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Review

Whole Transcriptome Insight into Kawasaki Disease

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Abstract

Kawasaki disease (KD) is an acute pediatric vasculitis and the leading cause of acquired heart disease in children, with coronary artery aneurysm representing its most serious complication. Despite decades of investigation, the molecular mechanisms underlying the disease onset remain incompletely defined, and clinically reliable biomarkers for accurate diagnosis and prognostic stratification have yet to be established. In recent years, transcriptomic analysis has emerged as systems-level strategy for elucidating disease pathobiology and advancing biomarker and therapeutic target discovery, and has been increasingly applied to complex immune-mediated disorders such as KD. Whole-blood gene expression studies in KD have demonstrated reproducible perturbations in innate immune and cytokine-related pathways, whereas tissue-level and single-cell analyses have provided additional insights into coronary artery inflammation and immune cell dynamics. Transcriptomic studies in KD are limited by cohort heterogeneity and technical variability. To address these challenges, integrative approaches such as cross-cohort meta-analysis and multi-omics validation have been adopted to improve robustness and enhance the reliability of findings. These integrative efforts hold promise for advancing transcriptomic research in KD toward clinically actionable applications, including improved diagnostic precision and risk stratification for coronary complications. This review provides an overview of recent advances in experimental and computational approaches in KD transcriptomics, evaluates analytical limitations, and discusses integrative strategies with potential clinical implications.

Keywords: Kawasaki Disease; Transcriptome; Coronary Aneurysm

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis that predominantly affects children under five years of age, and represents the leading cause of acquired heart disease [1]. A major complication of KD is the development of coronary artery aneurysms (CAA), which occurs in approximately 5% of treated patients and at a substantially higher rate in untreated cases [2,3].

Despite decades of investigation, the precise etiology and molecular pathogenesis of KD remain incompletely defined. Previous studies have suggested that disease onset results from a complex interplay among genetic susceptibility, infectious triggers, and dysregulated immune responses [4–6]. The markedly higher incidence observed in East Asian populations, including Korea and Japan, provides epidemiological support for the contribution of environmental factors to disease

development [7].

The diagnosis of KD is primarily clinical and relies on characteristic constellations of symptoms, including prolonged fever accompanied by mucocutaneous features such as conjunctival injection, oral mucosal changes, polymorphous rash, extremity changes, and cervical lymphadenopathy [8]. Incomplete KD presents a particular diagnostic challenge, as patients may not fulfill the full clinical criteria yet remain at risk for coronary artery involvement, and its presentation often overlaps with other febrile inflammatory illnesses. In such cases, supportive laboratory evidence and echocardiographic assessment are frequently used to strengthen diagnostic confidence and guide timely treatment [8]. Delayed recognition is associated with an increased risk of CAA formation. Intravenous immunoglobulin (IVIG) has long been established as the standard first-line therapy for KD and significantly reduces the incidence of coronary complications. However, approximately 15%–20% of patients exhibit resistance to initial treatment and remain at substantially elevated risk for coronary artery involvement [9]. Consequently, there is a growing demand for molecular biomarkers that can enhance diagnostic precision, predict treatment response, and ultimately inform the development of individualized therapeutic strategies.

Methods

Relevant studies were identified through searches of PubMed and related databases using keywords including “Kawasaki disease,” “transcriptome,” and “RNA sequencing.” Studies were selected based on their relevance to transcriptomic profiling in KD, with a focus on investigations providing insights into disease mechanisms, clinical stratification, or therapeutic response. This review was conducted as a narrative synthesis and did not follow a formal systematic review protocol.

From Genomics to Whole Transcriptome Profiling: Conceptual and Technical Advances

Advances in high-throughput molecular technologies have significantly advanced biomedical research. Omics approaches, including genomics, transcriptomics, proteomics, and metabolomics have enabled comprehensive profiling of biological systems at multiple layers. In KD, genome-wide association studies have identified susceptibility loci such as *ITPKC*, *HLA* class genes, *FCGR2A*, and *BLK*, providing important insights into genetic predisposition [10,11]. However, while genomic variants illuminate inherited risk, they offer limited insight into the dynamic inflammatory processes that characterize acute KD. Genomic variation defines inherited risk but does not adequately account for the dynamic immune responses that underlie the complex and dynamically regulated immune pathology of KD.

Transcriptomic profiling characterizes transcriptional alterations and the molecular pathways underlying physiological and pathological states. It has been extensively applied to identify diagnostic and prognostic biomarkers and to enable molecular stratification in

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complex inflammatory diseases. Advances in transcriptomic technologies have enabled a transition from targeted gene assessment to comprehensive, systems-level profiling. Early transcriptomic studies relied on single-gene assays, followed by microarray platforms capable of simultaneously measuring thousands of predefined transcripts. Microarrays detect gene expression by hybridizing labeled RNA to arrays of complementary DNA probes, enabling simultaneous quantification of thousands of transcripts in a single experiment. Although microarrays represented a substantial advance, their dependence on predefined probes limited comprehensive transcript discovery. The introduction of high-throughput sequencing in the 2000s enabled the development of RNA sequencing (RNA-seq), which provides relatively unbiased and high-resolution profiling of the entire transcriptome. RNA-seq quantifies the average gene expression across millions of cells in a given sample, offering a population-level transcriptional snapshot that is well-suited for biomarker discovery and pathway-level analysis. More recently, single-cell RNA sequencing (scRNA-seq) has extended this capability by profiling gene expression at the resolution of individual cells, enabling the characterization of cellular heterogeneity and the identification of rare or functionally distinct cell populations within complex tissues. This shift established transcriptomics as a systems-level analytical framework [12,13].

Whole-blood transcriptomic profiling could represent a promising approach for molecular stratification and biomarker discovery in complex inflammatory diseases. Transcriptomic technologies have demonstrated translational utility across diverse diseases, including clinically implemented multi-gene diagnostic assays in breast cancer and pathway-based therapeutic target discovery in neurodegenerative disorders such as Parkinson's disease [14–16]. In KD, where pathogenesis remains incompletely defined, transcriptomic analysis may serve as a key analytical approach for the development of novel diagnostic biomarkers and the identification of therapeutic targets, ultimately supporting personalized treatment strategies.

Transcriptomic Insights into Kawasaki Disease

Whole-transcriptome approaches have been increasingly integrated into research aimed at clarifying the pathobiology and clinical stratification of KD. A reproducible whole-blood transcriptional signature could complement clinical assessment and conventional inflammatory biomarkers, thereby enhancing diagnostic precision during the early phase of disease. Transcriptomic stratification also offers promise in predicting therapeutic responses and vascular outcomes. This proactive stratification could guide timely escalation to adjunctive therapies, such as corticosteroids or anti-TNF agents, rather than relying on a reactive approach after IVIG failure.

A 2018 multicenter cohort study by Wright et al. [17] used microarray-based transcriptomic profiling of peripheral blood samples from patients with acute KD, other inflammatory conditions, bacterial or viral infections, and healthy controls. This comparative analysis identified a 13-gene signature capable of distinguishing KD from other inflammatory conditions. Several hub genes, including *ITGAX*, *LILRB2*, *C3AR1*, *MAPK14*, *TLR5*, and

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MYD88, were upregulated during the acute phase and declined following IVIG therapy, suggesting that transcriptional patterns may reflect disease activity and treatment response. Cohort studies have also explored prognostic implications. Hoang et al. [18] performed whole-blood microarray analysis of acute and convalescent KD patients, validated by RT-PCR, identifying predominant upregulation of innate immune and IL-1 signaling pathways in the acute phase, with transcriptomic differences observed between treatment response groups in T cell– and natural killer cell (NK) cell–related pathways. These findings may reflect immunological correlates of IVIG responsiveness, though prospective validation is needed. In parallel, transcriptomic signatures have been linked to CAA development, underscoring the potential of gene expression patterns to reflect both treatment responsiveness and vascular outcomes. While bulk transcriptomic approaches provide clinically relevant signatures reflecting the systemic inflammatory state of KD, they are limited by their inability to resolve cell type–specific contributions due to the averaging of heterogeneous cell populations.

Transcriptomic research has recently pivoted toward tissue-level and single-cell analyses to delineate organ-specific alterations. Rowley et al. analyzed coronary artery tissue in KD and identified a vascular immune microenvironment characterized by cytotoxic T-cell infiltration and an enrichment of type I interferon–responsive programs [19]. This tissue-specific localization offers direct mechanistic insights into coronary artery injury that systemic profiles cannot capture. At the cellular level, emerging single-cell studies have begun to dissect the immune heterogeneity underlying distinct clinical phenotypes of KD. Chen et al. [20] conducted scRNA-seq on PBMCs from patients with and without coronary artery lesions, revealing that coronary artery lesion (CAL) development was associated with expansion of pro-inflammatory intermediate monocyte subsets such as Mono_CD14^{+}CD16^{+} and Mono_CD14^{+}CD16^{-}VCAN clusters, and megakaryocytes, along with a cytotoxic CD8^{+} T-cell subset (CD8_Pro) implicated in vascular injury. Fan et al. [21] further reported that IVIG-resistant KD is associated with distinct immune dysregulation, particularly involving natural killer cell–mediated cytotoxicity and aberrant innate and adaptive immune signaling pathways. These single-cell approaches enable the identification of cell type–specific immune programs driving disease pathogenesis and treatment response, providing mechanistic insights that complement bulk transcriptomic findings.

Transcriptomic investigations in KD have further expanded to encompass the regulatory roles of non-coding RNAs. Although protein-coding genes represent only a small fraction of the human transcriptome, non-coding RNAs such as lncRNAs and miRNAs exert broad regulatory influence over gene expression at the transcriptional, translational, and epigenetic levels, offering a layer of insight into why certain patients sustain exaggerated inflammatory responses that protein-coding analyses alone cannot fully explain. Ko et al. [22] reported that knockdown of the long non-coding RNA *XLOC_006277* reduced the expression of vascular injury related mediators such as *MMP-8* and *MMP-9*, suggesting that *XLOC_006277* may have relevance as both a biomarker and a potential therapeutic target in CAA.

Many transcriptomic datasets have been deposited in publicly accessible repositories, enabling cross-cohort integration and independent validation. In KD, several studies have

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conducted integrative analyses of these public resources. Representative investigations have identified immune-related differentially expressed genes (DEGs) with diagnostic potential, including *IL1B*, *ADM*, *PDGFC*, and *TGFA*, and have delineated gene modules enriched for cytokine regulation, T-cell activation, T-cell receptor signaling, and NK cell–mediated cytotoxicity [23,24]. Collectively, these studies underscore recurrent immune pathway perturbations across independent cohorts rather than cohort-specific transcriptional signals.

Spanning whole-blood microarray, tissue-level profiling, single-cell sequencing, and non-coding RNA analyses, these complementary approaches collectively highlight a molecular landscape associated with key pathobiological features of KD, including innate immune activation, lymphocyte dysfunction, and aberrant cytokine signaling. These insights provide a foundation for improving diagnostic precision and advancing therapeutic stratification.

Current Challenges and Future Directions in KD Transcriptomics

Transcriptomic research has substantially expanded our understanding of disease biology; however, important challenges remain regarding reproducibility and clinical translation. Considerable heterogeneity across studies, including differences in cohort composition, ethnicity, age distribution, timing of sample collection, disease severity, and analytical platforms, results in variability in differential expression results. Many investigations are further limited by small sample sizes, restricting statistical power and increasing susceptibility to false-positive or cohort-specific signals. In transcriptomic investigations of KD specifically, these issues are compounded by disparities in bioinformatic pipelines, contributing to inconsistent gene signatures across studies. These factors collectively restrict the development of reliable biomarkers and complicate the identification of therapeutically actionable targets for clinical application.

To address the constraints imposed by small sample sizes and cohort-specific variability, meta-analytic strategies have been increasingly applied in transcriptomic research. By integrating data from multiple independent studies or combining summary statistics, meta-analysis increases statistical power and attenuates study-specific noise [25,26]. This cross-cohort integration facilitates the identification of more consistent molecular signals across heterogeneous datasets. Such approaches have been widely implemented across diverse diseases, including neurodegenerative disorders, renal diseases, and oncology, where integrative analyses of public datasets have helped delineate reproducible pathways and clinically relevant targets [27–29]. Nevertheless, meta-analytic frameworks require careful handling of between-study heterogeneity and batch effects. Rigorous statistical harmonization, appropriate normalization, and sensitivity analyses remain essential to ensure robust and biologically meaningful inference.

Cross-validation with proteomic data enables prioritization of transcriptomic signals that are consistently supported at the protein level. This integrative approach helps narrow candidate signatures to those with greater biological credibility and translational potential, thereby strengthening the clinical applicability of transcriptomic findings. In KD, recent

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studies incorporating proteomic analyses have evaluated transcriptome-derived candidates at the protein level [30]. These investigations provide complementary evidence supporting the biological relevance of selected gene programs. Concordant alterations observed across transcriptomic and proteomic datasets increase confidence that these signals reflect disease-associated inflammatory processes and coronary involvement. Integrative multi-omics approaches may therefore strengthen molecular stratification and advance the development of clinically actionable biomarkers in KD.

Ultimately, the long-term objective of transcriptomic investigation in KD extends beyond identification of novel biomarkers. Through rigorous multi-layer validation and integration with complementary omics data, these efforts seek to establish stable molecular frameworks that support development of diagnostic platforms, identification of therapeutic targets, and implementation of mechanism-informed individualized treatment strategies. Such advances may shift KD management from phenotype-driven decision-making toward biologically grounded precision care.

Conclusion

Transcriptomic investigations have substantially advanced the molecular understanding of KD, revealing reproducible immune pathways associated with disease activity, treatment response, and coronary involvement. Nevertheless, challenges related to cohort heterogeneity, limited sample sizes, and technical variability continue to constrain reproducibility and clinical translation. Integrative strategies, including cross-cohort meta-analysis and multi-omics validation, provide promising avenues to enhance robustness and prioritize biologically meaningful signals. Future efforts should emphasize large-scale harmonized datasets, prospective validation, and functional characterization of candidate pathways. Through such approaches, transcriptomics may evolve from a descriptive tool into a clinically actionable framework that supports precision diagnostics and mechanism-based therapeutic strategies in KD.

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