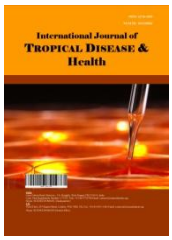

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Advances in the Co-Host Immune Response to Multisystem Inflammatory Syndrome and Kawasaki Disease in Children with AI-Guided Features

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

Purpose: To explore the role of artificial intelligence in the immune response mechanism of children with multi-system inflammatory syndrome and Kawasaki disease. Methods: To search the domestic and foreign literatures about the immune response mechanism of these two diseases, and analyze the literatures according to the characteristics of artificial intelligence. Results: AI analysis showed that the two kinds of children's syndrome were concentrated in the cytokine storm centered on il-15/IL15RA, which confirmed that the two diseases had the same initial immune pathway, but the differences in immune phenotype, cytokine, cell count and other aspects suggested that KD and MIS-C were two different diseases. Conclusion: It shows the applicability of AI in this research direction, and points out the limitations of the current research scope and

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samples. The difference between the results of KD and MIS-C research guides the direction of future research. Accurate and comprehensive laboratory indicators and parameters can be applied to artificial intelligence and provide basis for diagnosis and treatment of diseases. As the number of infected people increases, the problem of sample limitation in the current work can also be improved.

Keywords: Artificial intelligence; kawasaki disease; multi-system inflammatory syndrome (mis-c); immune response.

1. INTRODUCTION

Multiple systemic inflammatory syndrome (MISC) caused by SARS-CoV-2 infection has overlapping characteristics with Kawasaki disease, suggesting that vasculitis and possible autoimmune etiology, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a human coronavirus. Coronavirus appeared in December 2019 and spread rapidly around the world, bringing us huge medical and life challenges. In April 2020, children with symptoms similar to incomplete Kawasaki disease (KD) or toxic shock syndrome were reported in the UK, and then similar children were reported in other parts of the world. Jiao Fuyong believes that KD is very similar to coronavirus infectious diseases such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), 2019 Coronavirus Disease (COVID-19) in terms of epidemiological distribution patterns: it has obvious seasonal characteristics. Combined with a few coronaviruses that can infect humans through cross-species transmission and have symptoms very similar to Kawasaki disease, Kawasaki disease can be regarded as a new manifestation of COVID-19 in children and should be treated [1]. The disease was later defined as coronavirus-associated multisystem inflammatory syndrome in children (MIS-C), which can be fatal in severe cases. Children's multisystem inflammatory syndrome (MIS-C) and Kawasaki disease are highly inflammatory diseases related to infectious diseases, but are they different syndromes or continuous? The characteristics of AI guidance provide new insights for us to understand the co-host immune response of children with multi-system inflammatory syndrome and Kawasaki disease. This article reviews the progress in the study of host immune mechanism of children with multiple system inflammatory syndrome and Kawasaki disease

2. FOREIGN RESEARCH STATUS

The SARS - CoV - 2 pandemic has inspired many research groups to find innovative ways to understand the host's immune response to the virus, of which the proportion of out-of-control is related to death. Through searching multiple (>45000) gene expression datasets of GEO and ArrayExpress, more than 45000 pandemic transcriptome datasets were analyzed, 166 gene signatures were extracted with ACE2 as the "seed" gene, and ViP and severe ViP features were named. Researchers have analyzed 166 genes of H1N1 and H3N2 pandemic infection samples and bacteria and fungi in vitro and in vivo, and found that VIP characteristics are surprisingly conservative. This feature largely enriched genes in the immune system pathway, such as interferon and cytokine signaling pathway. In other words, this feature is widely accepted as a typical host immune response for host defense during any infection. At the same time, 20 gene clusters of 166 genes related to "severity" were found. Through the study of samples of mild and severe diseases during the pandemic of avian influenza (H7N9), IAV (H3N1 and others) and swine influenza (H1N1) viruses, the ViP characteristics of 166 genes and the severity characteristics of 20 genes were similar in the classification of control and mild diseases, but the latter was significantly better in the classification of mild and severe diseases. The 20 gene clusters related to "severity" enrich a completely different set of cell processes, namely DNA damage, stress-induced aging, neutrophil degranulation and cell cycle change. Moreover, severe vip characteristics (sViP) can predict the outcome of COVID-19 patient cohort. The only cytokine/receptor pair in these 166 gene clusters is interleukin 15 (IL15/IL15RA), and cytokine storm (166 genes, including IL15/IL15RA) is induced in a variety of cell types; However, the 20 gene ViP characteristics of disease severity and mortality are most significantly induced in two cell types: (i) known airway epithelial cells that produce il - 15 after virus infection and (ii) known target cells NK cells with physiological and excessive il - 15 response. Airway epithelial cells (especially bronchus) constitutively express IL-15 and IL-15RA/B genes. Virus infection and IFNg can induce the effect of its synthesis and secretion of IL-15. Prolonged and excessive IL-

15 stimulation can lead to significant depletion and reduction of NK cells in severe COVID-19 infection cases, and this reduction occurs as early as 6 days after symptoms appear. We conclude that fatal COVID-19 is characterized by a contradictory immune response, that is, inhibiting the function of epithelial cells and NK cells in the context of cytokine storm (excessive immune response) (immunosuppression). Researchers are trying to determine whether SARS-CoV-2 virus can induce ViP characteristics and whether these characteristics can track the treatment response. The first method is to use n - hydroxycytidine, the mother of the prodrug MK4482. We analyzed the lungs of golden Syrian hamsters infected with sars - cov - 2 by RNA sequencing. These hamsters received the drug or carrier control treatment respectively. The ViP signals of 166 and 20 genes were induced in the vector treatment group and effectively suppressed to the level of non-infected control group in the drug treatment group. The second method is to use the sars - cov-2 neutralizing antibody, which binds to the receptor binding domain (RBD-A) of SARS-CoV-2 spike protein in a way that prevents binding with the host ACE2. It has been proved to be effective in preventing infection and weight loss symptoms in the cell-based infected hamster model and in vivo infected hamster model, respectively. There are three key findings: (i) They inhibit 166 and 20 vip signatures, These signatures were induced in infected lungs; (ii) Protect the lungs from immune cell infiltration and alveolar space occlusion; (iii) The expression of IL-15 and IL-15 receptor was significantly lower than that observed in infected lung. These results verify the calculation method of recognizing ViP signature centered on ACE2. When using antiviral drugs or neutralizing antibodies, the signature is suppressed. The results also show that the reversal of signal and the storm of il - 15 can be used as a reading of therapeutic efficacy. The increase of IL-15 is independently related to mortality. In patients who died and recovered during hospitalization, the level of cytokines is always high. Problems in this study: since the public transcriptome data set of sarscov-2 infection samples is still relatively small, any conclusion drawn from such a small number of samples using any calculation method may lack robustness. The selected calculation method, Boolean analysis, filters some key information. This requires more accurate and specific COVID-19 data set to provide more accurate evidence [2].

Given that children's multi-system inflammatory syndrome (misc) and Kawasaki disease syndrome (KD) have many similar clinical features, PradiptaGhosh et al. used two genetic marker calculation tool packages developed in the context of SARS-CoV-2 infection to compare the two syndromes. Namely, viral pandemic (ViP) and severe ViP signatures, as well as 13 transcript signatures previously proved to be able to diagnose KD. This study confirmed that compared with the healthy control group, the ViP and sViP characteristics in blood and tissue samples of KD patients were up-regulated. Because the diameter of CAA was a predictor of coronary artery sequelae, the development of coronary artery aneurysm (CAA) was used as a marker of disease severity. It was found that the differential expression of the two ViP characteristics in patients with giant aneurysms and patients without aneurysms could distinguish acute KD patients with giant aneurysms, Since ViP signature represents the host's immune response to different pathogens, the research results show that the up-regulation of ViP signature in KD is consistent with the assumption that KD is triggered by multiple infections, some of which may be viral. When the misc group and acute KD group were compared with the control (subacute KD) samples, the following conclusions were drawn: (i) The host immune response detected by qualitative method using ViP characteristics was similar in KD and MIS-C, and had IL15/IL15RA shared components; (ii) The degree of this host immune response measured quantitatively by ViP signature score is stronger than KD in misc. These findings are consistent with the fact that misc is the host's immune response to SARS-CoV-2 exposure. The research results are also consistent with previous work, that is, the serum level of il - 15 in patients with acute KD is significantly increased, about 10 times as compared with that in subacute KD and normal control group. In order to avoid over-reliance on a group of markers (ViP/sViP), Ghosh et al. subsequently used Kawasaki disease specific gene expression markers, which were previously used to identify Kawasaki disease in children with fever. The study found that KD specific 13 transcript signature could not distinguish misc and KD. In addition, the two non-overlapping signatures, sViP and KD-13, are significantly induced in KD and misc, and are independent of each other. This shows that these two characteristics reflect two fundamentally different and unrelated biological domains in host immune response; Whether their diagnostic/prognostic capabilities have additional

benefits remains to be explored. The similarity of KD-13 features and ViP/sViP signatures induced by KD and misc in two independent queues further supports our research. KD and misc are the same in the basic aspects of host immune response. The whole blood transcriptome and cytokine panel reveal the subtle difference between misc and KD. Although the induction of most cytokines in acute KD and misc is not different, there are obvious exceptions. Compared with KD, in misc, TNF α、 IFN γ、 IL10, IL8 and IL1 β They all increased to a greater extent, but did not reach statistical significance. These findings indicate that the target TNF approved by the fda α And IL1 β The way of treatment may be beneficial to the treatment of misc. IL-1 receptor is expressed in almost all tissues, and its antagonistic effect is blocked by anakinra (the recombinant form of IL-1Ra41) α Or IL-1 β Receptor binding. Similarly, tumor necrosis factor α The chimeric antibody infliximab has been reused in COVID-19. Analysis shows that this drug is expected to be used in the treatment of misc. The researchers tried to understand how similar host cytokine responses triggered two different clinical syndromes, and analyzed the samples of misc and acute KD using cytokine analysis (MSD) and clinical/laboratory parameters. The results showed that: (1) compared with KD, the level of cytokine in patients with misc was higher, the decrease of whole blood cells was more serious, and the host immune response of MISC was significantly higher than that of KD; (2) Misc has the key distinguishing characteristics of thrombocytopenia and low eosinophil count, and both of these characteristics are negatively correlated with serum il-15 and VIP levels. Eosinophilia seems to be a significant common feature between misc and COVID-19, but not KD. These findings are consistent with the fact that KD is known to exhibit higher (rather than lower) eosinophil counts. Thrombocytopenia has been shown to be significantly associated with mortality. Like thrombocytopenia, persistent eosinophilia after admission is associated with the severity and low recovery rate of COVID-19. (3) Misc had impaired cardiac contractility, but KD did not. These two kinds of pediatric syndromes focus on the cytokine storm centered on il-15/il15ra, suggesting that there is a common proximal pathway for immune pathogenesis. However, they differ in other laboratory parameters (platelets, eosinophils) and cardiac phenotype (cardiac function decline, coronary artery dilation). These relevant clinical/laboratory parameters (low PLT and AEC) may be useful indicators of disease severity and prognosis, and can be used to guide hospital treatment and nursing decisions. The current limitation of this experiment is still that the sample size of misc subjects is relatively small. Therefore, the accuracy of analysis can be improved by using the informatics method, that is, Boolean equivalent correlation clustering. This method can identify the basically unchanged (generally conservative) gene expression relationship based on any biological field; Different from some mainstream computing methods (such as differential expression, Bayesian and correlation network analysis, etc.), it can identify the entire spectrum of host immune response, the Boolean equivalence relationship, and mainly identify the potential function-related gene set, and to some extent, it misses some key information. Moreover, due to the small sample size, we cannot obtain the cardiac tissue of KD and misc subjects and determine the possible impact of IL-15/IL15R expression in the heart [3].

Subsequently, Jonathan Y Lam et al. developed a deep learning algorithm called KIDMATCH (Kawasaki disease vs pediatric multi-system inflammatory syndrome), which is based on a two-stage model composed of a precursor neural network and uses the patient's age, five classic clinical signs of Kawasaki disease and 17 laboratory indicators to identify the disease. This is also the first algorithm for diagnosis, which can distinguish misc, kawasaki disease and other similar febrile diseases. However, due to the lack of the gold standard for Kawasaki disease or misc diagnosis, and the limited data of febrile disease and Kawasaki disease used for external verification, the existing algorithms are only optimized for the laboratory test values collected during the initial evaluation. At present, it is not clear how the end user should deal with the patients marked as uncertain, and how it will deal with the data collected at a later point in time. More professional detection methods such as ferritin, troponin, b-type natriuretic peptide or n-terminal b-type natriuretic peptide precursor and d-dimer, as well as anti-SARS-CoV-2 IgG antibody, may be a better solution [4].

The study on the immune mechanism of children with multi-system inflammatory syndrome (misc) and Kawasaki disease (KD) focuses on multiple directions. At present, the study on host immunity of misc and kawasaki disease by artificial intelligence has a short time and lacks relevant literature. The number of studies on the

pathogenesis of these two diseases was relatively large in the past. Here is a brief introduction:

Marques et al investigated the transcriptional groups of 1596 individuals, including COVID-19 patients, and compared them with the healthy control group, other acute inflammatory states (HLH, children's multi-system inflammatory syndrome, Kawasaki disease) and different respiratory infections (seasonal coronavirus, influenza, bacterial pneumonia). In the study, it was found that a group of neutrophil-related genes reflected a widespread high inflammatory state, and these genes were abnormally regulated at the protein level, which could lead to excessive activation of neutrophils in patients. Studies have shown that severe COVID-19 disease and other acute inflammatory diseases (such as HLH, KD and bacterial pneumonia) have the same characteristics of neutrophil activation. Studies have shown that the accumulation of neutrophils in the inflammatory tissue of COVID-19 patients is the result of the release of pro-inflammatory cytokines and chemokines driven by T cells. The number and dysfunction of neutrophils are related to the outcome of COVID-19. The inhibition of CCR5-CCL4 axis through Leronlima (anti ccr5 monoclonal antibody), or through Tocilizumab (anti il - 6r), Adalimumab (anti tnf- α) Or Anakinra (anti il1r) blocks cytokine signaling pathway, which has been proved to improve severe symptoms of COVID-19 in some cases. In addition, Ruxolitinib is a JAK1/JAK2 inhibitor that acts on jak-dependent chemokines/cytokines (such as IFN- γ、 IL-1 β、 IL-6, TNF, G-CSF, CXCL9 and CXCL10), the inhibitor has shown good effect in the treatment of COVID-19, and neutrophil elastase inhibitor has also been suggested to relieve the symptoms of SARS-CoV-2. The limitation of this study is that it did not investigate the effect of different SARS-CoV-2 variants on the transcriptome of COVID-19 patients. Therefore, it is necessary to further study how different variants of SARS-CoV-2 intersect with other highly inflammatory diseases we investigated. At the same time, the influence of age, sex and complications on the common transcriptome characteristics of COVID-19 and other highly inflammatory diseases was not considered [5].

Michael J. Carter's "Peripheral Immunophenotypes of Children with SARS-CoV-2 Infection-Related Multiple System Inflammatory Syndrome" believed that the level of cytokines, including interleukin-1, increased in the acute infection stage of misc β (IL-1 β)IL-6, IL-8, tumor necrosis factor- α、 IL-10, IL-17, interferon- γ (IFN- γ) And IL-2 receptor agonists, CRP and ferritin increased, which was the same as that of acute infection stage of Kawasaki disease. However, the increase of fibrinogen, the increase of d - dimer and the decrease of platelets in the acute phase of Misc suggest the procoagulant state, which is not a common feature of Kawasaki disease. The number of neutrophils and monocytes in the misc cohort was not increased, but higher in Kawasaki disease. In Kawasaki disease, CD4 and CD8 counts were higher than those observed in our misc cohort, while the proportion of hla - dr positive CD4+T cells was lower in Kawasaki disease. This study proposes a direction. These differences suggest that misc may be a unique immunopathogenic disease, but it needs to be confirmed by simultaneous immunotyping of Kawasaki disease and multi-system inflammatory syndrome. The limitations of this study are that only HLA-DR is used as a marker of T cell activation, and there is a lack of evaluation of potential genetic susceptibility [6].

Camila Rosat Consiglio et al. found that some genetic variations with medium effect size, such as ITPKC, CD40, FCGR2A and BLK, were related to KD. The inflammatory response of misc has several common characteristics with Kawasaki disease, but it is different from Kawasaki disease in T cell subsets, interleukin (IL) - 17A and biomarkers related to arterial injury. Compared with children with Kawasaki disease, the lymphocyte reduction in children with misc is more obvious. The levels of c-reactive protein (CRP) and ferritin in children with misc are also significantly higher, and the platelet count is also lower. The study evaluated the phenotype of peripheral blood mononuclear cells (PBMC) by flow cytometry. Compared with patients with Kawasaki disease, the naive CD4+T cells and TFH in MISC patients were lower, the central memory subgroup and effective memory subgroup were increased, and the CD57 marker was higher in mis-c. This indicates that there are some specific differences between the immune cell response of misc patients and Kawasaki disease patients. IL-17A is very important in Kawasaki disease, but IL-17A is significantly reduced in misc patients, which indicates that there are differences in the underlying immunopathology. IL-17A blockers, such as secukinumab, can be considered for use in serious Kawasaki disease patients in future trials.

The researchers detected antibodies in plasma samples using human proteome chips, and found many antibodies with differences between MIS-C and Kawasaki disease. The overexpression of EDIL3 autoantibodies was the most obvious in Kawasaki disease patients. CSNK and MAP2K2 family proteins were significantly increased in MIS-C. Autoantibodies may be the pathogenesis of misc and Kawasaki disease. IVIGs can neutralize some immunopathological effects of autoantibodies and be used for the treatment of both diseases [7].

Alice Castaldo published an article on the differentiation of misc and Kawasaki disease by peripheral blood cell immunophenotyping. The white blood cell populations of 46 misc and 28 KD patients were studied by flow cytometry, and compared with 70 age-matched healthy children. The results showed that misc patients had significant lymphopenia, involving B and T, while KD patients showed significant neutropenia and thrombocytosis, which overlapped with previous research results. The granulocyte/lymphocyte ratio is helpful for the diagnosis of misc and KD and has high diagnostic sensitivity, while the multivariate analysis of the number of granulocyte and T lymphocyte is helpful to distinguish these two diseases. The analysis of a group of circulating cells is helpful for early diagnosis and differentiation of these two diseases [8].

3. DOMESTIC RESEARCH STATUS

At present, there is no comparison between the two kinds of disease immunity guided by AI features in China. Li Shihua, Li Huimin and others found that HLA-drb1 and HLA-micaA4 are related to KD, and LA-B is considered as the risk allele of severe infection of COVID-19. Autoimmune vasculitis of KD, KDSS or MISC is caused by HLA, Fc γ Genetic variation of R and/or ADE mediates excessive inflammation of Th17/Treg imbalance The correlation of genetic susceptibility in KD and/or COVID-19 was determined [9].

4. CONCLUSION

The above studies confirmed that MIS-C and KD have a common initial immune pathway, but in cytokines (IL-17A increased in Kawasaki disease and significantly decreased in misc patients), T cell subsets (CD4 and CD8 counts in Kawasaki disease were higher than misc,), immunophenotypes (CD57 markers were higher in misc), antibodies (the overexpression of EDIL3 autoantibodies in Kawasaki disease was the most obvious, and CSNK and MAP2K2 family proteins were highly expressed in MIS-C) There are differences in blood coagulation status (fibrinogen increase, d - dimer increase and platelet decrease in acute phase of Misc, not in Kawasaki disease), cell count (neutrophil and platelet increase in KD, and eosinophil count decrease in misc), etc. In view of the difficulties caused by the global pandemic of COVID-19, it is particularly important to use artificial intelligence to help medical researchers lock key molecules and pathways from complex data, study disease mechanisms and carry out drug treatment. The limitations of previous studies include the relatively small sample size and the limited number of public misc data sets that can be independently verified. In the future, strict data research is still needed. In the future, we hope to find more extensive and accurate gene features in existing studies (related to cytokines, cellular immunophenotypes, antibodies, gene susceptibility, etc.), use artificial intelligence algorithms to define and layer diseases from clinical or laboratory parameters, and identify the phenotypes and complications of disease spectrum, including cardiogenic shock (such as MIS-C shock and Kawasaki disease shock syndrome), MAS (cytopenia and coagulation dysfunction related to cytokine storm caused by infection), Kawasaki disease (typical and complete Kawasaki disease phenotype, caused by SARS - CoV-2 or other infectious factors), and provide evidence for the formulation of treatment strategies [10]. In the future, the amount of research data should be further expanded in clinical practice, and the special method of artificial intelligence should be used to diagnose, differential diagnosis and treatment of the above diseases to serve the clinical.

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CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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