3	Type-3 IP_3R	Releases Ca^{2+} from the ER
SLC8A1	Na^+/Ca^{2+} exchanger 1	Sets up influx of extracellular Ca^{2+} or removal of intracellular Ca^{2+} depending on the Na^+ and Ca^{2+} gradients
PLCB1/PLCB4	Phospholipase Cß1/4	Catalyzes the formation of IP_3 and diacylglycerol

3. Susceptibility genes to KD

A recent systemic review and meta-analysis revealed that 62 genes may be correlated with the susceptibility to KD, and that 47 genes may be associated with the incidence of coronary artery lesions [42]. Several functional single-nucleotide polymorphisms (SNPs) were discovered in genes that encode proteins linked to Ca^{2+} signaling (Table 1). These genes are discussed below.

3.1. ITPKC

The *ITPKC* gene encodes IP_3 3-kinase C. This enzyme terminates intracellular Ca^{2+} signaling by converting the Ca^{2+}-mobilizing second messenger IP_3 to IP_4.

The *ITPKC* gene is the first and probably the most important candidate gene predisposing to KD. Onouchi et al. [27] performed a genome-wide linkage study for KD and identified region 19q13 as a region where microsatellite alleles were shared more commonly than expected. They subsequently reported that the functional SNP rs28493229 in the *ITPKC* gene in that region was associated with an increased KD susceptibility and with subsequent development of coronary artery lesions [23]. SNP rs28493229 consistently associates with KD susceptibility and with coronary artery lesions across diverse ethnic/racial populations [42–47]. Some studies found no association between SNP rs28493229 and KD [48–52] but this could be attributed to the matching of the control group, to the lower frequency of the risk-conferring C allele in some populations, or to an insufficient sample size. Also other SNPs in the *ITPKC* gene have been reported. SNP rs2290692 was associated with susceptibility to KD and with coronary artery lesion formation in Han Chinese children [50] but not in Korean children [47]. SNP rs7251246 was associated with coronary artery lesion formation and therefore with the severity of KD [53].