Researchprogressontheroleof inflammationinKawasakidisease

Abstract:

Asthepathogenesis ofKawasaki disease continues toevolve,researchers haveproposedanumberofhypotheses, fromviralinfections, geneticandenvironmentalinfluences,totoxin-mediated autoinflammatoryresponses.Moreandmoreattentionhasbeenpaidtotheroleofinflammationin KD (Kawasaki disease)pathogenesis.Objective:Toexplore theroleofinflammation inKawasaki disease andtoprovide anewideaforthediagnosis andtreatmentofKD.Methods: A systematicsearchwasconductedfromPubMed andCNKIdatabases (lastupdated onMarch31,2023)forrelevant andqualified articles evaluatingtheroleofinflammation inKD.Results: Theresearchresultsofthelastfiveyearswereselectedfromthesearticlesfor meta-analysis.Conclusion: Throughcomprehensiveanalysis, weconcludethatinflammatoryresponseisthemainprocessofvasculardamageinKawasakidiseas e, especially theNLRP3inflammasomewhich playsanimportant role.However, the etiology and pathogenesis of KD are very complex, and inflammation is only one manifestation. More and more studies have shown that inflammation plays a crucial role in the pathogenesis of Kawasaki disease, which has been recognized,and we comprehensively describe some important roles and latest research perspectives of inflammation in Kawasaki disease.

Keywords: Inflammation;Inflammatorycorpuscles;Kawasakidisease;

Introduction

Kawasakidisease(KD)isacommonvasculitisthattendstooccurinchildrenunder5yearsofage. Itisusuallyacute,self-limited,andhighlyinflammatoryinitsearlystages,mainly involvingcoronary arteries, butitspathogenesishasbeenunknown.Inrecent years,theincidence ofKDhasbeenincreasing yearbyyear,whichisoneofthemostcommon causes ofacquired heartdisease inchildren[1]TheroleofinflammationinKawasakidiseaseissummarizedfromthefollowingaspe cts:

1. Histopathology

"TheinitialstudyofKDinflammation wasahistopathologicalexamination oftheheartandcoronary vessels ofdeceased patients.Early inthedisease,stageI,alargenumberofmixedinflammatoryinfiltratesofneutrophils, eosinophils, macrophages, and lymphocytes are seen , involvingtheinnerandoutermembranes ofcoronary arteries"[2]. "Inthesecond stage,coronary aneurysmsmaydevelopduetoproliferativeinflammationoftheintimaanddamageto the smoothmusclecellsandelasticfibers.Again,thisinfiltrationismixedandincludes lymphocytes,monocytes,macrophages,plasmacells,andfibroblasts"[3].

"Generally,M1macrophages arethought tobepro-inflammatory andmayreflect activation ofinnateimmune stimuli.InastudyofKDcoronaryartery disease, a large number of immune inflammatory cells, especially M1macrophages,werefoundtobethemainphenotypeofKD"[4]. "Abnormalactivationofimmunoactivecellssuchasmacrophages,monocytesandly mphocytesis the main process of inflammatory damage in KD.Thesecellssecrete variousinflammatory**cytokines**andchemokinessuchasIL-1β(Recombinant Human Interleukin-1β),TNF-α(Tumor necrosis factor-α),therebycausesvasculitisin theendothelialcells"[5]." Vasculitisendothelial cellsplayavitalroleinmaintainingthenormal function ofbloodvessels.Studieshaveshowthatendothelialcellinjury,including inflammation andapoptosis, isthemainpathologicalmechanismofKD"[6].

Withthedeepeningofexploration andthesupport oftechnology,thestudyofKDinflammatoryresponsehasbeenupgradedfromhistopath ologytotheanalysis ofwholegeneexpression profile, suchasthemousemodelofKDpatients intheacutestage, suchasLCWE(Lactobacillus casei cell wall,extract) mousemodel,andtranscription profile analysis, which confirmed the up-regulation of multipleimmunepathways.Includingintracellularsignal transduction, Tcellactivation, B celldevelopment, etc.[7],thesestudies further suggest theroleof immune inflammatory response inKD.Herewediscuss the role of innateimmunityandadaptiveimmuneinflammationinKD.

2. Congenitalimmuneinflammatoryresponse

2.1. Inflammatoryfactor

“Highlevels ofIL-1β havelongbeenthought tobeatthecoreofKD'sacute inflammatory phase”[8].“IL-1β is produced by a variety of immune andnon-immunecelltypesaspartoftheinnateimmune response.IL-1β hasavariety of pro-inflammatory effects, the most important of which is the directactivation of coronary endothelial cells, resulting in the up-regulation of celladhesion molecules, andtheproduction ofIL-6(Recombinant Human Interleukin-6)andIL-8(Recombinant Human Interleukin-8),bothofwhichareimportantinflammatoryfactors”[9].

“InadditiontoIL-1β,cytokinesalsohaveTNF-α.Relevantreportshave showedthatthelevels ofTNF-α released bymacrophages andmonocytes intheserumofKDpatients aresignificantly higher,whichplaysafacilitatingroleininducingcoronary arteryinflammation andpromoting thedevelopmentofcoronaryartery aneurysms” [10].However,research hasconfirmed that activating the inflammasomes can stimulate the production of inflammatory cytokines.

2.2 Inflammatory bodies

Inflammatorybodiesareintracellularprotein complexesoftheinnateimmunesystemthatrespondtopathogen-associatedmolecularpatterns(PAMPS)or damage-associated molecular pattern(DAMPS).

“Nod-likereceptorprotein3(NLRP3) activationisthekey to inflammatoryactivationintypicalinflammatories and there is acorrelationbetweenNLRP3andtongue-associatedspeck-likeprotein,apoptosis-associatedspeck-likeprotein(ASC),and cysteinylaspartate-specificproteases-1 (caspase-1) containing cysteine combined to form inflammatorybodies. By regulating caspase-1 activation,promotingmaturation and release ofinflammatory factors such as IL-1βand IL-18, and playsa pro-inflammatory roles” [11].“Inaddition, the activation ofatypical inflammatorieshasbeenreported tobeassociated withcaspase-4orcaspase-5-dependentpyrodeath is known to be induced by intracellular lipopolysaccharides(LPS)inGram-negative bacteria”[12,13].“At thesametime,

activationof caspase-4/5 also induces typical NLRP3 inflammasome.mRNA levels ofTIFA(TRAF-interacting protein with FHA domain-containing protein A),NLRP3,CASP1(caspase-1),CASP4,CASP5andIL1βweresignificantlyincreasedinacuteandconvalessiveKDpatients.Therefore, studies have confirmed that both NLRP3/Caspase-1 and Caspase-4/5 are involved in the pro-inflammatory immune response of KD patients at the transcriptional level" [14].

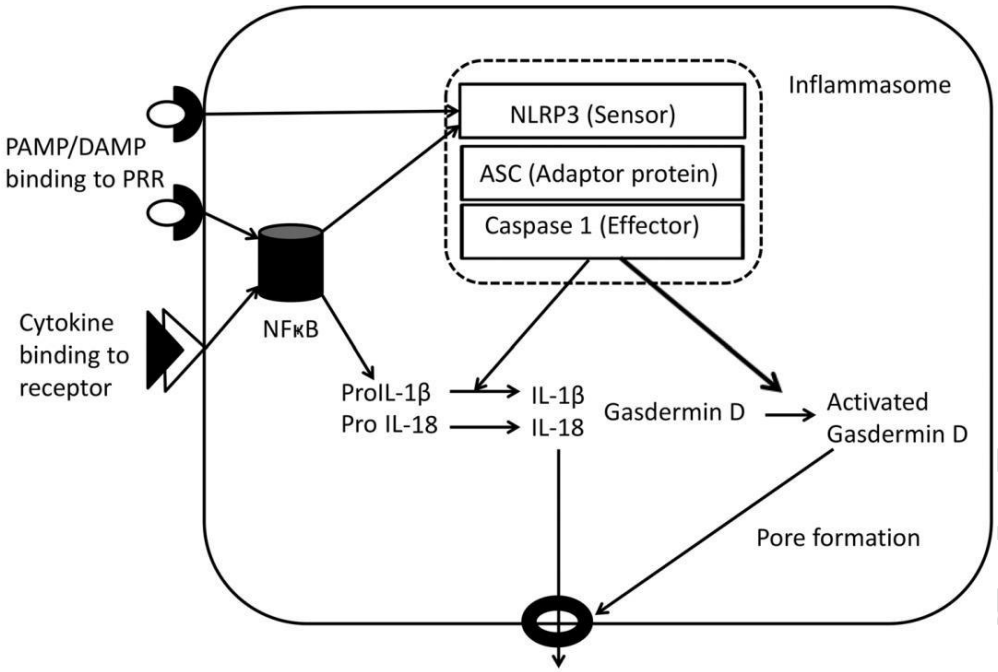
2.3 ActivationofNLRP3inflammasome:

StudieshaveshownthattheNLRP3inflammasomeisacomplexcomposedofthreesubunits,andactivationoftheNLRP3inflammasomerequirestwosignals.

The firstsignal causes NFB(Nuclear factor-B)activation, whichleadstoincreased NLRP3andpro-IL1βlevels.Bindingofpathogen-associatedmolecular patterns(PAMP)ordamage-associatedmolecularpatterns(DAMP)topattern recognitionreceptors(PRRS)results inNFBactivation.NFBisatranscriptionfactorthatincreases NLRP3andpro-IL1β incells,whichiscalledpriming.

"The second signal leads to the assembly of the named body protein, further leading to the activation of cystatin 1, which is called activation.Caspase-1convertspro-IL1βtoIL1βandconvertspro-IL18 toIL18,respectivelyalsoleads toprogrammed inflammatory celldeaththrough theformation ofporesin thecellmembrane,withtheendresulting inbeingtherelease ofinflammatorycytokinesandinflammatorycelldeaththrough theformation ofcellmembranepores".[15]

Figure1.NLRP3inflammasomeactivationpathway[16]:



2.4 RegulationofNLRP3inflammasome

1.MicroRNAs (miRNAs) are endogenous non coding RNA molecules that play important roles in various cellular and metabolic pathways, including cell proliferation, differentiationand apoptosis. MiRNAs are also involved in regulating inflammatory responses and maintaining immune stability[17].RecentstudieshaveshownthatMicroRNA-223(miR-223)limits the development of cardiovascular diseases by down-regulating

"NLRP3inflammasomeactivityandsubsequent IL-1βproduction.miR-223

maybeapotential biomarker fortheearlydiagnosis ofKDinhumans, andmaybepromisingasanoveltherapyforKDinthefuture" [18].

2. Studiesatdifferentperiods consistentlyfoundthatITPKC(inositol 1,4,5-trisphosphate3-kinaseC)polymorphismisassociatedwithKDsusceptibility, andITPKCcontrolsNLRP3activation byregulating calcium ionmobilization.ITPKCisagenethatencodesinositol triphosphate3-kinase,whichconverts inositol triphosphate(IP3)toinositol tetraphosphateandterminates thepropagationofCa2+signaling pathways.Recentstudies haveshownthatreduced functionofinositol 3-kinase triphosphate leadstoaccumulation ofIP3[19]. "IncreasedIP3leadstoincreasedintracellularCa2+andactivationofNLRP3.Increase d

IP3alsoleadstoactivation ofTcellsthrough Ca2+/NFAT(nuclear factorthatactivatesTcells)pathway"[20].

TheroleofITPKC,NLRP3andcytokines suchasIL1βandIL18in childrenwithacuteKDhasbeeninvestigated.TheyfoundthatITPKCwasdown-regulated and NLRP3 was up-regulated in the children.IL18 levels areelevated andassociated withinflammatory markers.IL1βlevels werenot significantly elevatedinchildrenwithKDcomparedtocontrols, butwerehigher inIVig-resistant children intheircohort.Thesestudies mayindicatethatNLRP3inflammator-drivenIL-1βplaysanimportantroleindisease developmentinchildrenwithIvig-resistantKD,andalsosuggest thatinaddition toIL-1β, itis also a therapeutic target forKDthrough theregulationofNLRP3inflammator-resistant[21].Management ofthewater-solubleportion ofCandida albicans(CAWS)isamousemodelthatcauses KD coronaryarteritis.Thismodel wasusedtoshowthatdamage toKDvascular inflammation is mediated by NLRP3 activation and IL-1β production, as thecontrol group suggested that NLRP3 deficient mice did not develop vasculitis[22].In bothstudies, NLRP3bodieswerefoundtobeinvolved inKDpathogenesis.

Basedontheabovestudies,itcanbeseenthattheactionprocessofinflammatoriesin KDisthatwhenthebodyissubjectedtoinvasion byexogenous pathogenic toxins orstimulation byendogenous danger signals,inflammatoriesareself-activatedandformactive substances (caspase-l),whichfurtherpromote maturationofmoredownstreampro-inflammatoryfactors (suchasIL-1βandIL-18), thuspromoting cellular inflammatory response.Evenapoptosis.The production of inflammatory factors can furthercausetheactivationofimmunecellssuchasTcellsandNKcells,andtherelease ofinterferon-γ (IFN-γ), tumornecrosis factor-α (TNF-α) andotherinflammatoryfactors.Suchrecurrentandevendiffuseinflammationleadsto thedamage of vascular endothelium, which may play a role inKD systemicvascular inflammation and CAL.Althougha single mechanism such as

inflammasomemaynotfullyexplain thepathogenesis ofKD,suchresearchwillcertainlypromotethedevelopmentofnewdiagnosticmarkers andtherapeutictargetsinKD.

3. Adaptiveimmuneinflammatoryresponse

Inadditiontotheroleofinnateimmuneresponseingeneratinginflammationin KD, relevantstudies haveshownthatantigen-specificadaptive immuneresponse alsooccurs inKDpatients.Forexample, bothBcellsandCD8+T cellshavebeenreported tohaveoligonclonal amplificationinacuteKD.Autoantibodiesagainstvarious myocardial,endothelial,andextracellularmatrixproteinshavebeendocumentedinm anystudies.Theclinicalsignificanceoftheseautoantibodiesisunclear.

"In a long-term follow-up study, 22% of patients detected autoantibodiesseveralyearsafterdiagnosisofKD"[23].However,thereisnoconvinci ngevidencethatKDpatientsareathigherriskofdeveloping autoimmunediseaseslaterinlife.

3.1. Bcellactivatingfactor(BAFF)andIgAreactions

1. "Bcellactivating factorisanimportant cytokine forB cellactivationanddifferentiation.Inautoimmunediseases characterizedbyautoantibodyproduction, BAFF is usually highly expressed and is a target for therapeuticintervention" [24,25]."Children with KD also showed high levels of BAFF andreturned tonormal afterIVIGtreatment"[26,27]."The increase inBAFFmayberelated to theincrease inthepercentage ofantiboy-secreting cells inacuteKD,whichdecreasedaftertreatment"[28].

2."InKDpatients,IgAproducingplasmacellsinfiltratethecoronarywall.Thefreq uency of IgA plasma cells isalsohigher inthe upper respiratorytractofKDpatients. A recent studyhassuggested thatIgA response inKDmaybeanimportantfactorinvascular injury.LCWEmousemodelisanexample ofPAMP-inducedcoronaryarteritis, andLCWE-induced KDmodelwasusedtodemonstratethatadaptiveimmune response isinvolved invascularinjuryinKDpatients.Foreignscholarshaveprovedthatvascular inflammation is related to the increase of serum IgA level and IgA+Bcells inlymphoidtissue"[29]. "DepositionoftheIgA-C3immune complexwasalsonotedintheheartandaortaofLCWE-treatedmice.Inthismodel,vascular

inflammationanddamagewereIgAdependent,becauseIgAdeficientmicedidnotdevelopcoronaryvasculitis”[29].

3.2. CD8+Tcells

“LCWEmousemodelexperimentssuggestthatCD8+Tcellspromotevascular inflammationandinjury”[30].The coronaryarteries ofLCWE-treated mice showed infiltration of CD4+ and CD8+T cells as well asregulatory T cells, dendritic cells, neutrophils, andmacrophages.EliminationofCD8+T cellswithmonoclonal antibody significantly alleviated vasculitisandmyocarditisinLCWE-treatedmice.The clearance ofCD4+Tcellsandothercellsdidnothavethesameeffect[30],indicating thatCD8+TcellsplayedaroleinKDvasculitisinjury.

Conclusion

KDinflammationmainlyinvolvesinnateimmune inflammatoryresponseandadaptiveimmuneinflammatory response,including theinvolvement ofinflammatory cells,inflammatory factors andinflammatory bodies,amongwhichinflammatory bodies playanimportantrole.EarlydetectionoftheexpressionofNLRP3inflammatorybodies inperipheralbloodandinterventiontherapymayprovidenewideasforthediagnosis andtreatment ofKD.However, howspecific inflammatory bodiescausedamagetobloodvesselsinKDpatientsstillneedsfurtherstudy.Byexploring the specific pathogenesis of inflammation in Kawasaki disease, wehopetoprovide newguidance forclinical diagnosis andtreatment, soastoreducetheincidenceofKawasakidisease, especially thecoronary arteryinjury.

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