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Review Article

IL-1RA autoantibodies: insights into mechanisms and associated diseases

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Abstract: The association of neutralizing autoantibodies targeting interleukin-1 receptor antagonist (IL-1RA) with multisystem inflammatory syndrome, IgG4-related disease, and vaccine-related myocarditis is increasingly recognized. The detection of IL-1RA autoantibodies can be notably affected by the techniques and methods employed. Two categories of assays are available: solid-phase immunoassays, which detect binding of IL-1RA autoantibodies, and functional IL-1 signaling reporter cell assays, which offer greater specificity by determining whether circulating autoantibodies can impede interleukin (IL)-1β signal transduction pathways. It is as yet unclear why only a minority of individuals produce pathogenic anti-IL-1RA autoantibodies in response to coronavirus disease 2019 (COVID19) or vaccination. This review article discusses our current knowledge of the process of IL-1RA autoantibody generation, the underlying pathogenesis, detection, and potential treatment strategies for associated diseases.

Keywords: Vaccine-induced myocarditis, IgG4-related disease, multisystem inflammatory syndrome, IL-1β, IL-1RA autoantibodies

Introduction

Anticytokine autoantibodies (AutoAbs) are found in both human health and various diseases, with their role in immunopathology varing widely from none to being directly causal. Biological plausibility has been established in the genetic defects of adaptive immunity wherein breakdown of tolerance, resulted in AutoAbs development targeting multiple cytokines, including type I interferons, gamma interferon (IFNγ), pro-inflammatory cytokines (e.g., interleukin (IL)-6, IL-17, IL-22, IL-23), and colony-stimulating factors [1-5]. It is becoming increasingly recognized that higher levels of both binding and neutralizing anticytokine antibodies (NAbs) can lead to various potentially life-threatening diseases [6, 7]. The reason why only a minority of individuals show an elevated occurrence of AutoAbs targeting specific cytokines, as opposed to others, remains unclear. NAbs targeting interleukin-1 receptor antagonist (IL-1RA), specifically of the immunoglobulin subclass G (IgG), have been observed in uncommon yet severe hyperinflammatory disorders that impact individuals across different age groups, from children to adults [8, 9]. The IL-1RA is an important anti-inflammatory cytokine that competes with and inhibits the binding of IL-1α/-1β to their common activating receptor, the IL-1 type-I receptor (IL-1RI) [10]. Multiple lines of evidence indicate that the IL-1α/-1β/-1RA axis is involved in various illnesses within multiple tissues, such as the heart, digestive tract, pancreas, and blood vessels. This review article discusses our current knowledge of the process of IL-1RA AutoAbs generation, the underlying pathogenesis, detection, and potential treatment strategies for associated diseases.

IL-1RA AutoAbs: generation and features

NAbs to IL-1RA are reported to be correlated with multisystem inflammatory syndrome [8], IgG4-related disease [9], and vaccine-related myocarditis [11]. Moreover, the severity of certain inflammatory diseases is linked to the administration of rabbit anti-IL-1RA antibodies or the alteration of endogenous IL-1RA in vivo

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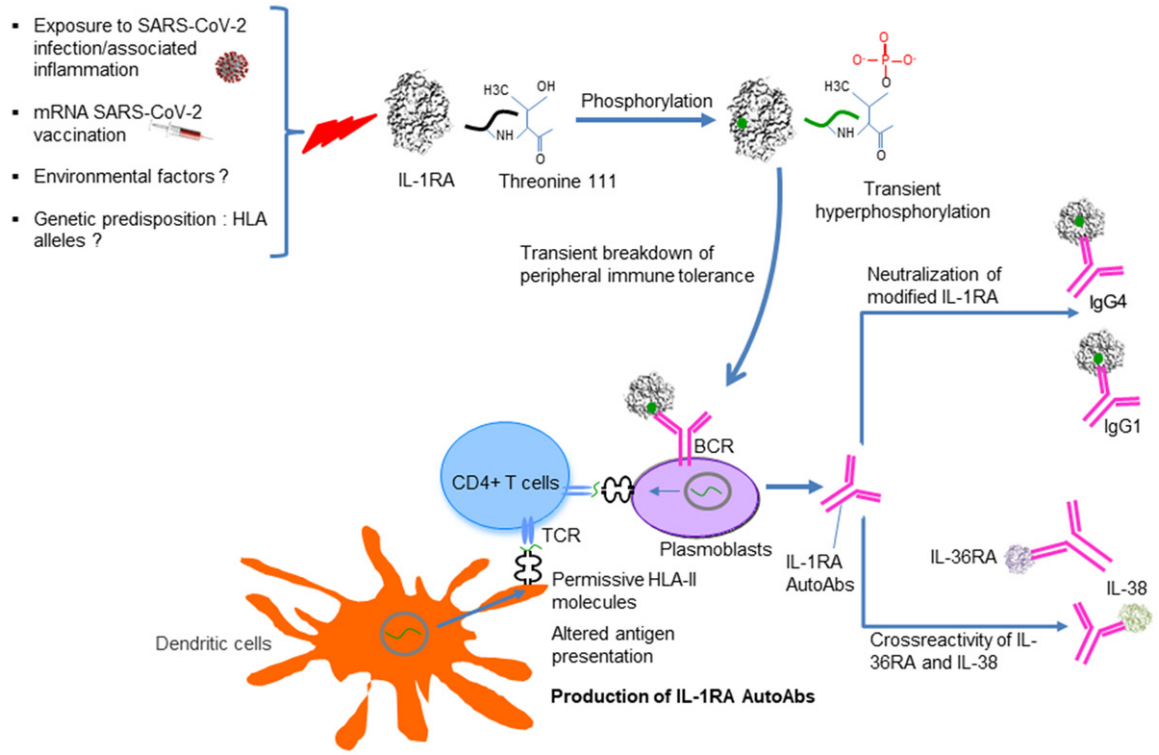

Figure 1. The hyperphosphorylated IL-1RA model and its role in the breakdown of peripheral tolerance. Exposure to SARS-CoV-2 infection, mRNA SARS-CoV-2 vaccination, and environmental factors can induce phosphorylated threonine 111 on IL-1RA isoform. The modified IL-1-RA peptides may be recognized by CD4+ T cells and Plasmoblasts. Modified IL-1-RA can be phagocytosed by dendritic cells and modified peptides can be presented via HLA-II molecules. As CD4+ T cells may not recognize the modified peptide as self any longer those can subsequently provide T cell help to Plasmoblasts. Plasma cells mount an antibody response primarily directed against the modified priming IL-1RA but may also cross-react to IL-36RA and IL-38. BCR: B-cell receptor; TCR: T-cell receptor; HLA: human leucocyte antigen; IL-1RA: interleukin-1 receptor antagonist; IgG: Immunoglobulin G; Th cells: helper T cells; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; mRNA: messenger RNA.

[12]. However, IL-1RA AutoAbs could be observed in less than 1% of Dutch and Austrian population without clinical symptoms [13]. Such pre-existing antibodies recognize the unmodified IL1RA antigen. Various hypotheses can be considered to elucidate the generation of these AutoAbs (**Figure 1**).

Like other anti-cytokine AutoAbs, nAbs against IL-1RA may potentially play a regulatory role by preserving immune system homeostasis and mitigating excessive anti-inflammatory responses [14, 15]. Notably, subjects suffering from certain inflammatory diseases have demonstrated a decrease in nAbs against IL-1RA titers over time as the diseases gradually resolve [9, 13]. Similarly, patients with various infections have shown a decrease in IFN-γ AutoAbs titers with clinical resolution [16, 17]. Furthermore, the inverse relationship between IL-1RA AutoAbs level and severity in subjects with vaccine-associated myocarditis [13] supports speculation that they can result from physiological homeostatic mechanisms following infections or vaccinations, as in rheumatoid arthritis [2].

Several self antigens have been described as targets for phosphorylation by serine/threonine kinases, and they can then be recognized by AutoAbs [18, 19]. Notably, the abnormal phosphorylation of IL-1RA seems to significantly influence its immunogenicity in individuals with MIS-C and vaccine-associated myocarditis [8, 13] (**Figure 1**). Nevertheless, breakdown of peripheral immune tolerance does not result in sustained IL-1RA hyperphosphorylation. This observation is supported by recent research of the AutoAbs targeting interferon (IFN)-alpha (α) and -beta (β) in individuals with critical viral infections and systemic autoimmune diseases

[7, 20, 21]. For instance, subjects with severe coronavirus disease 2019 (COVID19) exhibit a short-lived response of high-level nAbs against IFN-α/-β [7]. Additional research is required to determine whether hyperphosphorylated IL-1RA actually induces MIS-C/vaccine-induced myocarditis or if it merely serves as an indicator or a secondary phenomenon of other risk factors.

Neutralization capacity of IL-1RA AutoAbs may also explain the acquisition of auto-reactivity and pathogenic effects in IL-1RA-associated diseases development. Notably, Thurner et al. [13] showed that subjects with nAbs to IL-1RA, with low levels of neutralizing activity, did not have COVID-19 vaccine-associated myocarditis, suggesting that not only the amount of the antibody but also their ability to impede IL-1RA bioactivity is required for pathogenicity. Neutralizing activity also requires IL-1RA AutoAbs to be of relatively high affinity and/or avidity. The affinity maturation-mediated peripheral tolerance checkpoints of B cells might clarify why spontaneously occurring IL-1RA AutoAbs in healthy, asymptomatic individuals generally exhibit lower titers or functionality than those in individuals with active inflammation. Many studies consider somatic hypermutation in centroblasts that enhance autoantibody affinity maturation to drive pathology [22]. The predominant isotypes among nAbs targeting IL-1RA are IgG subclasses 1 and 2 [8, 9]. The immune reaction to epitopes on IL1RA, along with the isotype switching of AutoAbs to the IgG class, suggests the involvement of helper T (Th) cells and antigen presentation in the initiation of IL-1RA AutoAbs associated diseases (**Figure 1**). During exogenous antigen processing, human leukocyte antigen class II (HLA-II) molecules present specific peptides to Th lymphocytes. Meyer et al. [23] have demonstrated that these molecules bind phosphoepitopes with extraordinary affinity and present them at the cell surface for recognition by Th lymphocytes, leading to more robust T-cell dependent B-cell responses. Additionally, polymorphisms in HLA-DRB1 molecules were associated with an elevated risk of IgG4-RD [24], while variations in HLA-DQB1 molecules were linked to myocarditis development [25]. However, whether these HLA loci also influence the character of B cell response to IL-1RA has not yet been analysed.

Effect of anti-IL-1RA AutoAbs on its downstream elements

IL-1RA, functioning as an immune checkpoint cytokine, binds to IL1RI without initiating signal transduction [26]. Its broad expression is observed across diverse cell lineages [27]. IL-1 receptor is a multimeric protein complex composed of two membrane-bound molecules, called accessory protein (IL1RAP) and IL-1R1. The intracytoplasmic tail of each molecule contains a Toll/IL-1R/resistance protein (TIR) domain with conserved tyrosine residues. Upon phosphorylation of TIR domains, myeloid differentiation protein 88 (MyD88) stimulates nuclear factor κB (NFκB) and p38 mitogen-activated protein (MAP) kinase. The released NFκB and MAP kinase complex subsequently triggers the transcription of inflammatory cytokines [28-30] (**Figure 2**). The clinical importance of IL-1RA is further illustrated by uninhibited binding of IL-1α/-1β to IL1RI in children deficient in IL1-RA [31, 32]. It is also therapeutically harnessed for managing IL-1-related illnesses [33]. Neutralization of IL1RA-IL1RI interaction is overall considered a main pathogenic mechanism for anti-IL-1RA AutoAbs and was demonstrated in several inflammatory diseases (**Figure 2**). The consequence of such a block could be the uninhibited binding of IL-1α/-1β to its receptor, causing secretion of secondary mediators (e.g., IL-6, matrix metallopeptidase 9 (MMP-9) and IL-33) [9]. In addition to stimulating unrestricted IL-1 signaling hyperinflammation, neutralizing IL-1RA AutoAbs could also impact the disease activity. In this case, IgG4-RD individuals with IL-1RA AutoAbs have multiple organ failure [9]. Additionally, IL-1RA antibody with neutralizing activity can enhance bacteria-induced hepatitis and liver damage in vivo [34]. The relationship between the neutralization level of IL1RA AutoAbs and disease activity still needs to be investigated.

Anti-IL-1RA AutoAbs and pathology

Anti-IL-1RA AutoAbs were found in several disorders, including MIS-C, COVID-19 vaccine-associated myocarditis, IgG4-RD, rheumatoid arthritis, and systemic lupus. Despite this observation, the underlying reasons for the diverse clinical presentations associated with IL-1RA AutoAbs are not yet clearly elucidated.

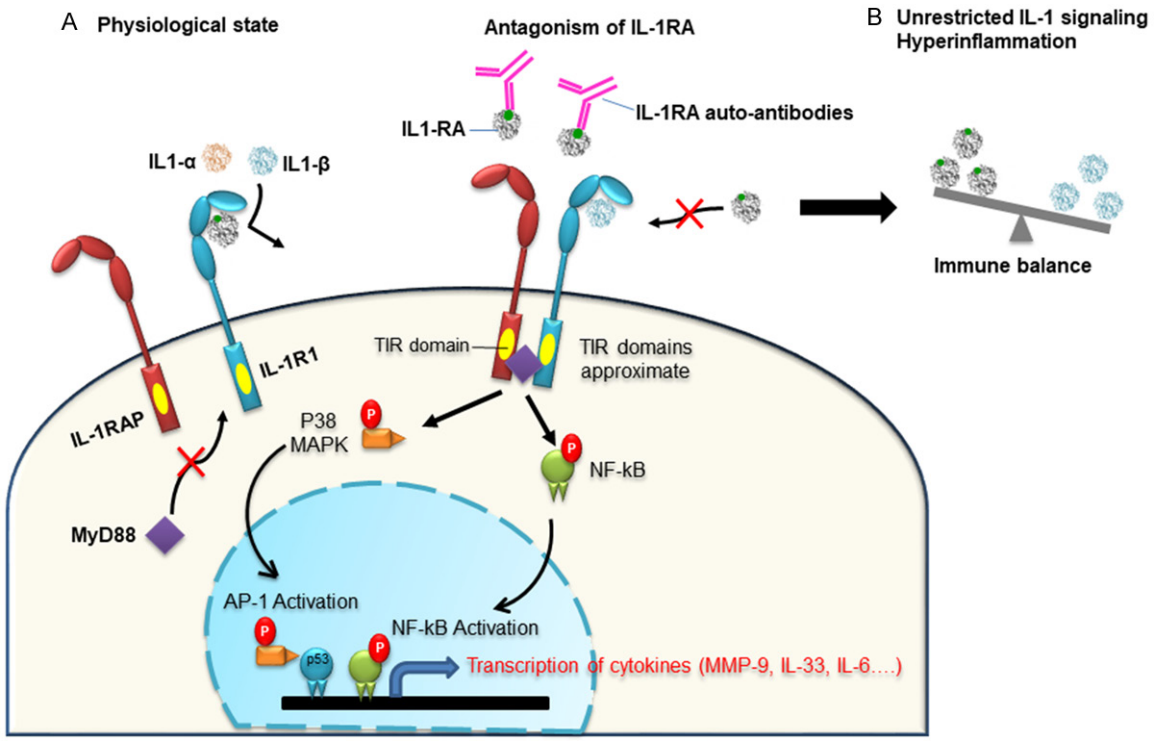

Figure 2. Proposed mechanism of action for IL-1RA AutoAbs. A. In the physiological state (left), IL-1RA antagonizes the effects of IL1-α and IL1-β by binding to IL-1R1 without triggering the inflammatory signaling pathways. B. Inflammatory imbalance in the IL1-α and IL1-β-pathway due to neutralizing IL-1-RA-AutoAbs. The functional impact of the modification of phosphorylated threonine 111 on IL-1RA isoform is still not fully understood or clarified. IL-1RA: interleukin-1 receptor antagonist; NFκB: Nuclear factor κB; p38 MAPK: p38 mitogen-activated protein kinase; AP-1: activator protein 1; MyD88: Myeloid differentiation primary response gene 88; IL-1RI: IL-1 type-I receptor; IL-1RAP: Interleukin-1 receptor accessory protein.

MIS-C

MIS-C commonly manifests 2-6 weeks after COVID-19 in older children. It exhibits symptoms resembling Kawasaki disease (KD), including persistent fever, gastrointestinal symptoms, myalgia, cephalalgia, tiredness, myocardial dysfunction and multi-organ failure [35-37]. The prevalence of anticytokines AutoAbs in MIS-C, as detected by different protocols and techniques, varies markedly. Notably, these antibodies are most frequently directed against IL-1RA (62%) [8] and IFN-γ (~80%) [38] (**Table 1**). AutoAbs specific to secreted IL-1RA bind to a defined region extending from amino acids 98 to 143, resulting in decreased plasma concentration and activity of IL-1RA [8]. It is hypothesized that these antibodies could be induced by a transient hyperphosphorylated IL-1RA isoform, with their levels gradually decreasing over time. It is then possible that their expression may, in part, be due to increased release of IL-1RA in acute COVID-19. This could initiate a polyreactive or autoreactive B cell response that secretes high-titer nAbs in a hyperinflammatory context [39, 40]. Additionally, AutoAbs to IFN-γ are transient and exhibit partial neutralization in both KD and MIS-C [38]. Thus, the breakdown in immune tolerance to cytokines in MIS-C is specific to particular targets and contexts, rather than solely arising from prolonged or excessive inflammation. The increase in IL-1R1 signaling is thought to contribute to systemic inflammatory responses and microvascular alterations in MIS-C [41, 42].

Myocarditis related to COVID19 vaccines

Myocarditis associated with COVID19 vaccines is an infrequent inflammatory adverse reaction that can occur after receiving COVID-19 vaccines. The principal features include chest pain, frequently associated with coronary spasm or pericarditis, along with fever and dyspnea [43]. The prevalence of vaccine-related myocarditis is higher in young adults males than females

Table 1. The frequency, biological activity, and clinical impact of IL-1RA AutoAbs in health and disease

Population	Frequency	In vitro Evidence for Biological Activity	Clinical impact
Healthy	1% of healthy controls	-	Unclear significance
Vaccine-induced myocarditis	75% of patients <21 years and 11% of patients ≥21 years	Neutralizing anti-IL-1RA AutoAbs shown by ELISA Depletion of IL-1RA levels and occurrence of immune complexes with an atypical IL-1RA shown in Western blots Reduction of IL-1RA bioactivity demonstrated in vitro with IL-1β signaling reporter assay	Associated with milder disease course and early symptoms, with a decline towards normal values as disease resolves; negative correlation between IL-1RA plasma levels and heart damage
IgG4-Related Disease	Up to 15.6% of patients	Neutralizing IgG4 anti-IL-1RA AutoAbs shown by ELISA Increased embryonic alkaline phosphatase demonstrated in vitro with IL-1β reporter cells Because of high homology with IL-38 and IL-36Ra, these anti-IL-1RA cross-react with IL-36RA and IL-38	Those with neutralizing anti-IL-1RA AutoAbs had more affected organes; associated with increased serum IL-6, IL-33 and MMP9
MIS-C	62% of children with MIS-C	Transient anti-IL-1RA IgG1 AutoAbs shown by ELISA (1:200, 1:800) Transient IL-1RA phosphorylation shown by isoelectric focusing and western blotting Depletion of IL-1RA levels and occurrence of immune complexes with an atypical IL-1RA shown in Isoelectric focusing and western blotting Neutralizing effect functionally demonstrated in vitro with IL-1β signaling reporter assay	Neutralizing IL-1RA antibody responses rapidly decay (5 weeks)

for unknown reasons [44]. Despite almost 75% of individuals with myocarditis having nAbs to IL-1RA, most patients do not develop prolonged and severe manifestations of illness [13] (**Table 1**). Similarly, higher levels of nAbs to multiple cytokines may be correlated with milder disease course and eventual resolution in different clinical situations [3, 45, 46]. Although Jaycox et al. reported eight cases of vaccine-related myocarditis, none of these subjects had IL-1RA AutoAbs [47]. Possible explanations for this observation could include IL-1RA autoantibodies being more of an association than a direct causative factor or limited inflammatory and cardiac damage due to the negative regulation of the IL-1β signaling cascade by other mediators such as IL-1R2. It is clearly established that IL-1R2 significantly attenuates monocyte infiltration into the heart following ischemia/reperfusion dammage in vivo [48].

The mechanisms triggering neutralizing anti-IL-1RA AutoAbs production during vaccine-associated myocarditis are not yet fully understood. Exposure to environmental factors can modify autoantigens, making them more immunogenic, leading to the breakdown of immune tolerance. MIS-C is similar to vaccine-associated myocarditis in that both diseases result from atypical hyperphosphorylation in IL1RA isoform, generally leading to direct impairment of IL1RA bioactivity and systemic inflammation [13]. Phosphorylated autoantigens and derived peptides may alter HLA-restricted antigen presentation. Notably, genetic polymorphisms in HLA-II can result in varying binding affinities to epitopes in certain autoimmune or drug-induced myocarditis [49-51]. The association between certain HLA alleles (i.e., HLA DQB1*0303, HLA DQB1*02) and a favorable prognosis in myocarditis [25, 52] implies that variation in HLA alleles can significantly influence disease outcomes. Therefore, more research is needed to identify high-risk HLA alleles that could influence the development of myocarditis when exposed to environmental triggers such as COVID-19 vaccines.

IgG4-RD

IgG4-RD refers to an immune disorder characterized by multiorgan involvement, migration of IgG4-positive plasmablasts within a tissue, obliterative phlebitis, and storiform fibrosis [53]. Jarrell and colleagues [9] detected IgG4 nAbs targeting IL-1RA in more than 15.6% of individuals with IgG4-RD, establishing their association with multi-organ involvement (**Table 1**). Additinally, subjects with IgG4-RD displayed elevated ratios of IgG4/IgG and IgG4/IgG1 [54]. Thus, plasmablasts/plasma cells generating nAbs against IL-1RA exhibit some features of T-cell-dependent antibody responses in that they have undergone class-switch recombination (**Figure 3**). The strong genetic relationship between HLA-DRB1*04:06 and -DRB1*09:01 with IgG4-RD [24] highlights the pivotal role of these genes in pathogenesis, as in rheumatoid arthritis [55].

Histopathologically, accumulation of IgG4-positive plasmablasts and storiform fibrosis are seen in IgG4-RD, along with other autoimmune and malignant diseases [56-58]. It is clearly established that in vitro, plasmablasts from subjects with IgG4-RD directly stimulate fibroblasts, thereby contributing to tissue fibrosis [59]. As noted above, nAbs to IL-1RA can specifically bind abnormally hyperphosphorylated IL-1RA. Nevertheless, these AutoAbs can also demonstrate cross-reactivity with other cytokines belonging to the IL-1 family, including IL-36RA and IL-38. Supporting this observation, there is evidence indicating a high structural homology among IL-1RA, IL-36RA, and IL-38 [60]. However, the immunopathogenic role of IL-36RA, in particular of IL-38, in IgG4-RD remains undefined. NAbs against IL-36RA correlate with in vivo anti-inflammatory activity in psoriasis [61]. The observation that IL-1RA treatment prevented fibrotic development and reversed established fibrosis in mice [62] implies that nAbs against IL-1RA can mediate tissue fibrosis by inhibiting IL-1RA/IL-1R interaction (**Figure 3**). This, in turn, offers a partial explanation for the resolution of fibrotic damages seen with B lymphocyte depletion [63]. Conversely, several reports describe a lack of relationship between various AutoAbs, including IgG4- and IgE-specific galectin-3 AutoAbs [64], antineutrophil cytoplasmic antibodies, and IgG4 prohibitin AutoAbs [65, 66] and IgG4-RD. These AutoAbs are primarily of the IgG subclass 1 and target intracellular autoantigens. However, they are unlikely to serve as the initial trigger for autoimmunity due to their limited accessibility.

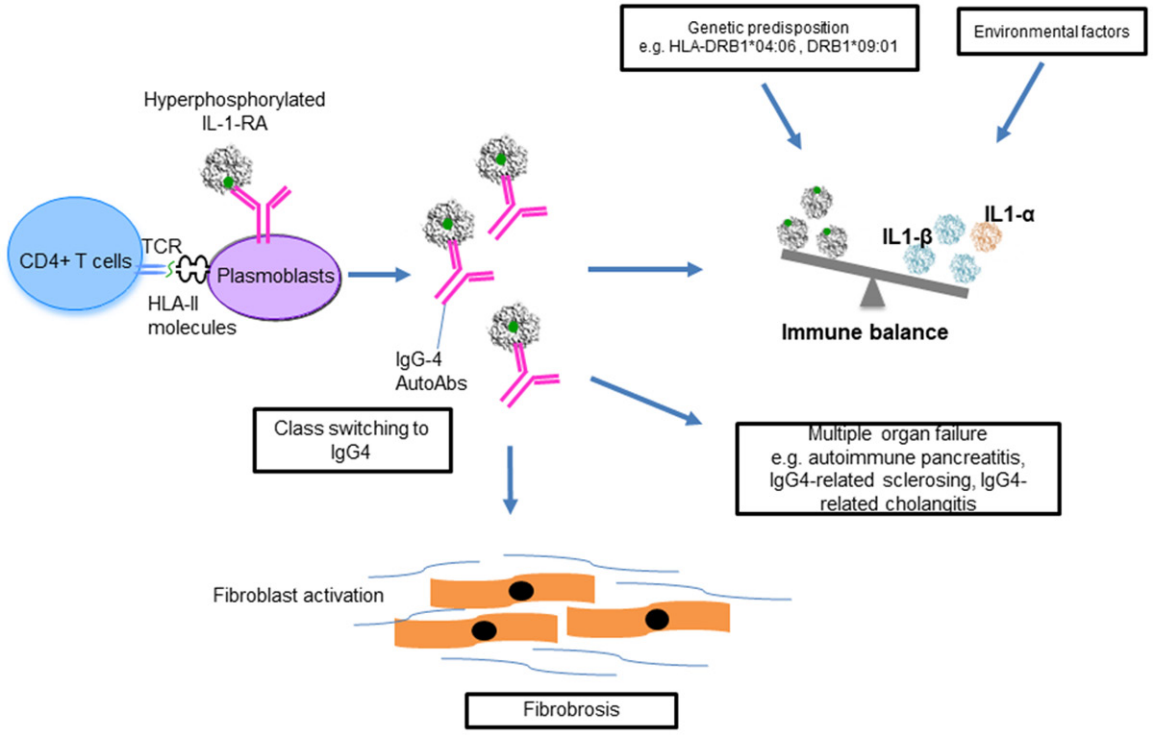

Figure 3. The image illustrates the mechanisms underlying IgG4-RD in patients with neutralizing antibodies to IL-1RA. IgG4 IL-1RA autoantibodies play crucial roles in IgG4-RD by neutralizing the IL1RA-IL1RI interaction. Additionally, IgG4 nAbs against IL-1RA are presumed to mediate fibrosis and inflammation by inhibiting IL-1RA/IL-1R interaction and secretion of proinflammatory cytokines, potentially leading to the induction of multiorgan failure. IL-1RA: interleukin-1 receptor antagonist; IL-1RI: IL-1 type-I receptor; TCR: T-cell receptor; HLA: human leucocyte antigen; NAbs: Neutralizing antibodies; IgG4-RD: IgG4-related disease; HLA: Human leucocyte antigen; IgG: Immunoglobulin G; Th cells: helper T cells.

Detection and functional evaluation of anti-IL-1RA AutoAbs

As noted above, there are notable inconsistencies in different reports concerning the presence of nAbs against IL-1RA in diverse inflammatory disorders. Determining whether these variations arise from population heterogeneity or the methodology used for autoantibody detection poses a significant challenge. Clinical lab detection of anti-IL-1RA AutoAbs is performed using two categories of assays: solid-phase immunoassays, such as in-house immunoenzyme-linked immunosorbent assay (ELISA) and isoelectric focusing, which identify the binding of IL-1RA AutoAbs; and functional IL-1β signaling reporter cell assays that provide enhance specificity by assessing whether circulating AutoAbs can either impede or stimulate NF-κB and MAP kinases signal transduction pathways (**Table 1**). Results from isoelectric focusing and alkaline phosphatase treatment reveal a hyperphosphorylated pattern in IL-1RA at residue threonine 111 and its complexes in individuals seropositive for IL-1RA AutoAbs [13]. Experiments involving IL-1β signaling reporter assays detect the secretion of embryonic alkaline phosphatase when a patient's serum containing IL-1RA AutoAbs is incubated with human embryonic kidney (HEK) IL-1β reporter cells, IL-1β, and IL-1β with recombinant human IL1RA (rec hIL-1RA). If IL-1RA antibodies are clinically significant, they bind to rec hIL-1RA, resulting in uninhibited binding of circulating IL-1 to its receptor on HEK cells and subsequent secretion of embryonic alkaline phosphatase [67]. However, the relationship between observed dysfunction of IL-1RA bioactivity and antibody titer remains unclear.

Clinical management of IL-1RA AutoAbs

The primary approach to resolving inflammatory state in diseases associated with IL-1RA

AutoAbs is through anti-inflammatory therapy. The management of subjects with MIS-C involves a regimen that combines corticosteroids and intravenous immunoglobulin (IVIG) [68, 69]. IgG4-RD is effectively manageable and exhibits a prompt response to steroid therapy [70]. Steroids and colchicine have been employed in the clinical management of individuals with persistent mild symptoms of vaccine-related myocarditis [71]. An alternative and successful therapy for recurrent COVID-19 vaccine-associated pericarditis resistant to steroids and colchicine [72] and refractory MIS-C [73, 74] involves biological drugs, such as rec hIL-1RA monoclonal antibody. Nevertheless, the employment of these biological molecules can be correlated to the development immunogenic antibodies, particularly in juvenile idiopathic arthritis [75], severe cryopyrin-associated periodic syndromes [76], and rheumatoid arthritis [77]. Another question that arises is whether the employment of rec hIL-1RA in inflammatory conditions could be linked to IL-1RA AutoAbs-associated diseases.

Conclusion

Anti-IL-1RA AutoAbs may play both pathogenic and regulatory roles in the human body. An imbalance between these antibodies and IL-1β signaling, along with unidentified genetic factors, may contribute to inflammatory diseases in particular tissues. Additionally, detection of nAbs to IL1-RA may be impacted by ELISA protocol used, highlighting the crucial role of standardization to enhance analytical precision. Further exploration is needed into the mechanisms of IL-1RA AutoAbs production and their long-term effects in rare but severe hyperinflammatory syndromes and illnesses.

Disclosure of conflict of interest

None.

Abbreviations

AutoAbs, Autoantibodies; Nabs, Neutralizing antibodies; MIS-C, Multisystem Inflammatory Syndrome in Children; IgG4-RD, IgG4-related disease; IL, Interleukin; IL-1RI, IL-1 type-I receptor; IL-1RAP, Interleukin-1 receptor accessory protein; IL-1RA, interleukin-1 receptor antagonist; IFNγ, Interferon gamma; IFNα, Interferon alpha; IFNβ, Interferon β; BCR, B-cell receptor; TCR, T-cell receptor; HLA, Human leucocyte antigen; NFκB, Nuclear factor κB; p38 MAPK, p38 mitogen-activated protein kinase; MyD88, Myeloid differentiation primary response gene 88; TIR, Toll/IL-1R/resistance protein; IgG, Immunoglobulin G; ELISA, Enzyme-inked immunosorbent assay; COVID-19, coronavirus disease 2019; Th cells, helper T cells; KD, Kawasaki disease; HEK, Human embryonic kidney; rec hIL-1RA, recombinant human IL-1RA.

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