Review

Immunophenotype of Kawasaki Disease: Insights into Pathogenesis and Treatment Response

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Review

Immunophenotype of Kawasaki Disease: Insights into Pathogenesis and Treatment Response

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Abstract: Kawasaki disease (KD) is a systematic inflammatory condition that results in vasculitis and possible progression to the development of coronary artery lesions if left untreated. Disease pathogenesis is not fully understood, and diagnosis is based on clinical symptoms, with limited reliability considering that KD progression is time sensitive. This is further complicated by the shared clinical characteristics with other febrile diseases. Early diagnosis and prompt treatment start are associated with good prognosis in most patients. However, up to 20% of patients are resistant to available therapeutic agents and would benefit from alternative regimens. Therefore, identification of biomarkers that can provide insights on disease pathogenesis are necessary to enable early diagnosis and initiation of treatment, as well as to predict treatment responses. To this end, immunophenotyping, most commonly by flow cytometry, has been crucial in identifying central factors in KD pathogenesis. The available literature on such factors is vast and may include contradictory findings. Therefore, we aimed to summarize the available literature of the last decade on the immunophenotype of KD, focusing on biomarkers associated with disease pathogenesis and those associated with treatment response. Our review highlights the role of cells of both the innate and adaptive immune system in disease pathogenesis, as well as the role of various secreted and cell surface proteins, including inflammatory cytokines, chemokines, complement receptors, and chemoattractants both in KD pathogenesis and in treatment response.

Keywords: biomarkers; immunity; adaptive; immunity; innate; immunophenotyping; intravenous immunoglobulins; kawasaki disease

1. Introduction

Kawasaki disease (KD) is a pediatric inflammatory disease affecting the blood vessels. The clinical characteristics of KD include fever, rash, mucocutaneous manifestations, lymphadenopathy, and elevated inflammatory parameters. Unfortunately, these features are common among several febrile illnesses in pediatric populations (e.g., measles, adenoviral infection, scarlet fever, dengue fever), thus complicating KD diagnosis [1].

The etiopathogenesis of KD remains unknown, although several factors have been considered since the first report of KD cases by Kawasaki in 1967, including infectious agents, genetic factors, and immune system anomalies [2,3]. The interplay of these factors leads to hyperactivation of the immune system, which ultimately contributes to vascular inflammation and damage. Generally, KD has a good prognosis, achieved with prompt treatment; however, coronary artery lesions (CALs), a severe complication of KD, may have fatal outcomes if left untreated [4].

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In the context of immune system hyperactivation, immunophenotyping has emerged as a pivotal tool for characterizing the cellular and molecular profiles associated with the disease and for aiding in diagnosis. Immunophenotyping—the detailed analysis of cellular and protein markers [5]—has provided critical insights into the roles of various immune and non-immune cells in KD. These include neutrophils, monocytes, T cells, B cells, endothelial cells, and platelets, each contributing uniquely to vascular inflammation and remodeling in KD [6]. These immune profiles are closely associated with the response to standard treatments, including intravenous immunoglobulin (IVIG) and corticosteroids, as well as that to newly developed therapies, including anti-cytokine biologics. Therefore, the utility of immunophenotyping extends beyond pathogenesis, offering valuable insights into treatment response. This is critical, considering that up to 20% of patients are resistant to IVIG [7], highlighting the need to develop markers for patient selection. To this end, immunophenotyping has helped identify biomarkers such as elevated interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) levels, which are associated with IVIG resistance [8] and may serve as targets for adjunctive therapies.

This comprehensive narrative review explores KD's immunophenotype in relation to its pathogenesis and treatment response, highlighting recent advances in our understanding of this enigmatic disease.

2. Literature Search

We performed a literature search in PUBMED, CENTRAL, Google Scholar, and Science Direct for articles in English published between 31-01-2014 and 31-01-2025 using the following search terms or their variants: Kawasaki disease, immunophenotype, innate immunity, adaptive immunity, cytokines, chemokines, biomarkers, pathogenesis, treatment response, IVIG, biologics. Most study types were included apart from case reports, editorials, and letters to the editor. Articles were selected initially based on the presence of the keywords in the title and/or abstract. The selected articles were then screened for content relevant to the topic of the review. Studies reporting findings on cell-surface proteins and proteins secreted from immune cells were included since these are mainly tested by immunophenotyping methods. Studies were excluded if they reported findings on other cell types or other proteins involved in KD, gene polymorphisms or gene expression analyses (as immunophenotyping does not test for these). Animal studies and in vitro studies were also excluded.

Information on immunophenotyping relevant to KD pathogenesis and prediction of treatment response was extracted manually from the selected publications. If pertinent information was detected in a review article, the source article was used to extract further details. Since this was a narrative review, no statistical analysis was performed, and the extracted data were synthesized in a qualitative/narrative manner.

3. Immunophenotyping Kawasaki Disease: Insights for Disease Pathogenesis

Although KD pathogenesis is complex and governed by many factors, immunophenotyping studies have helped elucidate key mechanisms involved in the acute and subacute phases of KD.

3.1. Cellular Mechanisms

3.1.1. Innate Immunity

The innate immune system, including neutrophils, monocytes, macrophages, and dendritic cells, is heavily implicated in the early stages of KD, with increased proportions of all innate cell types compared with the corresponding numbers in healthy samples [9]. These changes are restored in convalescent KD samples. The innate immune system is also critical for the development of coronary vasculitis in patients with KD [10].

Acute KD is characterized by infiltration of neutrophils in coronary arteries, contributing to the damage of the blood vessels through the release of reactive oxygen species (ROS) and proteolytic enzymes. Hu et al. showed that the rate of neutrophil activation is higher in patients with KD than in

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healthy controls and higher in patients with KD complicated by CALs [11]. The same group also demonstrated that children with KD have higher levels of the brain natriuretic peptide, an essential modulator of neutrophil activation that regulates ROS production [11]. Further, the neutrophil-to-lymphocyte ratio has been demonstrated as a diagnostic marker for predicting CAL formation [12].

Another characteristic of acute KD is the increased infiltration of circulating monocytes and macrophages into coronary arteries, which is associated with cytokine production, thus promoting inflammation. Moreover, Furukawa et al. reported more CD14+ macrophages in KD patients with coronary artery abnormalities (CAAs), suggesting that the number of CD14+ monocytes may serve as a marker of KD severity [13].

Contradictory findings have been reported for dendritic cells (DCs) in KD. Takahashi and Suda et al. showed fewer circulating myeloid DCs (mDCs) in acute KD, and Wang et al reported fewer numbers of both mDCs and plasmacytoid DCs (pDCs). In contrast, Burns et al. found increased circulating mDCs, but not pDCs, in acute KD [14–17]. Moreover, Yilmaz et al. showed significantly more mDCs in the CALs of patients with KD than in controls [18]. In contrast, no differences in DC subsets were reported by Wang et al. between patients with CALs and those without [17]. Such conflicting findings may result from the different markers used for classifying DCs. Although contradictory, these findings suggest abnormal numbers of DCs in patients with KD and a potential shift of circulating DCs toward the affected arteries where they may enhance T-cell activation, thus promoting coronary arteritis in KD.

A characteristic finding of the subacute phase of KD is thrombocytosis, as indicated by increased platelet counts (>500,000/mm^3) [19]. The occurrence of thrombocytosis is positively correlated with poor outcomes in patients with KD [20]. Furthermore, Park and Choi reported that higher platelet count is associated with longer fever duration and the length of admission of these patients [20]. Ueno et al. demonstrated that the rate of platelet-neutrophil aggregate formation is significantly higher in patients with KD than in those with bacterial infection and normal volunteers [21]. This rate was also significantly higher in patients with CAA than in those without. The authors also reported a trend toward higher rates shortly after IVIG administration than those before, as well as non-significantly higher rates in IVIG non-responders than in responders [21]. Monocyte-platelet aggregates (MPA) were also higher in KD than in febrile and healthy control samples. Importantly, the levels of MPAs remained high even 3 months after KD diagnosis, suggesting that activated platelets remain long after inflammation has decreased [22].

3.1.2. Adaptive Immunity

Cells of the adaptive immune system are also affected in acute KD. Brogan et al. found fewer CD8 T cells in the circulation, while Brown et al. reported more CD8 T cells aggregated in coronary arteries [23,24]. Ehara et al. demonstrated an increase in CD69$^+$ CD8 T cells [25], Wang et al. showed an upregulation of T helper cell type 1 (Th1) and Th2 cells [26]. Jia et al. indicated increased numbers of Th17 cells and decreased numbers of T regulatory cells (Tregs) in acute KD [27]. Consistently, retinoic acid receptor-related orphan receptor gt (RORgt), a Th17 transcription factor, was found to be significantly upregulated in acute KD [27,28], whereas Treg factors such as forkhead box P3 (FoxP3), glucocorticoid-induced TNF receptor family-related protein (GITR), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) were significantly decreased in acute KD [27,29]. The increased number of Th17 cells has been associated with the induction of inflammation, a characteristic of KD, further enhanced by the downregulation of Tregs [28]. In their study, Guo et al. found that while patients with KD had higher levels of Th17 cells, they had lower percentages of CD4$^+$ T cells [30]. In agreement, Wang et al showed fewer peripheral CD4+ T cells in patients with KD than in healthy subjects [17]. In contrast, Ding et al. reported more CD4+ T cells in the KD group than in healthy controls but found fewer circulating CD3 and CD8 T cells in patients with KD than in febrile and healthy controls, as well as fewer CD16 and CD56 cells (natural killer [NK] cells) in both the KD and febrile groups than in the healthy control group [31]. The authors also demonstrated that different lymphocyte subsets could discriminate between complete and incomplete KD [31].

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Increased numbers of B cells (CD19+) have also been reported in KD relative to those in healthy controls [31]. This increase might be driven by a specific B-cell subset, CD19+CD27^{high} peripheral blood antibody-secreting B cells, suggesting its role in KD development [32]. Variations in subsets of antibody-secreting cells and memory B cells were also associated with KD pathogenesis, although the exact contribution of these cells is not known as variable results were obtained in terms of their correlation with laboratory findings [33].

Circulating follicular helper T (cTfh) cells have also been implicated in the pathogenesis of KD [34,35]. Although the total number of these cells does not seem to differ between control subjects and those with acute KD or KD in remission, Xu et al. reported variations in the percentage of subsets of these cells. Specifically, the percentages of ICOS^{high}PD-1^{high}, ICOS^{+}PD-1^{+}, ICOS^{-}PD-1^{+}, and CD45RA^{-}IL-21^{+} cTfh cells were significantly elevated in the acute phase of KD [34]. The authors hypothesized that the increase in these subsets, and specifically in ICOS^{high}PD-1^{high} cells, represents the activation of cTfh cells in KD, which seems to be maintained in the remission phase. In a second study, they showed altered numbers of two other cTfh subsets (more CXCR3^{+} CCR6^{-} and fewer CXCR3^{-}CCR6^{-} cells) in patients with KD and in those with CALs [35]. The involvement of these different subsets of cTfh cells in KD may be mediated by their secreted cytokines.

Collectively, the abnormal composition of the adaptive immune system promotes inflammation, which results in the vasculitis observed in patients with KD [30,36].

3.2. Secreted Proteins

The identified proteins secreted by immune cells that showed significant changes in KD or after treatment are listed in Table 1.

Table 1. Serum biomarkers for KD pathogenesis and treatment response.

Marker	Role in KD		Change at specific KD phase or after treatment[a]	References
	Pathogenesis	Treatment response		
Cytokines				
IL-1β	Y	Y	Serum levels: KD + CALs >> KD no CALs >> febrile and healthy controls ↓↓ after IVIG	[78,98]
IL-2 receptor	Y	Y	Serum levels: KD >> controls or reference range ↓↓ after IVIG	[99]
IL-6	Y	Y	Serum levels ↑ in KD, ↑ in acute KD KD + CALs >> KD no CALs	[29,30,38,39,40,84,88,98, 100,101]
			↓↓ after IVIG, plasma exchange, infliximab, or anakinra	[26,29,39,45,84,101,102]
IL-8	Y	-	↑ in acute KD, KD >> MIS-C >> healthy controls	[103]
IL-10	Y	Y	↑ in KD, ↑ in IVIG-resistant KD patients. ↓↓ after IVIG or anakinra	[26,88,98,101]
IL-17	Y	Y	KD >> febrile and healthy controls	[30,46,47,98,104]
			↓↓ after plasma exchange and gradually after IVIG	[30,45]
IL-18	Y	Y	KD >> healthy controls Associated with CAL.	[49,50]
			↓↓ after IVIG	[105]
Il-23	Y	-	KD + CALs >> KD no CALs >> infectious disease and healthy controls	[27]
IL-27	Y	-	Serum levels: KD + CALs >> KD no CALs >> healthy controls	[98]
IL-31	Y	Y	Serum levels KD >> febrile and healthy controls Significantly associated with CALs	[30,47]
			↑↑ after IVIG	[47]

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Marker	Role in KD		Change at specific KD phase or after treatment[a]	References
	Pathogenesis	Treatment response		
IL-33	Y	Y	Acute KD >> healthy controls; KD << febrile controls ↓↓ after IVIG	[106,107]
IL-35	Y	-	KD << febrile and healthy controls KD + CAL << no CAL	[52]
			KD >> healthy controls	[22]
IL-37	Y	-	KD << febrile and healthy controls	[53]
IFN-γ	Y	Y	KD + KDSS >> KD >> MIS-C >> healthy controls ↓↓ after IVIG	[26,40,103]
TNF-α	Y	Y	Acute KD >> healthy controls ↑↑ KD + CALs	[26,50,86]
			↓↓ after plasma exchange and infliximab treatment. ↓↓ after IVIG in KD patients without CALs and in IVIG responders ↑ after IVIG in KD patients with CALs and in IVIG-resistant patients; predictor of IVIG-resistance	[26,45,86,88,102]
Soluble TNFR1 and TNFR2	Y	Y	Acute >> subacute KD TNFR2 and TNFR1/2 ratio: KD + CALs >> no CALs ↓↓ after plasma exchange and infliximab treatment TNFR1 remains high in infliximab-resistant patients.	[45,102,108,109]
G-CSF	Y	Y	KD >> MIS-C >> healthy controls ↓↓ after plasma exchange, infliximab, and IVIG treatment Remains high in infliximab-resistant patients	[45,78,102,103]
sCD40L	Y	-	KD >> febrile controls	[107]
IP-10	Y	Y	↑ in KD ↓ after infliximab treatment	[102]
TGF-β	Y	-	↑ in acute KD >> infectious disease and healthy controls	[27]
Complement receptors				
CD11b	Y	Y	Mean CD11b ↓ in KD before and after IVIG	[110,111]
CD59	Y	-	subacute KD << acute KD KD + CAL << no CAL	[58,59]
Chemokines and cell adhesion molecules				
CXCL9 and CXCL10	Y	Y	Both ↑ in acute KD; CXCL9: KD + CAL >> no CAL ↓↓ after IVIG CXCL10: ↓↓ after anakinra treatment	[54,55,101,107]
MCP-1 (CCL2)	Y	Y	↑ in acute KD ↓↓ after IVIG	[55]
CCL5	Y	-	↑ in acute KD, KD >> healthy controls	[103]
Eotaxin (CCL11)	Y	Y	↑ in acute KD ↓↓ after IVIG	[55]
CCL17	Y	Y	KD >> healthy controls; KD + CAL >> no CAL	[55]
			↓↓ after IVIG	[112]
Semaphorin 7A	Y	-	Serum levels ↑ in KD	[57]
Semaphorin 4D	Y	-	Serum levels ↑ in acute KD and in patients with CALs ↓ in convalescent phase	[56]
P-Selectin (CD62P)	Y	-	2~3 fold higher expression in KD platelets than in healthy platelets	[113]

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Marker	Role in KD		Change at specific KD phase or after treatment[a]	References
	Pathogenesis	Treatment response		
Other				
VEGF (angiogenic factor)	Y	-	KD + CALs >> no CALs	[65]
CD84 (Signaling lymphocyte activation molecule)	Y	-	Robust expression in inflammatory cells in arterial walls in 6/7 acute and 4/5 chronic cases.	[65]
CRP	Y	Y	↑ in KD + CAL Level >100 mg/L at diagnosis is an independent risk factor of IVIG resistance.	[7,64]
Fcγ receptors	Y	Y	FcγRIII and FcγRIIa levels: KD >> controls	[67]
			FcγRIIb: KD << controls; KD + CALs << no CALs	[67]
			FcγRI (CD64): ↑↑ expression on neutrophils and monocytes at the onset of KD flare-ups. ↓↓ after IVIG	[66]
LILRs/ILTs (receptors involved in immune regulation)	Y	Y	LILRB4 (ILT3/LIR-5/CD85k):↑ in acute KD, expressed uniquely on antibody-secreting B cells; ↓ after IVIG LILRB1 (ILT2/CD85j): ↑ in acute KD and after IVIG in naïve and memory B cells, antibody-secreting cells, and monocytes.	[32]
HLA-DR (MHC molecule)	-	Y	↑ in IVIG-resistant KD patients.	[90]
LAIR-1 (receptor involved in immune regulation)	Y	-	Significantly increased in KD >> healthy controls; KD + CAL >> no CAL	[69]
YKL-40 (endothelial marker)	Y	-	Acute KD >> disease and healthy controls	[68]
S100A12 (calcium-binding protein)	Y	Y	↑↑ in acute KD KD + CAL >> no CAL ↓↓ after IVIG, no change in non-responsive patients ↓↓ after anakinra treatment	[72,101]
PAF (phospholipid mediator)	Y	-	Acute KD >> febrile and healthy controls KD + CAL >> no CAL	[74]
Activin receptor IIA	Y	-	Increased expression on CD8+ T cells and CD19+ B cells in KD.	[70]
Cathelicidin (LL-37) (anti-microbial peptide)		-	KD >> pneumonia and healthy controls	[114]

[a] Only significant changes are shown. Abbreviations: CAL, coronary artery lesion; CCL, C-C motif chemokine ligand; CRP, C-reactive protein; CXCL, CXC motif chemokine ligand; FB, complement factor B; Fc, fragment crystallizable; FcγR, Fc gamma receptor; G-CSF, granulocyte colony-stimulating factor; HLA-DR, human leukocyte antigen-DR; IFN-γ, interferon gamma; IL, interleukin; ILT, immunoglobulin-like transcript; IP-10, interferon gamma-induced protein 10; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; LAIR, leukocyte-associated Ig-like receptor-1; LILR, leukocyte Ig-like receptor; MCP-1, monocyte chemoattractant protein-1; MHC, major histocompatibility complex; MIS-C, multisystem inflammatory syndrome in children PAF, platelet-activating factor; sCD40L, soluble CD40 ligand; S100A12, S100 calcium-binding protein A12; TGF-β, transforming growth factor beta; Th, T helper; TNF-α, tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor; VEGF, vascular endothelial growth factor.

3.2.1. Inflammatory Cytokines

The inflammatory nature of KD is associated with a significant increase in cytokine and chemokine profiles. This is mainly due to changes in the composition of cells of the immune system.

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A common finding in patients with KD compared with healthy controls is a significant increase in inflammatory cytokines, playing a major role in KD pathogenesis [37].

Among inflammatory cytokines, IL-6 is identified as an important player in KD pathogenesis. Several studies have reported significantly increased IL-6 levels in different phases of KD. At least 20 times higher levels were reported in patients with KD than in healthy controls [38], and about 5 times higher levels were found in the acute phase versus the subacute phase of KD [39]. Moreover, it was shown to be a possible marker to differentiate between incomplete and complete KD [39]. IL-6 levels have also been linked with KD complications, being much higher in patients with Kawasaki disease shock syndrome (KDSS) and in those with CALs than in patients without such complications [26,40]. The proposed mechanism of the IL-6-mediated damage in KD involves the maturation of megakaryocytes, resulting in thrombocytosis, as well as the initiation of a series of events that leads to the production of polyclonal B-cell autoantibodies, resulting in acute inflammation and antibody-mediated endothelial damage, eventually causing vasculitis [37].

Another key cytokine in the pathogenesis of KD is TNF-α, which is also significantly elevated in the acute phase of KD, as well as in patients who develop CALs [41]. The action of TNF-α in KD is closely linked with its soluble receptors, TNFR1 and TNFR2. Through these receptors, TNF-α causes metalloproteinase 9 upregulation, which results in elastin breakdown and aneurysms in the vascular walls [42]. This has been inferred to be one of the contributing mechanisms of CAL formation in KD and supported by significantly higher levels of TNF-α in KD patients with CAL [43]. However, TNF-α has a pleiotropic effect in KD, with mechanisms involving leukocyte recruitment to target sites, modulation of the levels of other cytokines, as well as regulation of cell death [44]. The levels of TNFR1 and TNFR2 were shown to be significantly decreased after treatment with plasma exchange [45].

Other inflammatory cytokines with significantly higher levels in patients with KD than in healthy controls include IL-1b, produced mainly by macrophages but also by neutrophils, epithelial cells, and endothelial cells; IL-17, secreted by Th17 cells; IL-10, produced by various subsets of immune cells, including CD4+ T cells, follicular and extra-follicular T cells, and extrafollicular B cells; IL-18, produced by both hematopoietic and non-hematopoietic cells, including monocytes, macrophages, keratinocytes, and mesenchymal cells; IL-27, produced by activated antigen-presenting cells, such as macrophages and DCs; IL-31, produced by the Th2 cells; interferon gamma (IFN-γ), secreted by activated T cells and NK cells; and IL-33, produced by damaged epithelial cells, macrophages, and DCs (Table 1).

Some of these cytokines (IL-17, IL-18, IL-31, IL-10, IFN-γ) were also significantly elevated upon KD complications, including CALs, KDSS, and macrophage activation syndrome (MAS). IL-6 levels above 66.7 pg/mL, IL-10 above 20.85 pg/mL, and IFN-γ above 8.35 pg/mL were shown to pose a higher risk for developing KDSS [40]. Both IL-17 and IL-31 were found to be highly elevated in patients with CALs [49,50]. IL-17 was also found to be positively correlated with the coronary artery z-score, indicating that the higher levels predispose patients to the formation of CALs or aneurysms [46]. IL-18 was found to intensify coronary arteritis in KD [48] and to be a significant risk factor, as well as the best predictor, for CAL formation in KD compared to other biomarkers such as IL-17 and TNF-α [49]. Moreover, IL-18 levels were significantly elevated in patients with KD and MAS than in febrile controls [50,51]. Both IL-10 and IFN-γ were shown to be increased in patients with KDSS [40].

While consistent results have been reported in KD for the above-mentioned cytokines, contradictory findings are available in the literature regarding IL-35, an anti-inflammatory cytokine. One study showed decreased IL-35 levels in patients with KD and in those who developed CALs compared with controls (KD: 15.07±1.37 vs febrile control: 24.96±2.98, healthy control: 28.86±4.92 pg/mL; KD+CAL: 11.79±1.42 vs KD no CAL: 17.64±2.10 pg/mL) [52], whereas a more recent study reported robustly increased levels in KD as compared to healthy controls (2792±896.7 vs 1345±401.7 pg/mL) [22]. The notable difference in the measured levels of IL-35 in the two studies (possibly due to using different detection kits), as well as differences in the study samples might explain this discrepancy. IL-35 is produced by CD4+ Treg cells, activated DCs, macrophages, endothelial cells,

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and aortic smooth muscle cells, and is suggested to exert immunosuppressive effects and to decrease the risk of progression of inflammatory and autoimmune diseases. The authors who reported reduced levels in KD and in patients with CAL suggested a protective role for this cytokine by inhibiting inflammatory processes, thus further preventing CAL formation [52]. Despite reporting the opposite result in KD patients, the authors of other study reached the same conclusion by conducting several in vitro experiments where IL-35 suppressed activation of CD14+ monocytes. Further studies are required to decipher the exact mechanism by which IL-35 may participate in KD [22]. Evidence on another anti-inflammatory cytokine, IL-37, which was found to be lower in the serum of patients with KD, corroborate a protective role of anti-inflammatory cytokines in KD progression, also indicated by a series of in vitro experiments [53].

3.2.2. Chemokines and Cell Adhesion Molecules

A crucial aspect of KD pathogenesis is the infiltration of blood vessels by immune cells. This process in KD, but also in other vascular diseases, is mediated by chemokines and cell adhesion molecules. The levels of several chemokines, including CXCL9, CXCL10, CCL17, CCL11 (eotaxin), and monocyte chemoattractant protein-1 (MCP-1), were shown to be increased in the acute phase of KD, and those of CXCL9, CXCL10, and CCL17 were also higher in patients who developed CALs than in those who did not [54,55].

The circulating levels of the cell adhesion molecules semaphorin 7A and semaphorin 4D were also significantly elevated in KD, with semaphorin 4D also being elevated in patients with CALs [56,57]. As a transmembrane protein, semaphorin 7A is expressed on activated T cells, while semaphorin 4D is expressed on various immune cell types, including T cells, B cells, neutrophils, monocytes/macrophages, and platelets. When these molecules are cleaved from the cell surface, their soluble forms can activate the respective receptors expressed on different cell types. Semaphorin 4D was found to exert pro-inflammatory effects via its receptor plexin B in various inflammatory diseases. In KD, it was found to be cleaved by ADAM17 specifically from the surface of neutrophils and to induce the secretion of proinflammatory cytokines from endothelial cells [56], suggesting a role in KD pathogenesis and CAL formation.

3.2.3. Complement Factors

The damage to endothelial cells in KD results in systemic vasculitis or aneurysms in coronary arteries. Complement factors produced by vascular endothelial cells are important mediators of the inflammatory response, and the levels of several complement factors are lower in patients with KD than in healthy controls, possibly contributing to the dysregulated immune response in these patients [58,59]. Our literature search showed that the complement receptor CD11b, expressed in monocyte/macrophages, granulocytes, and NK cells, was also significantly decreased in patients with KD. Although no differences were noted in the levels of CD59, expressed on monocytes (among other cell types), between KD and healthy control or febrile control samples, increased levels were detected in the acute phase of KD versus the subacute one [58]. This finding warrants further investigation as the role of CD59 is to prevent the formation of the membrane attack complex of the complement system [60], and hence higher levels would be expected in the subacute rather than the acute phase of KD.

3.2.2. Other

C-reactive protein (CRP) is an acute-phase reactant protein that is released by peripheral blood mononuclear cells as a result of inflammation. Its secretion is induced by IL-6 and its effect is maintained by IL-1 [61]. In KD, CRP levels are significantly elevated compared with those in febrile controls [62]. CRP levels are also higher in patients with CALs than in those without [63,64]. Despite these findings, the mechanism of CRP in KD pathogenesis and CAL development is yet to be elucidated.

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CD84, expressed on T and B cells but also on various other leukocytes, including monocytes/macrophages, granulocytes, DCs, and mast cells, was found to be robustly expressed on inflammatory cells in the arterial walls of patients with KD. Its mRNA levels were also significantly higher in these patients than in healthy controls [65].

The activating Fcγ receptors (FcγR) I, III, and IIa, expressed on various immune cell types, were also highly expressed in KD samples versus controls. FcγRI (CD64) expression was specifically increased on neutrophils and monocytes at the onset of KD flare-ups, indicating a possible role in KD pathogenesis [66]. In contrast, the inhibitory FcγRIIb was found to be lower in patients with KD and also lower in those who developed CALs [67], suggesting a protective role in patients at risk of developing CALs..

Chitinase-3-like protein 1, also known as YKL-40, is a glycoprotein secreted from activated neutrophils and macrophages in different tissues as a result of inflammation. YLK-40 levels were found to be elevated in KD, specifically in the acute phase and remained high in the subacute phase, compared to those in healthy controls [68], suggesting YLK-40 may be a useful marker of KD activity.

Abnormal expression levels were reported for leukocyte-associated Ig-like receptor-1 (LAIR-1), which was found to be increased on neutrophils but decreased on CD4+ and CD8+ T lymphocytes of patients with KD. High neutrophil expression was also found in patients with CALs. IVIG treatment reversed this expression profile. Soluble LAIR-1 levels were elevated in the KD and KD-CAL groups compared with those in the healthy control and no CAL groups [69]. These findings suggest that LAIR-1 might be implicated in KD pathogenesis and CAL formation, while its soluble form might be useful as a biomarker for KD and CALs. Another receptor, activin type IIA receptor (ActRIIA), was found to be increased on the surface of CD8+ T cells, CD19+ B cells, and CD14+ monocytes in the acute phase of KD, whereas the serum levels of its ligand, activin A, were found to be decreased [70,71]. Activin A is synthesized and secreted by various immune cells such as T cells, B cells, monocytes, dendritic cells, and mast cells and was shown to inhibit ActRIIA expression on monocytes in KD [71]. Collectively, these findings suggest the overactivation of the above cell types in KD, contributing to disease pathogenesis, and further propose a possible protective role of activin A, which can be exploited when considering new treatments for KD.

Circulating neutrophils secrete S100A12 in the early stages of KD. Accordingly, serum levels of S100A12, as well as those of related molecules S100A8 and A8, were found to be elevated in acute KD. Serum S100A12 levels were also higher in patients with CALs than in those without. S100A12 was shown to activate monocytes and trigger the production of IL-1b, which in turn activates endothelial cells of the coronary artery, thus contributing to KD pathogenesis [72].

The levels of platelet-activating factor (PAF) were found to be significantly higher in KD samples than in healthy or febrile control samples. PAF is a potent proinflammatory molecule produced by various cell types, including macrophages, monocytes, and neutrophils, and can activate endothelial cells, neutrophils, and monocytes, leading to their adherence and migration. Moreover, activation of PAF receptors on monocytes leads to increased secretion of MCP-1 and TNF-α [73]. Collectively, these results suggest a role of PAF in KD pathogenesis. Further, PAF serum levels over 225.52 ng/mL were proposed to be a significant risk factor for CAL formation in patients with KD [74].

4. Immunophenotype and Response to Treatment

4.1. Response to IVIG Treatment

The standard treatment of KD mainly consists of IVIG combined with high-dose aspirin [75]. This regimen decreases fever and inflammation and reduces the risk of CAL development [76]. However, some KD patients develop resistance to IVIG, and thus, other adjunctive therapies including corticosteroids have been developed and are added to the standard dose [76]. The cause of IVIG resistance remains unclear, although certain clinical features and laboratory parameters, as well as gene polymorphisms, have been implicated in the process [77]. The mechanism by which IVIG

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aids in KD resolution is not entirely elucidated but it involves changes in the immune cell repertoire, which, in turn, affect the cytokine and chemokine profiles in KD patients [16].

Neutrophils and neutrophil lineage cells were shown to be massively reduced in the subacute phase of KD after treatment with IVIG, whereas the numbers of monocytes and eosinophils remained unchanged [78]. IVIG treatment also induced a more than 90% reduction in the numbers of IL-1β-expressing neutrophils in the circulation, as well as a significant reduction in the levels of IL-1β produced by neutrophils, whereas it did not seem to significantly alter the numbers of other IL-1β-expressing populations. Importantly, IVIG seemed to target the mature IL-1β-producing neutrophils and not neutrophil progenitors [78].

CD14+ CD16+ monocytes, which are elevated in the acute stage of KD, were significantly reduced after IVIG treatment [79]. Moreover, Kim et al. showed that this monocyte subpopulation, also termed "intermediate" monocytes, was significantly lower in IVIG-resistant patients than in IVIG-responsive patients before IVIG treatment [80].

Regarding the T lymphocyte population, increased CD69-positive CD8 T cells in acute KD were proposed both as a marker of disease progression and of IVIG response [25]. The number of CD4 T cells expressing human leukocyte antigen – DR isotype (HLA-DR) increased significantly after IVIG in both responsive and resistant patients, whereas that of HLA-DR-positive CD8 T cells, which was low before IVIG, significantly increased after treatment in IVIG-resistant patients but not in responsive patients in whom it remained the same [79]. Different lymphocyte subsets were reported to be able to discriminate between IVIG-responsive and non-responsive patients [31]. Combination of IVIG plus corticosteroids led to a more efficient increase in CD3+, CD4+, and CD4+/CD8+ T cell subsets ($p < 0.05$), and a more efficient decrease in CD8+ T cells [81].

IVIG infusion in patients with KD was further shown to increase the frequency of Tregs and the activation of the immunoregulatory $CD56^{high}$ NK cells and CD56+ T cells, whereas it reduced the frequency of CD107a-positive, $CD56^{low}$ cytotoxic NK cells. Moreover, it increased the proportion of $CD56^{high}$ NK cells expressing the activating receptor CD336 [82]. Reduced numbers of Th17 cells were observed in KD patients who received IVIG combined with aspirin [28].

Besides changes in the immune cell repertoire, different cytokine profiles have been associated with differences in the response to IVIG treatment. Kong et al. investigated the biomarkers of IVIG resistance and found that IL-6 levels were significantly higher in patients with IVIG-resistant than in those with IVIG-responsive KD [83]. Persistently high levels of IL-6 post-IVIG were also associated with the formation of CALs after IVIG therapy. In another study, Wu et al. found that although IL-6 was significantly elevated in the acute phase of KD, it returned to normal levels after IVIG therapy [39]. The study further found that IL-6 levels were positively correlated with CRP levels, which in turn were significantly reduced after IVIG therapy [39]. Zandstra et al. also showed significantly reduced CRP levels after IVIG [62]. Across different studies, however, high levels of IL-6 and CRP pre- and post-IVIG have been associated with the development of IVIG non-responsiveness [39,84]. Specifically for CRP, levels higher than 100 mg/L were shown to be an independent risk factor of IVIG resistance [7]. Moreover, the ratio of CRP to albumin was shown to be an independent risk factor for IVIG resistance [85].

Kong et al. did not find any significant difference in the levels of IL-2, IL-4, IL-2, IL-10, TNF-α, and IFN-γ between IVIG-responsive and IVIG-resistant patients [83]. In contrast, Hu et al. found increased TNF-α levels in patients who were unresponsive to IVIG therapy [86]. In another study, the levels of IFN-γ and TNF-α were found to be significantly higher in IVIG-responsive patients than in IVIG-resistant ones [87]. Higher levels of IFN-γ were also confirmed as an independent predictor of IVIG-resistance in KD by one more study [88]. In IVIG-responsive patients, Zhang et al. found that IVIG treatment resulted in a significant reduction in the levels of IL-10, with older children showing better changes than younger ones [89].

Increased levels of T-cell HLA-DR expression were reported to be associated with IVIG resistance in patients with KD [90]. The high levels of CD64 (Fcγ receptor I) were also significantly

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decreased after IVIG [66], and IVIG therapy was efficient in restoring the levels of abnormally expressed chemokines in KD patients (Table 1).

4.2. Response to Other Treatments

The elevated levels of inflammatory cytokines have prompted the discovery of targeted therapies to overcome cases of IVIG resistance in patients with KD. Such anti-cytokine therapies include the TNF inhibitors infliximab and etanercept, the IL-6 receptor inhibitor tocilizumab, and the IL-1 receptor antagonist anakinra, all of which have shown promising results in IVIG-refractory KD [16,91–93]. A previous systematic review and meta-analysis reported reduced frequency of treatment resistance when using anti-cytokine biologics, although these did not seem to be as effective in reducing the risk for CAL formation in KD patients [94]. Severe KD that is resistant to IVIG may also benefit from plasma exchange therapy [95].

Our review revealed a limited number of studies for these therapies. Infliximab therapy was shown to increase the frequency of Tregs in KD patients, as well as the number of Th17 cells [96]. In patients who underwent plasma exchange, however, no significant difference was observed in Th17 cell numbers [97]. Both infliximab and plasma exchange significantly reduced the numbers of CD14+ CD16+ monocytes [96,97]. Anakinra treatment was shown to reduce the levels of most serum inflammatory markers in patients with IVIG-resistant KD, with changes being more pronounced for IL-6, IL-10, CXCL10, and S100A12 [93]. Further studies are needed to identify how these treatments may affect KD immunophenotype and the mechanisms underlying their positive effects for patients.

5. Conclusions

We aimed to summarize the immunophenotype of KD focusing on pathogenesis and treatment response. Our review highlights the hyper-activation of the immune system, with altered frequencies of both innate and adaptive immune cells, elevated levels of pro-inflammatory serum cytokines such as IL-6 and TNF-α, and reduced levels of anti-inflammatory cytokines such as IL-35 and Il-37, as well as the role of several other inflammatory molecules in KD pathogenesis. Although IVIG treatment is shown to restore many of these changes, the abnormal levels of certain cells and factors persist in IVIG-resistant patients. Therapy with other agents, including anti-cytokine biologics and corticosteroids, seems to be beneficial in limited aspects of KD pathophysiology but may aid in reducing IVIG resistance. Overall, our study provides a comprehensive overview of the available literature on the immunophenotype of KD, pinpointing certain gaps and conflicting results that deem further research.

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Abbreviations

The following abbreviations are used in this manuscript:

ADAM17	A disintegrin and metalloproteinase 17
ActRIIA	activin type IIA receptor
CAA	coronary artery abnormalities
CAL	coronary artery lesions
CCL	C-C motif ligand

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CCR	C-C chemokine receptor
CRP	C-reactive protein
cTfh	circulating follicular helper T
CTLA-4	cytotoxic T-lymphocyte associated protein 4
CXCL	CXC chemokine ligand
CXCR	CXC chemokine receptor
DC	dendritic cell
FcγR	Fcγ receptor
FoxP3	forkhead box P3
GITR	glucocorticoid-induced TNF receptor family-related protein
HLA-DR	human leukocyte antigen-DR isotype
ICOS	inducible costimulatory
IFN-γ	interferon gamma
IL	Interleukin
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
KDSS	Kawasaki disease shock syndrome
LAIR-1	leukocyte-associated Ig-like receptor-1
MAS	macrophage activation syndrome
MCP-1	monocyte chemoattractant protein-1
mDC	myeloid dendritic cell
MPA	monocyte-platelet aggregates
NK	natural killer
PAF	platelet-activating factor
PD-1	programmed cell death protein 1
pDC	plasmacytoid dendritic cell
RORgt	retinoic acid receptor-related orphan receptor gt
ROS	reactive oxygen species
Th1/2	T helper cell type ½
TNF-α	tumor necrosis factor α
Treg	T regulatory cell

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