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Review

Fc receptors gone wrong: A comprehensive review of their roles in autoimmune and inflammatory diseases

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ABSTRACT

Systemic autoimmune and inflammatory diseases have a complex and only partially known pathophysiology with various abnormalities involving all the components of the immune system. Among these components, antibodies, and especially autoantibodies are key elements contributing to autoimmunity. The interaction of antibody fragment crystallisable (Fc) and several distinct receptors, namely Fc receptors (FcRs), have gained much attention during the recent years, with possible major therapeutic perspectives for the future. The aim of this review is to comprehensively describe the known roles for FcRs (activating and inhibitory FcγRs, neonatal FcR [FcRn], FcαRI, FcεRs, Ro52/tripartite motif containing 21 [Ro52/TRIM21], FcδR, and the novel Fc receptor-like [FcRL] family) in systemic autoimmune and inflammatory disorders, namely rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, idiopathic inflammatory myopathies, mixed connective tissue disease, Crohn's disease, ulcerative colitis, immunoglobulin (Ig) A vasculitis, Behçet's disease, Kawasaki disease, IgG4-related disease, immune thrombocytopenia, autoimmune hemolytic anemia, anti-phospholipid syndrome and heparin-induced thrombocytopenia.

1. Introduction

Antibodies are central mediators of the antimicrobial immunological defense, but when autoreactive, they can become deleterious and be functionally involved in the pathogenesis of various autoimmune and inflammatory disorders [1,2]. Among the multiple autoantibody-dependent mechanisms possibly contributing to autoimmunity, the ones which depend on the interaction of antibody fragment crystallisable (Fc) and several distinct receptors, namely Fc receptors (FcRs), have gained much attention during the recent years [3]. The statistical association between systemic autoimmune and inflammatory diseases' onset or response to treatment/propension to relapse and numerous single-nucleotide polymorphisms/copy number variations within classical FcRs-coding genes (e.g., *FCGR2A*, *FCGR2B*, *FCGR2C*, *FCGR3A*,

FCGR3B) have been known for years [4–6]. Beyond these statistical associations, lies a wide range of complex and partially known disease-specific Fc/FcR-dependent mechanisms, whose knowledge can guide future clinical research in the field.

This comprehensive review article aims at reporting and deciphering the known role of FcRs, ranging from the well-known immunoglobulin (Ig) G's FcγRs [7] to the more confidential IgD's FcδR [8] and the novel Fc receptor-like (FcRL) family [9], in systemic autoimmune and inflammatory disorders. An overview of all the diseases and the respective involved receptors discussed in this review, is summarized in Table 1, and the main reported deleterious mechanisms are presented in Fig. 1.

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Table 1
Fc Receptors involvement in autoimmune and inflammatory diseases.

Autoimmune/ inflammatory disease	Fc Receptors involved
Rheumatoid Arthritis	FcγRI [20,22,23,32], FcγRIIA [24,25,32], FcγRIIIA [16,22,106], FcγRIIB [22,30], FcγRIIIB [33,225], FcRn [49], FcαRI [73], FcεRII [78–80,82,83], Ro52/TRIM21 [126], FcδR [86–88], FcRL2 [90], FcRL4 [90–92]
Sjögren's Syndrome	FcγRI [100–102], FcγRIIA [100–102,225], FcγRIIIA [100–102,107], FcγRIIIB [113], FcγRIIIB [1225], FcαRI [120], FcεRII [121,122], Ro52/TRIM21 [126,137,139,140,142–146], FcRL4 [147]
Systemic Lupus Erythematosus	FcγRI [102,157,161,162,164,165], FcγRIIA [102,153,157,169,171], FcγRIIB [165,172–174], FcγRIIIB [1225], FcRn [178], FcαRI [182,183], FcεRI [187,189,195,196], FcεRII [121,199,200], Ro52/TRIM21 [135,203,205,206,209,213]
Systemic Sclerosis	FcγRIIA [223], FcγRIIIA [219,221], FcγRIIIB [1225], FcεRI [228], Ro52/TRIM21 [126,229–232]
Idiopathic inflammatory myopathies	FcγRIIIB [248], FcRn [248], FcεRI [196], Ro52/TRIM21 [126,206,242–247]
Mixed Connective Tissue Disease	FcεRI [255], FcεRII [200], Ro52/TRIM21 [256,257]
Crohn's Disease	FcγRI [262,263,265,266], FcγRIIIB [270], FcαRI [276]
Ulcerative Colitis	FcγRI [261,262,264,266], FcγRIIA [264,267], FcγRIIIA [267], FcγRIIB [267], FcγRIIIB [267,270], FcαRI [65]
IgA Vasculitis	FcαRI [282,283]
Behçet's Disease	FcγRI [289], FcγRIIIA [290], FcγRIIB [290]
Kawasaki Disease	FcγRIIA [298,299], FcγRIIIA [298], FcγRIIB [298,299]
ANCA-associated Vasculitides	FcγRIIA [171,303,310,318], FcγRIIIA [309], FcγRIIB [311], FcαRI [312]
IgG4-Related Disease	FcγRIIA [327]
Immune Thrombocytopenia	FcγRI [330], FcγRIIA [330,334,335], FcγRIIIA [330,334], FcRn [336]
Autoimmune Hemolytic Anemia	FcγRI [341,342], FcγRIIA [341,342], FcγRIIIA [341,342], FcRn [347]
Antiphospholipid Syndrome	FcγRIIA [347,355], FcRn [347,358]
Heparin-induced thrombocytopenia	FcγRI [362], FcγRIIA [360,361], FcRn [347]

FcγR, Fcγ receptor; FcRn, neonatal Fc receptor; FcαRI, Fcα receptor I; FcεRI, Fcε receptor; Ro52/TRIM21, Ro52/tripartite motif containing 21; FcδR, Fcδ receptor; FcRL, Fc receptor-like.

2. Adverse FcR engagement in systemic autoimmunity

2.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most prevalent systemic autoimmune disease, approximately affecting 0.5 to 1% of the adult population worldwide [10]. It is primarily involving the joints, causing inflammatory chronic pain and progressive tissue destruction which can eventually lead to deformities and definitive loss of function of the affected joints [11]. RA is also responsible for systemic inflammation, with its deleterious consequences (e.g., cardiovascular diseases and increased mortality), and extra-articular manifestations such as rheumatoid nodules, interstitial lung disease or vasculitis [11]. Due to its high frequency and the burden it causes for both individuals and the society [12], RA is the most studied systemic autoimmune diseases, with the highest number of approved drugs to date, but 20–30% of the patients are still refractory to current therapies [13]. RA's pathophysiology is heterogeneous and characterized by an abnormal inflammatory response, which involves several components of the immune system, including immune complexes (ICs) formation by anti-citrullinated peptides antibodies (ACPA), citrullinated self-proteins and rheumatoid factors (RF, *i.e.*, anti-IgG Fc autoantibodies) [14]. The presence of these ICs, as well as abnormal expression of FcγRs in circulating monocytes and resident synoviocytes from patients with RA, lead to an increase in the activating to inhibitory FcγR ratio, resulting in uncontrolled local and systemic inflammation [15,16]. The pathogenic involvement of activating FcγRs has been proven in multiple experimental models of

arthritis, but the specific role of each receptor is still unclear [15,16].

FcγRI, the highest affinity receptor among all Fcγ receptors, can be activated by monomeric IgGs, whereas the other FcγRs, such as FcγRIIA and FcγRIIIA bind IgGs with lower affinity and need to be cross-linked by ICs to be activated. They are mainly expressed on myeloid cells such as monocytes, macrophages, NK cells and neutrophils [17], and mediate effector functions: phagocytosis, antibody-dependent cell cytotoxicity (ADCC), or release of inflammatory cytokines and chemokines [18]. Under inflammatory conditions (as seen in RA), FcγRI and FcγRIIA expressions increase and expression of the inhibitory receptor, FcγRIIB, decreases on myeloid cells [19,20]. At the same time, proinflammatory cytokines such as TNFα, IL1, or IL6, are produced after activating FcγRs engagement, which enhance the proinflammatory environment [21]. All activating FcγRs have been involved in the induction and/or maintenance of arthritis, with possibly redundant effects according to the results from previous experiments using various mouse models with different FcγR knock out combinations [22]. Recently, functional FcγRI has been identified on dorsal root ganglion neurons, and animal models studies suggest that FcγRI-mediated signalling plays an important role in the development of articular pain [23]. Moreover, FcγRs and Toll-Like Receptors (TLRs) are partners in crime to induce TNFα production or macrophages differentiation towards an inflammatory phenotype [24,25]. Of note, FcγRs are also expressed on osteoclasts and their activation could be directly involved in the cartilage and bone destruction, a central hallmark in RA, but such mechanism has not been proven to date. However, the relationship between synovial inflammation and bone destruction has been demonstrated, and seems to be mediated by macrophages and neutrophils [16]. Recent experiments using knockout mouse strains for various combinations of FcγRs suggest that the murine ortholog of FcγRIIIA is the main FcγR involved on neutrophils and its activation induces the production of alarmins (namely S100A8 and S100A9, which account for 40% of the cytosolic proteins in neutrophils [26]) able to directly stimulate osteoclast activity *via* TLR4. Interestingly high levels of these alarmins are present in the synovial fluid of patients with RA [16,27].

Apart from their osteoclast-mediated role in joint destruction, neutrophils are thought to be key actors in the induction and maintenance of joint inflammation in RA, involving a self-propagating inflammatory loop [28]. In experimental arthritis animal models, their central role is clear, and their depletion has been associated with complete disease protection in some cases [29]. In human RA, neutrophils are the most frequent immune cells detected in inflamed joints, where they seem to be involved in an inflammatory amplification loop: they produce multiple modified proteins, including citrullinated proteins, which are targeted by ACPAs, hence resulting in ICs formation and further proinflammatory signalling through activating FcγR engagement and cross-linking [28,30,31]. Synovial mast cells are also involved in the pathogenesis of RA and can be activated *via* FcγRI and FcγRIIA engagement [32]. It is also noteworthy that FcγRIIIB seems to play a pivotal role in the secretion of toxic products (ROS and proteases) by neutrophils, in response to ICs found in abundance in the synovial fluid of patients with RA [33], however, selectively inhibiting FcγRIIIB does not seem to have a significant effect on the ability of human neutrophils to phagocytose and kill serum-opsonized pathogens [33]. This is probably due to the presence of non-FcγRIIIB-dependent mechanisms leading to phagocytosis and killing, and could lead way to the development of FcγRIIIB inhibitors, but tolerability has been an issue to date [3,34]. As recently reviewed elsewhere [3], targeting FcγRs has indeed brought much attention in autoimmune/inflammatory diseases during the past 10 years, with multiple approaches including recombinant Fc multimers, and Fc/FcγR-targeting treatments [3]. For example, a recombinant human IgG1 Fc hexamer was shown to be more efficient than plasma-derived intravenous human immunoglobulins (IVIg) in an ICs-mediated mouse model of RA [35]. A recombinant soluble form of the high affinity FcγRI was efficacious at blocking inflammation in both passive transfer models of ICs-mediated RA and in a T cell- and B cell-

dependent mouse model of RA [36]. Divalent targeting of FcγRIIIa by anti-FcγRIII F(ab)′2 fragments was also efficient in improving inflammation *in vitro* and *in vivo* (in an animal model of RA), via the induction of inhibitory ITAM (ITAMi) resulting from partial phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) on tyrosine residues (contrary to what happens after multivalent crosslinking of immunoreceptors by ICs, which leads to full phosphorylation of the tyrosine residues present in the ITAM) [6]. Alternatively, interfering with FcR-induced downstream signalling is also being evaluated, with multiple possible targets, such as spleen tyrosine kinase (Syk) or Bruton tyrosine kinase (Btk) [37,38].

FcγRIIb is broadly distributed on all innate immune cells, B cells, and at lower levels, on non-hematopoietic cells [39]. It binds IgG Fc with a low affinity and is the only inhibitory FcγR (due to its attached inhibitory motif named immunoreceptor tyrosine-based inhibition motif [ITIM]). Its role on B cells is noteworthy, as IC-dependent co-crosslinking of the B Cell Receptor (BCR) and FcγRIIb results in inhibiting activation, proliferation, antigen internalization and antibody secretion.

As described earlier, activating FcγR signalling in neutrophil is a key element in RA pathogenesis [40,41], however, there are several negative feedback mechanisms whose role is to regulate neutrophils pro-inflammatory behaviour. Among those, IL-4 and Colony Stimulating Factor 3 (which is released during acute inflammation) pathways are acting synergistically to induce neutrophil up-regulation of the inhibitory FcγRIIb and limit neutrophil migration to inflamed joints [30]. Regarding therapeutics, a recombinant soluble FcγRIIb was effective at improving the disease phenotype and reduce inflammatory cytokines production in an experimental arthritis mouse model [42]. Moreover, an innovative bispecific monoclonal antibody, obixelimab (Xmab5871), which is an engineered anti-CD19 monoclonal antibody whose Fc’s affinity for FcγRIIb has been greatly increased (approximately 400-fold compared to its non-engineered counterpart), is in clinical development in few autoimmune diseases, including RA [43]. It is able to co-engage the BCR complex and target B cells without the disadvantages associated with long-term B cell depletion [44]. A phase-Ib/IIa clinical trial evaluating obixelimab in human RA has been completed, and its

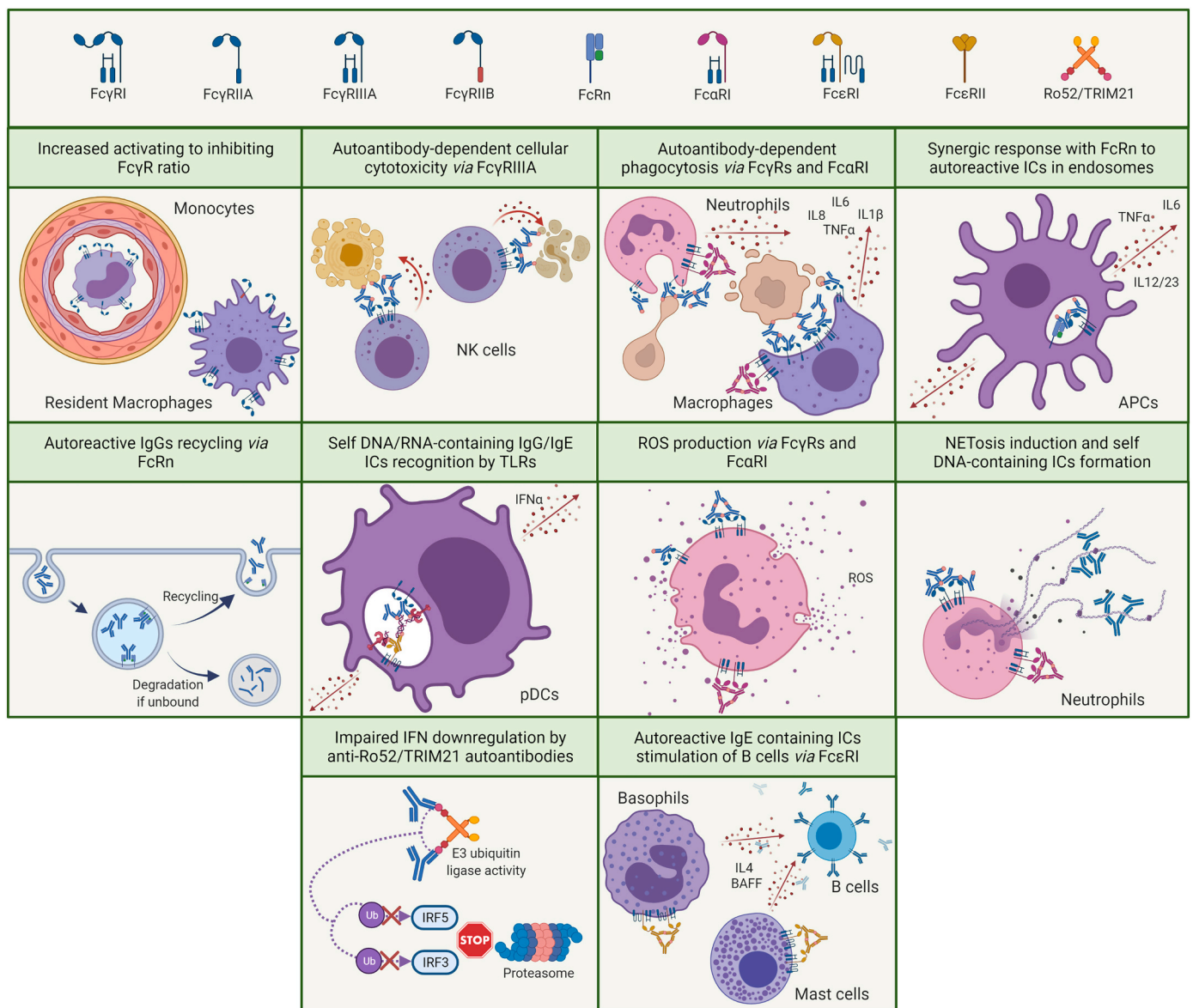


Fig. 1. Main Fc Receptors-related mechanisms reported in autoimmune and inflammatory diseases. FcγR, Fcγ receptor; FcRn, neonatal Fc receptor; FcαRI, Fcα receptor I; FcεR, Fcε receptor; Ro52/TRIM21, Ro52/tripartite motif containing 21; ICs, immune complexes; NK cells, natural killer cells; IL, interleukin; TNFα, tumour necrosis factor α; APCs, antigen presenting cells; Ig, immunoglobulins; TLRs, toll like receptors; pDCs, plasmacytoid dendritic cells; ROS, reactive oxygen species; NET, neutrophil extracellular trap; IFN, interferon; Ub, ubiquitin; IRF, interferon regulatory factor; BAFF, B cell activating factor.

preliminary results are encouraging [45].

The neonatal Fc receptor (FcRn) is ubiquitously expressed in human tissues, with the highest levels detected in lymphoid tissues (spleen and lymph nodes) [46]. As reviewed recently [47,48], the FcRn has a complex and incompletely elucidated role in autoimmunity. Its ability to recycle and maintain high levels of IgGs – including autoreactive IgGs – is well known to be involved in autoantibody-mediated diseases. It has also been involved in the regulation of multiple key functions in immune cells, such as phagocytosis, cytokine production or antigen/cross presentation (FcRn is highly expressed on dendritic cells and monocytes' cell surface), which are also involved in autoimmunity [47]. Recent studies have proposed further roles for FcRn, in combination with FcγRIIa, which are likely to be important in autoimmunity. FcRn seems to be involved in the induction of innate and adaptative immune responses to IgG ICs, by forming a ternary complex including FcγRIIa (especially its high affinity H131 variant) under acidic conditions found in intracellular endosomal compartments (where IgG ICs are pinocytosed and can cross-link FcRn) [49]. FcRn was also able to induce responses to IgG ICs on its own *in vitro*, however optimal responses required both FcRn and FcγRIIa. In a FcγR-dependent mouse model of rheumatoid arthritis, blocking FcRn with a monoclonal antibody specifically designed not to affect circulating autoantibody levels, induced a decrease in the disease features.

Among the possible therapeutic strategies, IVIg have been historically used for their immunomodulatory role in diseases such as immune thrombocytopenia (ITP) [50], Kawasaki Disease (KD) [51], or idiopathic inflammatory myopathies (IIM) [52] with success. The mechanisms behind their efficacy are incompletely understood, but they include multiple FcR-related functions: the saturation of FcRn and subsequent acceleration of circulating autoantibodies' clearance [53], upregulation and signalling through the inhibitory FcγRIIb [54,55], and induction of ITAMi signalling *via* monomeric engagement of the activating FcγRs [56]. IVIg are not routinely used to treat patients with RA, because of the lack of evidences to do so in human [57,58] and only very recent positive results in mouse models [59]. Of note, due to the main limitation of IVIg *i.e.*, being dependent on the supply of human plasma, multiple alternate FcR-targeting innovative molecules are being developed at the moment, as aforementioned [3,60].

FcαRI, which is constitutively expressed on the surface of neutrophils, eosinophils, monocytes, macrophages, Kupffer cells and platelets, is the main receptor to all forms of IgA [61]. Depending on the IgA form, either anti-inflammatory (with monomeric IgA binding) or pro-inflammatory responses can be induced, the latter being able to induce severe tissue damages – when uncontrolled – *via* IgA ICs-induced cross-linking of FcαRI [62] and activation of downstream functions including phagocytosis, neutrophil extracellular traps (NETs) formation (NETosis), ADCC, superoxide generation, release of inflammatory cytokines or antigen presentation [63–66]. Hence, FcαRI is potentially involved in all the autoimmune diseases whose pathogenesis include the presence of excessive IgA ICs or aberrant IgA autoantibody-containing ICs such as RA, but also IgA vasculitis, inflammatory bowel disease (IBD) or Sjögren's syndrome (SjS). In RA, the detection of high serum levels of the classical autoantibodies (RF and ACPA) of the IgA isotype has been associated with a more severe disease, including higher frequency of extra-articular manifestations [67]. Higher disease activity has also been described in patients with positive synovial fluid IgA RF and ACPA [68], whose IgA RF-containing ICs were able to induce FcαRI-dependant neutrophil activation, leading to the production of reactive oxygen species and NETosis [63]. More recently, the presence of anti-citrullinated peptide salivary IgA has also been associated with higher disease activity [69], and it has been hypothesised that NETosis, whose induction rely upon FcαRI at mucosal sites [70], could be the missing link between periodontitis and rheumatoid arthritis' shared pathogenesis [71,72]. IgA monomers and anti-FcαRI Fab fragments have demonstrated efficiency *in vitro* and in an experimental model of RA [73].

The low-affinity Fc receptor for IgE (FcεRI/CD23) is almost exclusively expressed on immune cells, especially on B cells, and is involved in IgE production regulation [74]. Despite its name, the fact that its membrane-bound form is trimeric (which induces a higher avidity) results in a net affinity comparable to that of the high affinity receptor for IgG, FcγRI [75]. FcεRII can also be released from cell surfaces in different forms (*i.e.* soluble FcεRII [sFcεRII]), all of which being able to bind IgE, with opposite resulting effects (the trimeric form enhances IgE production, whereas the monomeric form inhibits it) [76]. Soluble FcεRII forms also have cytokine-like activities with roles in lymphocyte (especially B cells) survival and cytokine release by monocytes, not surprisingly linking it to autoimmunity. The effects of autoreactive IgE-containing IC-dependent activation of FcεRII has not specifically been studied to our knowledge, however IC containing allergen-specific IgE seem to be able to activate B cells (but not monocytes which express a different isoform) and induce interferon (IFN) γ production [77]. In RA, an increased proportion of B cells expressing FcεRII, as well as elevation of sFcεRII levels in plasma and synovial fluid were described [78], especially in erosive forms [79]. Furthermore the administration of an anti-FcεRII antibody inhibited the activation of monocytes/macrophages isolated from RA patients [80] and ameliorated the disease phenotype in animal models of arthritis [80,81]. A population of FcεRII (+) CD21 (high) follicular B cells has recently been described in the inflamed lymph nodes of RA patients, where they can represent a third of all the cells and induced lymph node architecture's distortion [82]. They seem unaffected by anti-B cell treatments, but the specific role of FcεRII has not been explored yet [83].

Interestingly, IgD, both the most preserved throughout evolution and the less studied class of immunoglobulins in human, could be involved in autoimmune diseases' pathogenesis, including RA's [41,84]. Their functions are still poorly understood, but their membrane-bound form participates in maintaining the balance between self-tolerogenic and immunogenic B cell response through a complex interplay between surface IgD and IgM [84]. Secreted IgD are rare and have variable blood levels in physiological conditions, however, they are involved in maintaining mucosal immunity homeostasis and can bind respiratory tract commensals and pathogens. Class-switched IgD-secreting plasma cells are easily detectible in human tonsils and in other mucosal sites (such as lacrimal, salivary, or mammary glands) but not in the spleen or bone marrow. Secreted IgD can apparently interact with basophils, mast cells, monocytes, and dendritic cells *via* an elusive receptor, and subsequently lead to an IL4-and-basophil-mediated amplification of B cell responses to IgD-targeted antigens. Moreover, a Fcδ receptor (FcδR), which is able to bind membrane and secreted IgD (either in their monomeric or complexed forms), has been identified on T cells [8]. FcδR seems to be positively involved in antigen specific T-B cells interaction, leading to enhanced antibody production and T cell activation, but its full role remains to be explored [41,85]. In RA patients, blood IgD levels and FcδR expression on T and B cells were found to be increased, and associated with disease activity [86,87]. FcδR is also constitutively expressed on fibroblast-like synoviocytes, which are key resident cells in RA, at higher levels in patients than in controls [86,88]. Targeting the IgD-FcδR interaction has hence been viewed as a possible therapeutic target, with promising results *in vitro* as well as *in vivo* in an animal model of RA, where it has been able to improve the disease phenotype and suppress the abnormal T cell activation and proliferation [87,89].

Finally, the potential roles for Fc receptor-like (FcRL) molecules, a recently characterized family of receptors [9] expressed by lymphocytes, which share similarities with the classical FcRs, are being explored in autoimmunity. The level of expression of FcRL1, 2 and 4 (which are respectively thought to be activating, bifunctional and inhibiting receptors, given the nature of their associated immunoreceptor tyrosine-based motifs) has been studied in PBMCs from patients with RA and healthy controls [90]. Lower FcRL4 expression levels were reported in PBMCs from patients with RA and FcRL2 expression correlated with disease activity and autoantibody production. More

interestingly, FcRL4 has been identified on a specific memory subset of B cells which is enriched in the joints of patients with RA, and could contribute to articular destruction through RANKL expression [91,92].

2.2. Sjögren's syndrome

Sjögren's syndrome (SjS) is the second most frequent (approximate prevalence of 100 per 100,000 individuals [93]) systemic autoimmune disease, whose key feature is sicca syndrome *i.e.* mucosal dryness, mainly affecting the eyes and the oral cavity [94]. The lacrimal and salivary glands are infiltrated by immune cells (predominantly lymphocytes), but they are not the only affected organs. As a systemic disease, SjS has a broad clinical spectrum (*e.g.* joints, peripheral and central nervous systems, lungs, kidneys) with extraglandular manifestations in more than one third of the cases [95,96]. B cell hyperactivity is also a key feature in the disease, as attested by abundant production of autoantibodies, whose main targets are intracellular antigens Ro52/Tripartite motif containing 21 (TRIM21), Ro60/TROVE domain family member 2 (TROVE2) (altogether referred to as Ro/Sjögren's Syndrome A [SSA]) and La/Sjögren's Syndrome B (SSB) [97], but also by the increased risk of developing non-Hodgkin B cell (particularly mucosa-associated lymphoid tissue [MALT]) lymphomas [98].

The exact pathogenic role of the classical autoantibodies present in SjS, is still unclear, but seropositive patients are known for developing a more severe disease [99]. *In vitro* experiments using an activating FcγR-expressing human salivary gland cell line, demonstrated that anti-Ro/SSA and anti-La/SSB autoantibodies purified from patients with SjS were able to enter the cells *via* a FcγR-dependent (involving FcγRI, FcγRII and FcγRIII) mechanism, and could activate intrinsic and extrinsic apoptotic pathways [100]. More recently, the same authors also reported that these autoantibodies were able to increase the expression of the activating FcγRs in the same cell line, and could therefore contribute to the progression of the autoimmune disease [101]. Evidence about what is happening *in vivo*, in primary cells, and the events' order, are still lacking. Interestingly, anti-Ro/SSA and anti-La/SSB are able to opsonize late apoptotic cells and reduce their clearance by macrophages *via* a FcγR-dependent mechanism [102,103]. This effect could also contribute to the progression of the immunopathogenic progress by fuelling the inflammatory response. In patients with SjS, levels of mature CD14^{low} CD16/FcγRIII⁺ monocytes are increased, and monocyte tracking in a classical SjS mouse model suggested that they were migrating to the salivary glands to develop into dendritic cells (or proinflammatory CD14^{bright} CD16/FcγRIII⁺ monocytes), however the existence of a specific role for FcγRIII has not been explored in these studies [104,105].

IgM and IgG anti-FcγR autoantibodies have been detected in SjS and were associated with Raynaud's phenomenon, lung involvement and arthritis [106,107]. These autoantibodies mainly targeted FcγRIIIb and were frequently cross-reactive towards FcγRI and FcγRII, however they were apparently not able to bind to neutrophils, NK cells or different FcγR-carrying cell lines, suggesting that their target is a cryptic epitope revealed after post-cellular activation shedding [107,108]. There are few contradictory results about the later point [109], but because of the targeted epitope, it is unlikely that anti-FcγR autoantibodies are able to activate FcγR-bearing cells in SjS *in vivo*. A possible role in SjS-related neutropenia or in the historically reported defect in the reticuloendothelial Fc receptor function (determined by measuring the clearance from circulation of IgG-coated red blood cells) in SjS [110] (as described in RA or Systemic Lupus Erythematosus (SLE) [111,112]) has been suggested, but convincing evidences have not been provided for such mechanism to date, and anti-FcγR autoantibodies are not used in clinical practice.

Regarding the inhibitory FcγR, it has been reported that FcγRIIb expression on memory B cells was significantly reduced in active *versus* inactive SjS patients or healthy controls, and that expression correlated negatively with anti-SSA antibody titers and disease activity index

[113]. High dose corticosteroid treatment was able to upregulate FcγRIIb expression on these cells in patients, and dexamethasone was also able to elevate FcγRIIb expression on PBMCs *in vitro* in a dose-dependent manner.

As a mucosal autoimmune disease, the role of IgAs and autoreactive IgAs has been examined in SjS [114,115]. Apart from the presence of anti-Ro/SSA and La/SSB IgA in SjS patients [116], elevated plasma levels of monomeric and polymeric IgA, as well as IgA-containing IC and IgA RF have been described in the disease and correlated with disease activity [114,117,118]. Among the possible mechanisms behind this abnormally elevated IgA response, a defective clearance has been suggested. In line with this hypothesis, IgA1 and IgA2 glycosylation profiles were shown to be abnormal in SjS, with increased amounts of sialic acids in their Fab and Fc fragments [119]. This oversialylation of IgA1 and IgA2 Fc seem to be responsible for a decreased binding to FcαRI which could account for their defective clearance in SjS [120].

As in RA, elevated soluble FcεRII levels were detected in the plasma [121] and saliva [122] of patients with SjS. The main hypothesis being that elevated soluble FcεRII could arise either from polyclonal activation of B cells (which are known to be key components of SjS pathogenesis [123]) or by activation of monocytes. It is noteworthy as IgE autoantibodies against SjS classical autoantigens, SSA and SSB, have been described in the disease [124], however their potential FcεR-mediated pathogenic role has not been explored to date in SjS (our group is coordinating an ongoing clinical trial to address that question; NCT03003572).

Ro52/TRIM21 has first been identified as an important autoantigen in SjS and SLE [125], and has since been detected as a target for autoantibodies in several other systemic autoimmune diseases such as RA, Systemic Sclerosis (SSc), and IIM [126]. However, the potential pathogenic contribution of anti-Ro52/TRIM21 autoantibodies in these diseases is particularly difficult to assess, because of the complex and apparently opposite effector functions Ro52/TRIM21 has *in vivo*. It is now known that Ro52/TRIM21 is an ubiquitously expressed cytosolic E3 ubiquitin ligase and also an antibody Fc receptor which provides a cytosolic line of defense against invading pathogens [127]. It does so by acting as a sensor that intercepts antibody-coated microbes that have breached the cell membrane, and induces different mechanisms such as proteasome-mediated degradation, innate immune response induction (including type 1 IFN signalling, which is involved in multiple systemic autoimmune diseases), or killing by autophagy [127]. Induction of these effector functions seems to require a higher affinity interaction compared to Fc binding alone [128]. Apart from its cytosolic nature, Ro52/TRIM21 also distinguishes itself by two significant features: it is the highest affinity Fc receptor known in human [129], and it does not only bind all four IgG subclasses, but also IgM and IgA (with a sufficient affinity to induce effector functions) [129,130]. It has also been demonstrated that non-pathogenic complexes such as antibody-coated self-derived proteins or antibody-coated beads can be targeted by Ro52/TRIM21 [131,132]. So, in that sense, the presence of anti-Ro52/TRIM21 autoantibodies, which were reported to be exclusively binding to the E3 ubiquitin ligase activity-bearing domains (responsible for inducing the aforementioned effector functions [133]) in SjS, and not to the Fc binding domain [134], could have a protective role in autoimmunity, by limiting the proinflammatory response post-TRIM21/Ro52/IC cytosolic interaction. It could also induce some kind of immune deficiency in anti-Ro52/TRIM21 positive patients, but this aspect has not been particularly explored to our knowledge. On the other hand, independently of antibody binding, Ro52/TRIM21 is able to regulate both cytoplasmic and nuclear substrates *via* ubiquitination [135]. Among the reported substrates for TRIM21/Ro52-mediated ubiquitination there are multiple type 1 interferon and proinflammatory cytokine-inducing factors (*e.g.* interferon regulatory factors [IRF] 3, 5, 7 and 8, or the helicase DDX41 which is involved in the regulation of the type 1 IFN pathway activation secondary to cytosolic double stranded DNA [dsDNA] sensing [136]). In that sense, by inhibiting Ro52/TRIM21-

mediated ubiquitination and proteasome-related degradation of these proteins, anti-Ro52/TRIM21 autoantibodies are probably contributing to the well-known autoimmunity-related immune dysregulation, including type 1 interferon pathway overactivation [135,137]. More recently, Ro52/TRIM21 has also been involved in IRF3-downregulation via autophagy, another pathway that is possibly impaired because of anti-Ro52/TRIM21 autoantibodies [138].

In SJS, anti-Ro52/TRIM21 autoantibodies are positive in two third of the patients, frequently with another autoantibody, but their pathogenic role is not well established [97]. It has been recently demonstrated that Ro52/TRIM21 immunization in mice was able to cause salivary glands dysfunction, and interestingly, the passive transfer of Ro52/TRIM21-immune sera induced the same pathologic features but only when the murine innate immunity was previously activated [139]. Moreover, the authors reported that IgGs from Ro52-immune sera were actively internalized *in vivo* in the cytoplasm (where they can interact with Ro52/TRIM21) of a murine salivary gland cell line, probably via Ro52/TRIM21 (which can be relocated to the cell surface under certain conditions [140,141]) or a cross-reactive protein binding on the cell surface. A FcγR-mediated mechanism was also plausible for that entry, but less likely [139]. The same group reported similar anti-Ro52/TRIM21 mediated dysfunction and specific IgG deposits in the lacrimal glands of the same mouse model, but only in female, which is in line with the female predominance in patients [142]. Interestingly, *Trim21* $-/-$ mice develop systemic autoimmunity, with an abnormal B cell phenotype (increased polyclonal and antigen-specific antibody production associated with augmented BCR-dependent B cell proliferation and follicular B cell expansion), possibly linking TRIM21/Ro52 to the central role for B cells in the disease [143]. With regards to clinical data, patients with both anti-Ro52/TRIM21 and anti-Ro60 autoantibodies seem to have higher biomarkers of B cell hyperactivity and glandular inflammation [144], and the presence of anti-Ro52/TRIM21 antibodies has been associated with interstitial lung disease in recent publications [145,146]. Hence, preclinical, and clinical data, are more consistent with the potentially deleterious and proinflammatory effects of anti-Ro52/TRIM21 autoantibodies.

Finally, the FcRL4 protein which is normally expressed on a small subset of mucosa-associated B cells, has been detected in highly proliferative B cells present in the salivary glands (predominantly the parotid glands) of SJS patients [147]. FcRL4 expression is apparently increased in parotid mucosa-associated lymphoid tissue (MALT) lymphomas in SJS patients. Previously available evidences suggest that binding of IgA (possibly IgA autoantibodies reported in SJS, as aforementioned [115,116]) to FcRL4 could result in a switch from BCR-mediated activation to TLR-mediated activation [148], which is known to be important in SJS because of its role in type 1 interferon production [149]. Moreover, engagement of FcRL4-positive B cells in the salivary gland may inhibit differentiation towards plasma cells and enable the ongoing proliferation leading to lymphomagenesis.

2.3. Systemic lupus erythematosus

SLE is a rare (approximate prevalence ranging from 20 to 150 cases per 100,000 individuals, depending on the considered ethnicity) but prototypic systemic autoimmune disease with a proteiform clinical presentation: it can virtually affect any organ, but the most common manifestations affect the skin, joints, serosa, kidneys, and central nervous system [150–152]. SLE is a complex disease, with phenotypes ranging from mild symptoms to a catastrophic life-threatening disease, and our current understanding of the determinants behind these phenotypes is limited. In fact, some experts think that SLE probably represents several heterogeneous diseases, involving genetic and environmental (including infections or ultraviolet) factors at different levels [153]. Biologically, the disease is characterized by high levels of autoantibodies to various cytoplasmic and nuclear antigens, anti-dsDNA being a diagnostic hallmark of the disease [154].

Defective clearance of apoptotic debris, autoantibodies, and ICs has long been recognized in SLE pathogenesis, with an historically identified key role for defects in complement proteins (genetic deficiencies in C1q, C2 and C4 being associated with juvenile SLE) [155]. The implication of phagocytes, and their impaired ability to engulf dead cells in SLE was also described [156] and possibly related to malfunctions of pathways involving FcγRI and FcγRII in some SLE patients [157], but the description of the fine mechanisms supporting these findings is more recent. IgG fractions purified from SLE patients with different autoantibody profiles were able to bind late apoptotic cells and induce an inhibition of their clearance by macrophages, through a FcγRI- and FcγRIIa-dependent mechanism (as aforementioned in SJS) [102]. If formation of ICs containing various nuclear antigens has been accepted in SLE pathogenesis for a long time, these proteins must be readily available for both the induction of an immune response and the formation of ICs. It was suspected that apoptosis was an important providing source of nuclear antigens, because of their high concentration within surface blebs of apoptotic cells [158–160]. Hence, it has been recently demonstrated that PBMCs from SLE patients experiencing active disease, and hematopoietic cells from two genetically unrelated strains of lupus-prone mice, accumulated markedly elevated levels of surface-bound nuclear self-antigens [161]. On dendritic cells and macrophages, the self-antigens are part of IgG-containing ICs which promote FcγRI activation. In the same study, FcγRI deficiency improved the disease in mice (notably preventing lupus nephritis and reducing IgG ICs accumulation and BAFF production).

Monocyte FcγRI expression has been positively associated with disease activity in SLE patients [162], possibly due to the characteristic hyperactivation of the type 1 IFNs pathway (*i.e.*, the “interferon signature”), which is also associated with disease activity in SLE [163], and can induce FcγRI expression on monocytes. Moreover, the renal inflammatory response was inhibited by a lentivirus-mediated knockdown (mainly in macrophages) of FcγRI in a well-known mouse model of SLE, possibly via regulating the NLRP3 inflammasome-associated signalling [164]. It has also been recently described that renal macrophages in inflamed tissues were primed for IgG ligation (*i.e.*, exhibited an increased activating to inhibitory FcγR ratio) in two nephritic lupus-prone mouse models, and that FcγR cross-linking on these macrophages resulted in a switch to aerobic glycolysis [165]. Inhibiting glycolysis reduced FcγR-induced IL-1β and ROS production, neutrophil recruitment, and improved the renal disease of *FcγRIIb* $-/-$ mice which usually develop fatal glomerulonephritis. This could be of interest for tissue-resident macrophages in the ICs-mediated systemic autoimmune diseases reviewed here.

On neutrophils, FcγRI expression levels were reported to be higher during infections than during SLE flares [166], however, a recent study showed that IgG-aggregates were among the most potent known agonists for the induction of FcγRI expression on neutrophils [167]. It seems that FcγRI is critical in regulating ROS production. These findings are particularly relevant for an ICs-mediated disease like SLE, where neutrophils binding to deposited ICs in the kidneys of patients with SLE nephritis seems to be involved in the occurrence of this potentially life-threatening manifestation [168]. Interestingly, the up-regulation of FcγRI by heat-aggregated-IgGs was dependent on multiple pathways, including FcγRIIa engagement and activation of Syk [167].

FcγRIIa is also a key player in the IFNα-related part of SLE pathogenesis, because of its expression on the most potent IFNα-producing cells, plasmacytoid dendritic cells [153]. As mentioned earlier, SLE is characterized by the production of high levels of autoantibodies to various cytoplasmic and nuclear antigens, leading to the formation of ICs composed of self-DNA/RNA/autoantibodies which end up being internalized by plasmacytoid dendritic cells and induce IFNα production via endosomal TLR signalling. The internalization process was FcγRIIa- but not FcγRI- or FcγRIII-dependent, and could be inhibited by anti-FcγRII monoclonal antibodies or polyclonal heat-aggregated IgGs [153,169]. NETosis, which is induced by FcγRIIa-crosslinking, is the

missing link between neutrophils and IFN α production, because NETs are composed of self-DNA as well as mitochondrial DNA, which are targeted by the autoantibodies present in SLE, and can stimulate plasmacytoid dendritic cells via a Fc γ R- and TLR9-dependent pathway [170,171].

Decreased expression of the inhibitory Fc γ RIIb on memory B cells and plasma cells has been observed in patients with active SLE [172]. Moreover, *FcgRIIb* $-/-$ mice spontaneously develop a lupus-like phenotype, including severe nephritis, as aforementioned [173]. Interestingly, these mice develop osteopenia due to increased TNF α -mediated bone resorption without any change in bone formation. Using a recombinant soluble Fc γ RIIb was found effective at improving lupus-like disease and survival in NZB/NZW mice, without affecting B cell count, autoantibody titers or ICs glomerular deposition [174]. In line with this, co-engagement of BCR and Fc γ RIIb by a bispecific monoclonal antibody has been evaluated in SLE, as in RA [45]. The murine version of this monoclonal antibody was able to inhibit B cell activation in SLE-prone mice while not reducing B cell numbers [175]. In a phase II trial, obexelimab was well tolerated and was able to reduce disease recurrence in active patients with SLE [176]. Another group has recently evaluated a Syk inhibitor in mouse models of SLE, and reported improvements in proteinuria and proinflammatory serum cytokines, but only in the *FcgRIIb* $-/-$ model [177].

FcRn is most certainly involved in the recycling of autoreactive IgGs in SLE, however, its specific role in the disease has not been widely explored. However, a recent study using MRL/*lpr* mice has unveiled a possible role for FcRn in mediating the entrance of autoreactive IgGs derived from patients with lupus nephritis, paving the way to podocyte damages [178].

Autoantibodies of the IgA isotype, including anti-dsDNA, have been reported in SLE, with approximately the same prevalence as their IgG counterparts and are associated with disease activity, particularly with lupus glomerulonephritis [179]. Autoreactive IgA to type VII collagen were also anecdotally described in rare vesiculobullous forms of dermatologic SLE [180], and some cases of atypical lupus nephritis mainly have IgA deposits in their renal tissues [181], however the pathogenic potential of these autoreactive IgA, including their interaction with Fc α RI, has not been explored to our knowledge. On the other hand, targeting Fc α RI for its inhibitory effect has been explored in two experimentally-induced models of SLE, using transgenic mice expressing the human Fc α RI [182,183]. In both models, monomeric targeting of Fc α RI with an anti-Fc α RI Fab or monomeric IgA was able to reduce leukocyte infiltration, improve renal disease, decrease proinflammatory cytokine production, and could be an interesting therapeutic option. In line with this protective role for IgAs, IgA deficiency has long been associated with an increased risk for autoimmunity, including SLE [184].

Autoreactive IgE antibodies as well as IgE-containing ICs have been described in SLE more than 40 years ago [185,186] and are targeting the classical autoantigens identified in SLE: dsDNA, Sm, Ro/SSA, La/SSB. [187–189]. Anti-dsDNA IgE are the most prevalent, and have been associated with increased disease activity, correlated with disease activity scores and higher titers were associated with lupus nephritis [187–189]. The presence of autoantibodies of the IgE isotype and their link with disease activity are particularly interesting in SLE, because it is mostly seen as a Th1, type 1 IFN and complement activation-driven disease [153], whereas IgE are associated with Th2 responses and are unable to activate the complement system. Despite this apparent paradox, there are convincing evidence that autoreactive IgE are participating in SLE pathogenesis via the high affinity IgE receptor: Fc ϵ RI. Fc ϵ RI is highly expressed in mast cells and basophils, and at lower levels (which are dependent on IgE levels) on eosinophils, monocytes, macrophages, dendritic cells (including plasmacytoid dendritic cells) and some epitheliums [189–193]. Fc ϵ RI is also characterized by a very high affinity for IgE (100-fold the affinity of Fc γ RI for IgGs), hence, contrary to the other immunoglobulin isotypes, IgE is retained on its

receptor which is ready for crosslinking whenever the antibody meets its antigen [194]. Experiments in *Lyn* $-/-$ mice, a recognized model for SLE associated with an early basophil-dependent Th2 bias and high IgE responses to any immunization, allowed for the identification of the IgE/basophil Fc ϵ RI/Th2 axis involvement in the induction of a SLE-like phenotype [187]. Fc ϵ RI crosslinking on basophils by autoreactive IgE-containing ICs was able to induce their migration to lymph nodes, IL-4 production, contribution to the proinflammatory milieu, influence B cell survival (via BAFF) and amplify humoral responses and antigen presentation (via MHCII), with similar trends in humans with SLE [187,188]. As mentioned for their IgG counterpart and Fc γ RIIa, anti-dsDNA IgE/dsDNA-containing ICs promote IFN α (and other inflammatory cytokines) production by plasmacytoid dendritic cells, via Fc ϵ RI binding, IC internalization, and subsequent DNA sensing by TLR9 [189]. Moreover, experiments reproducing the unbalanced autoreactive IgG/IgE ratio in SLE serum reported that both types of IC were able to induce the production of comparable amounts of IFN α , and when both anti-dsDNA IgG and IgE were present in the IC it led to a synergistic effect (through a probable Fc γ RIIa and Fc ϵ RI collaboration) which was associated with disease activity. On the contrary, total polyclonal IgE (as monomeric IgE) which are also elevated in SLE (to a lesser extent than in allergic diseases) without inducing a higher incidence of atopic diseases, seem to play a protective role in the disease by regulating IFN α secretion in plasmacytoid dendritic cells via a non-crosslinking interaction with Fc ϵ RI [195]. In this study, an inverse correlation with total IgE levels and disease activity scores was described. Of note, anti-Fc ϵ RI IgGs have been historically detected in 20% of a cohort of patients with SLE, but they did not seem to have significant histamine-releasing activity and their functions have not been explored further [196]. Despite this multifaceted role described for IgE in SLE, lowering circulating IgE levels and decreasing Fc ϵ RI expression on basophils [197] using omalizumab, an anti-IgE monoclonal antibody approved for the treatment of severe asthma and used in allergy-related diseases, is being evaluated in SLE in clinical trials with promising results in early phase [198].

As previously described in RA, there is an increased proportion of circulating B cells expressing Fc ϵ RII [199] and increased soluble Fc ϵ RII levels in the plasma of patients with SLE [121,200], with a possible link with Epstein-Barr Virus which is known to be potentially involved in SLE pathogenesis, either specifically or more likely because of its ability to induce polyclonal B cell activation [201,202].

Anti-Ro52/TRIM21 autoantibodies are positive in approximately 25–30% of SLE patients [135,203], and may be associated with a more severe disease, including renal insufficiency [203]. A recent study in the MRL/*lpr* mouse model (a well-known mouse model for SLE, also displaying multiple key SjS features [204]) identified an innovative mechanism for the long-described accumulation of apoptotic debris-containing IgG ICs in SLE. Macrophages from this lupus-prone mouse model fail to mature their lysosome, which reduces their ability to degrade apoptotic debris/autoantigens contained within their IgG ICs and finally promotes their recycling and accumulation at the membrane [205]. Among other deleterious consequences (including prolonged TLR activation because of the nucleic acid-containing ICs), this defect causes phagosomal membrane permeabilization, allowing autoantibodies to leak into the cytosol where they can activate Ro52/TRIM21. Another group has studied the consequences of a *Trim21* knockout in MRL/*lpr* mice, and reported that these mice had a worsened renal disease, an abnormal B cell phenotype (i.e. increased anti-dsDNA titers, higher capacity to produce polyclonal antibodies upon stimulation, and higher B cell-to-plasmablast differentiation rates) and increased IRF5 protein expression due to decreased ubiquitination [206]. Moreover, heightened transcript expression of Ro52/TRIM21 (which is type 1 IFN-inducible) and Ro52/TRIM21-dependent genes have been described in PBMCs and keratinocytes from SLE patients [207,208], and Ro52/TRIM21 mRNA expression in PBMCs correlated with disease activity in SLE [209]. Interestingly, a negative correlation between Ro52/TRIM21 mRNA expression and IFN α and IFN β mRNA expression has been

reported in healthy controls, highlighting the type 1 interferon down-regulating role of Ro52/TRIM21 in normal setting. In anti-Ro52/TRIM21 antibody-positive SLE patients, the correlation was inverted, probably via an antibody-dependent mechanism [209]. Finally, in anti-Ro52/TRIM21 antibody-positive SLE patients, B cells had the same abnormal phenotype than what had been described in *Trim21* $-/-$ MRL/*lpr* mice *in vitro*, linking antibody-dependent Ro52/TRIM21 impairment to SLE's B cell-related pathogenesis [206]. Interestingly, in SLE, it was reported that a subset of anti-dsDNA IgGs [210,211] was able to enter cells in their free form and induce cytokine production via activation of the NF κ B pathway [212]. This activation required Fc interaction, however it was apparently not dependent on Ro52/TRIM21 but possibly on a novel cytosolic FcR. Interestingly, among its various functions, Ro52/TRIM21 was reported to be involved in inducing apoptosis by repressing Bcl-2 protein production and could be an important gatekeeper of cell damage [213]. This function, which is dependent on Ro52/TRIM21 E3 ubiquitin ligase activity-bearing RING domain [214], may be impaired in patients with anti-Ro52/TRIM21 autoantibodies and could be restored using Bcl-2 inhibitors currently under clinical development in SLE [215].

2.4. Systemic sclerosis

SSc is a rare (approximate prevalence of 20 per 100,000 individuals) but severe (with the highest mortality among rheumatic diseases) systemic autoimmune disease characterized by microvasculopathy, fibrosis in the skin and internal organs (including the lungs, heart, kidneys and digestive tract) and an altered immune response including the production of specific autoantibodies (mainly anti-centromere in the limited form of the disease and anti-Scl-70/anti-RNA polymerase III in its diffuse form) [216]. Autoantibodies are of particular interest in SSc for multiple reasons: diagnosis (even in early forms), classification and prognosis [217,218], however, the Fc-dependent functions of the classical autoantibodies have largely been under evaluated. The fact that SSc patients seem to have an increased monocyte population compared to healthy donors, with the Fc γ RIII-positive monocyte subpopulation being associated with severity of skin and lung fibrosis and particularly increased in patients with diffuse (and more severe) SSc [219], suggests a non-explored role for Fc γ RIIIa in SSc pathogenesis.

Apart from the classical anti-centromere, anti-Scl70 and anti-RNA polymerase III autoantibodies, rarer autoantibodies have been described in SSc [220]. Among these autoantibodies, none seem to be very specific for SSc, however, two of them are interesting regarding their FcR interaction. Firstly, anti-endothelial cell antibodies (which have also been detected in RA, SjS and SLE, and whose main target is the centromeric protein B [CENT-B]) seem to be able to induce endothelial injuries via ADCC which is possibly mediated by Fc γ RIII-bearing NK cells without robust evidences [221] and contradictory results [222]. Florey *et al.*, have also reported that anti-endothelial cell IgG binding to activated endothelial cells found in SSc, could enhance leukocyte adhesion through the ability of Fc γ RIIIa and CXCR-1/2 to synergize in activating β_2 integrins [223]. Contrary to Fc γ RIIIb-mediated neutrophil recruitment, which requires Fc γ RIIIb crosslinking, this mechanism can occur with the binding of monomeric IgGs. Secondly, as in RA, SLE and SjS, anti-Fc γ R autoantibodies have been described in SSc [224] and can probably contribute to the disease through different aforementioned mechanisms (e.g., reduced clearance of ICs, neutrophil activation and cytokines/ROS production, delay in apoptosis) [225].

No specific autoreactive IgE antibodies were reported in SSc, but anti-IgE IgG and IgM autoantibodies, which can theoretically form IgE-containing ICs and cross-link IgE Fc Receptors, have been described in SSc, especially in its limited form [226]. *In vitro* exposure of basophils with anti-IgE containing serum from these patients, was not able to induce histamine secretion, however, increased numbers of Fc ϵ RI-bearing mast cells (whose vesicles are the main source of transforming growth factor (TGF)- β , a key profibrotic cytokine in the disease [227])

have been detected in the derma of patients with multiple fibrosing diseases, including SSc [228]. This potential IgE-containing IC/dermal mast cell interaction and its link to fibrosis in SSc remain to be investigated.

In SSc, anti-Ro52/TRIM21 autoantibodies (which are positive in approximately one third of the patients) are associated with interstitial lung disease, poor survival, and possibly pulmonary arterial hypertension in a very recent study [229–231]. The potential pathogenic role for these autoantibodies has not been explored to date, but it's interesting to note that anti-Ro52/TRIM21 antibodies in patients with SSc do not seem to be targeting the same epitopes as their counterparts detected in SjS or SLE, especially when there is no concomitant anti-Ro60 (which has been historically described as a part of the same ribonucleoprotein complex as Ro52/TRIM21) autoreactivity, which is a lot more frequent in SjS and SLE than in SSc [232].

2.5. Idiopathic inflammatory myopathies

IIM are a group of rare (approximate prevalence of 15 per 100,000 individuals [233]) systemic autoimmune diseases, whose key features include muscle inflammation and motor weakness of varying severity and phenotype, as well as extramuscular manifestations. According to the most recent myositis-specific autoantibody-based classification, IIM are composed of 4 subgroups: inclusion body myositis, dermatomyositis, immune-mediated necrotizing myopathy, and anti-synthetase syndrome [234,235].

Myositis-specific autoantibodies are thought to play an important role in this group of diseases, most of these autoantibodies being particularly associated with a distinct clinical phenotype and prognosis e.g. interstitial lung disease is a prominent manifestation of anti-synthetase syndrome (which is defined by the presence of antibodies to certain amino-acyl transfer RNA [tRNA] synthetases), anti-TIF1 γ antibodies are associated with myositis-associated cancer, anti-SRP and anti-HMGCR antibodies with immune-mediated necrotizing myopathy, and anti-cN1A antibodies with inclusion body myositis [236,237]. Despite the muscular phenotype of IIM, myositis-specific autoantibodies are targeting ubiquitously expressed intracellular antigens involved in key cellular mechanisms, like most autoantibodies detected in systemic autoimmune diseases. Although very important, these specific autoantibodies have almost exclusively been studied with regards to their antigen-recognition capacity and very few studies have been exploring their Fc-related functions. Only one recent study has analysed Fc-glycosylation profiles of purified IgGs from patients with IIM [238], and reported profiles enriched with agalactosylated glycans, as in other autoimmune disorders [239]. Moreover, anti-histidyl tRNA synthetase (anti-Jo1) antibodies purified from patients with severe anti-synthetase syndrome associated with interstitial lung disease, had a similar glycosylation profile as ACPA antibodies in RA [240] i.e. higher abundance of fucosylated forms and reduced proportion of bisecting residues [239]. As afucosylated-Fc-glycans are known to increase IgG binding to Fc γ RIIIa and induce ADCC [241], the presence of increased fucosylation in anti-Jo1 Fc could be in line with a non-Fc-dependent pathogenic role for these autoantibodies, however further explorations are warranted.

Apart from specific autoantibodies, few interesting non-specific autoantibodies have been described in IIM. Anti-Fc ϵ RI autoantibodies have been detected in more than one third of a cohort of patients with dermatomyositis, but contrary to their counterparts detected in chronic urticaria, they did not display any significant histamine-releasing activity by basophils [196]. Functional anti-Fc ϵ RI autoantibodies detected in urticaria were predominantly of the IgG1 and IgG3 isotypes (contrary to the ones detected in dermatomyositis and SLE which were mainly IgG2 and IgG4), hence this difference could be FcR- or Complement-related (the latter being suggested by the authors).

Another non-specific type of autoantibodies present in IIM is anti-Ro52/TRIM21 [242]. As aforementioned, anti-Ro52/TRIM21 autoantibodies can be detected in multiple systemic autoimmune diseases, with

at least various clinical implications but the functional consequences of such autoantibodies are only partially known [206]. In IIM, anti-Ro52/TRIM21 frequently co-occur with anti-Jo1 in adults and anti-melanoma differentiation-associated protein 5 (MDA5) in kids, and are classically associated with a worse disease: more severe interstitial lung disease, more frequent lung fibrosis, reduced response to immunosuppressive drugs and decreased survival [242–247]. Interestingly, in a small retrospective study, rituximab, the anti-CD20 therapeutic monoclonal antibody, was equally effective in anti-Ro52/TRIM21 positive IIM patients than in their negative counterparts [243], whereas positive patients had not responded to prior classical immunosuppressive drugs, indirectly linking the potential pathogenic role of anti-Ro52/TRIM21 autoantibodies to B cells, as previously suspected in other autoimmune diseases [143,206].

Regarding treatments, the immunomodulatory intravenous immunoglobulins (IVIg) are frequently used in combination with immunosuppressive drugs in IIM. Their exact mechanisms of action are not completely understood, but interestingly they are able to induce upregulation of the inhibitory FcR, as well as reduction in half-life of autoantibodies due to displacement from FcRn binding sites [248].

2.6. Mixed connective tissue disease

The concept of mixed connective tissue disease (MCTD) is still complex almost 50 years after its first description by Sharp *et al* in 1972 [249]. As indicated by its name, it is characterized by overlapping features of other autoimmune diseases (namely RA, SLE, SSc and IIM), but any association between such features should not be called MCTD. In fact, the concept of MCTD, as a defined entity, is supported by the existence of a specific clinical pattern (whose key features include Raynaud's phenomenon and "swollen" fingers/hands), a characteristic antibody (anti-U1 small nuclear ribonucleoprotein particle [U1RNP] which is common to all classification criteria contrary to clinical features), and associated specific immunological and genetic findings [250]. Its approximate prevalence is 3.5 per 100,000 individuals [251].

Historical publication reported that anti-U1RNP IgG were able to penetrate monocytes and lymphocytes *via* FcRs and react with intranuclear RNP [252]. It was further demonstrated that anti-U1RNP IgG were also able to penetrate B cells, NK cells, as well as T cells, more efficiently than other autoantibodies or pooled IgGs, and that such enhanced entrance was mediated by both the Fc portion and the Fab (by interaction with their target antigen on the cell surface) [253,254].

FcεRII expression on B cell surface has not been studied in MCTD to our knowledge, however sFcεRII levels were increased in patients' plasma, as in other autoimmune diseases [200]. Anti-U1RNP IgE have recently been detected in almost 80% of the patients in a cohort of MCTD [255]. As in SLE, basophils are activated (with a different phenotype, involving the CCR3/CCL11 axis) and seem to be accumulating in lymph nodes in MCTD, where they may support autoantibody production. The authors did not specifically explore the role of FcεRI, however, IgE deficiency (induced in a mouse model of MCTD) completely prevented basophil activation and accumulation both in lymph nodes and lungs, suggesting that the role of basophils depends on IgE-mediated activation [255].

In line with the results in SSc and IIM, anti-Ro52/TRIM21 positive MCTD patients (which represent approximately one third of all MCTD patients) are more likely to develop lung fibrosis [256,257].

3. Adverse FcR engagement in other systemic inflammatory diseases

3.1. Inflammatory bowel diseases

IBD, namely Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders mainly affecting the gastro-intestinal tract, but also causing extraintestinal manifestations in more than a

one-third of the patients [258]. Their approximate prevalence is 0.3% in western countries, and it is rising in South America, Eastern Europe, Asia, and Africa, highlighting the role of environmental factors in these diseases [259]. IBD have a complex and incompletely understood etio-pathology, but disruption of the mucosal digestive barrier is one of their key features [260]. This disruption leads to abnormal responses against commensal fecal bacteria and harmless food proteins, because of immunoglobulins' leakage from the blood to the intestinal lumen, but also abnormal absorption of bacterial products and/or food antigens. The level of food antigen-specific IgG is higher in the blood and colonic biopsies from active UC patients (*versus* inactive patients and controls), and are bound *in situ* to FcγRI on neutrophils, making them "antigen-specific" or "sensitized", and able to induce the release of pro-inflammatory cytokines (e.g. TNFα) when exposed to their specific antigen [261]. Interestingly, the proportion of the other FcγRI-expressing resident myeloid cell types, such as mast cells [262,263] and intestinal macrophages [264], is increased in the inflamed mucosa of IBD patients. These cells are also contributing to IBD's pathogenesis by locally producing TNFα post-FcγRI engagement, a mechanism that is enhanced in mast cells from CD patients because of the existence of synergies between FcγRI-signalling and microbial products recognition (e.g. lipopolysaccharide [LPS] recognition by TLR4 [263] or flagellin-specific immune response [262]). It has previously been described that FcγRI expression correlated with inflammatory markers, disease activity scores and could be a good biomarker for mucosal inflammation in adult and pediatric patients with IBD [265,266]. The levels of anti-commensal IgG responses and IgG-opsonized microbes are higher in the inflamed mucosa of patients with UC, as well as in the classical dextran sodium sulfate-induced mouse model which also displays increased systemic anti-commensal IgG responses [267]. Of note, levels of IgG-opsonized microbes were a better reflect of colitis severity in mice in that study, than their IgA-opsonized counterparts, and it has been reported by another group that microbe-opsonization by IgG (but not IgA) correlated with disease activity in UC patients [268]. In CD patients, disease activity was associated with increases in both IgA and IgG-bound bacteria, suggesting different pathogenic mechanisms in both diseases. Moreover, activating FcγR gene transcripts (FCGR2A and FCGR3A/B), were among the most differentially expressed genes in inflamed UC biopsies compared with biopsies from UC patients in remission, non-inflamed UC biopsies and healthy control biopsies [267]. In contrast, the inhibitory receptor transcript FCGR2B was more modestly induced, resulting in an increase in the mucosal activating to inhibitory FcγR ratio subsequently leading to IL-1β production (*via* the inflammasome pathway), Th17 immunity, and the exacerbation of inflammation.

As in multiple systemic autoimmune and inflammatory diseases, NETosis seems to play a part in IBD: NETs have been described in the inflamed digestive mucosa, stool and blood from IBD patients, especially in UC, and seem to be correlating with disease activity [269]. The role of Fc Receptors in this effector function has not been specifically explored in IBD to our knowledge, but a study reported that, when activated, neutrophils shed soluble FcγRIIb, whose concentration in gut lavage fluid closely correlated with mucosal inflammation [270]. A hypothesis for NETosis induction could involve antineutrophil cytoplasmic antibodies. These autoantibodies can be detected in IBD, as in ANCA-associated vasculitis, and can form ICs with neutrophil granule components such as proteinase 3 and myeloperoxidase [271].

As mentioned, in IBD, the disruption of the mucosal digestive barrier leads to the sub-epithelial lamina propria invasion by commensal fecal bacteria, where they are likely opsonized by locally produced dimeric IgA (dIgA). Contrary to secretory IgA, it was demonstrated *in vitro* and *in vivo* that dIgA were able to induce neutrophil activation *via* FcαRI cross-linking, as well as leukotriene-B4-dependent recruitment of new neutrophils, leading to a perpetuating inflammatory loop in UC [65]. In line with this, neutrophils are thought to be important contributors in IBD pathogenesis [272], however other cell types have also been involved, for example, the circulating T cell population is enriched with activated

cells in patients with IBD, possibly due to increased microbial translocation [273]. T cells are not constitutively expressing FcRs, but their expression can be induced upon activation [274]. In historical publications, an increased number of activated T cells expressed Fc α RI in the blood and inflamed mucosa of IBD patients, but their potentially pathogenic role has not been widely explored [275]. Of note, IgA (but also IgM) Rheumatoid Factors, as in RA, have been described in the serum of active CD (but not UC) patients and seem to be produced at high levels by lamina propria mononuclear cells found in their inflammatory intestinal tissues [276]. Due to their anti-IgG Fc specificity, they can theoretically bind to IgG-bacteria ICs and induce Fc α RI-dependent cell activation.

These elements suggest that targeting Fc γ Rs in IBD (with more evidence in UC than in CD), with means aiming at decreasing the activating to inhibitory Fc γ R ratio (e.g. by blocking the activating receptors, their signalling, or by using Fc γ RIIb agonists), could be interesting [3,267]. Another interesting option (because of IBD mucosal tropism), which has been recently reviewed elsewhere, would be the targeting of Fc α RI [277]. Its blocking could be an interesting option in treating IBD and all IgA-mediated inflammatory diseases, whereas enhancing ITAMi signalling by monomeric targeting (i.e. monomeric serum IgA cannot cross-link their receptor) of Fc α RI could also be interesting in IgG-autoantibodies-mediated diseases, because in that case, the inhibitory signals transduced via the Fc α RI-FcR γ -chain complex are able to dampen pro-inflammatory responses induced by other Fc receptors [278].

3.2. IgA vasculitis

IgA vasculitis (IgAV; formerly known as Henoch-Schönlein purpura), is an IC-mediated vasculitis of the small vessels, characterized by IgA1-dominant immune deposits [279]. It is the most common systemic vasculitis in childhood, with an approximate annual incidence of 20–25 cases per 100,000 individuals per year [280]. It is approximately 20 times less frequent in adults [281]. IgAV classically involves the skin, gastrointestinal tract, joints, and kidneys [279]. The exact pathogenesis of IgAV is unclear, but multiple potential triggers have been incriminated in the disease, especially mucosal infections in children. In adults, malignancy may be associated with IgAV.

IgA levels can be elevated in IgAV, but more significantly, IgA1 exhibit an aberrant O-linked glycosylation profile in the hinge region [282]: their galactose deficiency induces an exposure of the N-acetylgalactosamine (GalNAc)-residues which can be targeted by autoantibodies (possibly cross-reactive antibodies initially targeting GalNAc residues on the surface of pathogens) and lead to ICs formation and deposition. Circulating IgA-soluble Fc α RI complex levels are increased in IgAV patients, with higher urinary levels detected in patients with IgAV-associated renal disease [283]. Anti-endothelial cells IgA have been reported in IgAV, and were able to enhance endothelial cell production of IL8 (which can induce the recruitment of neutrophils) and correlated with disease activity [284,285]. As aforementioned, Fc α RI cross-linking on neutrophils can induce inflammatory processes (such as ROS production and NETs formation) [282]. It has not been specifically proven in IgAV, but these mechanisms are thought to be responsible for vascular damages and leakage of red blood cells into the skin and could be involved in the typical cutaneous purpuric lesions in IgAV.

3.3. Behçet's disease

Behçet's disease (BD) is a complex inflammatory disease, involving vasculitis of both the arteries and the veins of any size, mainly characterized by recurrent oral and genital aphthous ulcers, as well as skin, ocular and neurological manifestations [286]. BD is the most frequent in Turkey (approximate prevalence of 200 per 100,000 individuals), then along the ancient Silk Road (approximately affecting 15 per 100,000 individuals), whereas it is rare in Western countries (lower than 1 per

100,000 individuals). As most diseases discussed in this review, BD has unknown causes, but current theories suggest that it is probably triggered by exogenous (microbial or environmental) agents in genetically predisposed individuals (it is strongly associated with the HLA-B51 allele which is located within the major histocompatibility complex locus) [286,287]. T cells are thought to be central in the disease, however Fc γ R-bearing cells, such as neutrophils and NK cells are their partners in crime, with described abnormal functions and infiltration in affected tissues [288]. Interestingly, Fc γ RI expression on neutrophils increases during exacerbations of BD, however it seems to be related to the inflammatory milieu, and not a BD specific feature [289]. Recent findings also reported that monocytes from patients with BD expressed lower levels of Fc γ RIIb and higher levels of Fc γ RIIIa, which correlated with disease activity and systemic inflammation [290]. These monocytes were also able to produce higher levels of IL6 and TNF α post-IgG-induced crosslinking.

Regarding autoantibodies, none have been validated for diagnostic purposes in clinical setting, however, as aforementioned for SSC, anti-endothelial cell antibodies have been reported in BD and seem to be associated with vasculitis symptoms [291]. Multiple possible autoantigens have been identified in BD for these anti-endothelial cell antibodies, including Annexin A2 which could be associated with the higher risk for thrombosis in the disease. They are also possibly associated with endothelial injuries induction and enhanced leukocytes adhesion, without BD-specific evidences [221,223].

3.4. Kawasaki disease

Kawasaki disease (KD) is an acute vasculitis of the small and medium-sized arteries which preferentially affects children younger than 5 years old [292]. Its prevalence is significantly higher in Japan or in children of Japanese descent, but it has now been described all around the world. KD's cause is still unknown, however epidemiologic, biological and recent COVID-related data suggest an infectious etiology of viral origin which probably enters the body through the mucosal tissues [293–297].

IVIg have been historically used in KD [51], to reduce the incidence of coronary arteries abnormalities (dilatation and aneurysm, possibly leading to life-threatening situations) which develop in approximately 25% of the untreated individuals, making KD the main cause of pediatric acquired heart disease in industrialized countries. The mechanism behind these coronary arteries abnormalities is unknown, but probably involves Fc γ Rs, due to the beneficial effects of IVIg. Hence, a recent study has reported that patients with KD had higher levels of Fc γ RIIa and Fc γ RIII on their monocytes, when compare to controls [298]. Moreover, patients with KD complicated with coronary arteries abnormalities had lower levels of the inhibitory Fc γ RIIb than patients with uncomplicated KD, suggesting a particular role for this Fc γ R in the pathogenesis of KD-related coronary arteries abnormalities [298,299].

3.5. ANCA-associated Vasculitides

The antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are a group of rare (approximate prevalence of 10 per 100,000 individuals [300]) but severe systemic vasculitis of the small arteries, which include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Even though approximately 10% of the patients with AAV are seronegative, the presence of anti-myeloperoxidase (MPO) or anti-proteinase 3 (PR3) autoantibodies, globally referred to as ANCAs, is a hallmark of the disease and there are multiple evidences supporting their pathogenic role [301–304]. Neutrophils have been particularly studied in AAV because of the presence of two types of interaction between ANCAs and neutrophils: one between their Fab and the membrane bound MPO and PR3, and the second between their Fc and neutrophils'

FcγRs (mainly the constitutively expressed FcγRIIA and FcγRIIIB, without any clear idea about a potential predominant role for one of them) [303]. The importance of the FcR-related part has been highlighted by *in vitro* and *in vivo* experiments where deglycosylation of IgG ANCA significantly reduced their neutrophil activation potential as well as the ability of anti-MPO IgGs to induce renal disease in mice [305]. That being said, recent glycan profiling studies have revealed that anti-MPO autoantibodies were hyperglycosylated in their Fab region as well, with probable consequences in terms of Fab-related functions [306]. *In vitro* activation of neutrophils by ANCA results in induction of an adherent phenotype, induction of NETosis, production of ROS, degranulation and production of pro-inflammatory cytokines, ending up in inflammatory vascular damages [303,307]. As previously described in RA, neutrophils from AAV patients are involved in an inflammatory amplification loop: increased NETosis involves more PR3 and MPO exposure to ANCAs, resulting in increased immune-complex formation and signalling through activating FcγRs, leading to further inflammation (including IL8-mediated recruitment of additional inflammatory cells). The role of ANCAs on monocytes has been less studied than in neutrophils, but a role for FcγRs has also been reported. Interestingly, anti-MPO autoantibodies could be promoting inflammation by inhibiting the production of the anti-inflammatory cytokine IL10, in an enzymatic myeloperoxidase- and FcR-dependent manner [308]. Moreover, MPO expression has been reported to correlate with FcγRIII expression on monocytes, but blocking FcγRIII did not alter their capacity to produce IL1β *in vitro* [309], whereas anti-MPO- or anti-PR3-induced production of ROS by monocytes seem to be a FcγRIIA-dependent process [310].

On the other hand, experiments using *FcγRIIb* *-/-* mice demonstrated that FcγRIIb was useful in the negative regulation of anti-MPO autoimmunity and glomerulonephritis through mechanisms involving dendritic cells, B cells, T cells and neutrophils [311]. On a side note, a recent study has reported that FcγRI expression levels on neutrophils were higher in bacterial infections than during flares of autoimmune diseases, including AAV [166].

Because of the important upper respiratory tract mucosal involvement in GPA, the role of IgA ANCAs (which are positive in approximately 30% of the patients) has been explored. Anti-PR3 IgA are able to induce neutrophil degranulation and NETs formation *in vitro*, as their IgG counterparts, but only in a FcαRI-allele dependent way (*i.e.*, when the proinflammatory variant is present) [312]. Interestingly, stimulation with anti-PR3 IgA and IgG together reduced neutrophil activation *in vitro* (possibly because of the dual inhibiting/activating potential of FcαRI and/or a competition for their target), in line with their lower prevalence in patients with severe renal disease. IgM ANCAs have been historically reported [313] and recent studies indicate that anti-PR3 IgM are present in 10–40% of the patient (they can be missed because they seem to be transient most of the time), and could be associated with a severe pulmonary form of AAV: alveolar hemorrhages [314]. However, the functional role of IgM ANCAs, which have also been detected in healthy individuals [315], and their interactions with their specific receptor has not been explored to date [316,317].

Finally, a recently published preclinical study reported that using an effector-function-deficient anti-FcγRIIA monoclonal antibody was able to inhibit anti-MPO and anti-PR3 antibody-induced ROS production from neutrophils [318]. Moreover, this therapeutic monoclonal antibody did not seem to significantly impair the main antimicrobial neutrophil functions *in vitro*. Alternatively, inhibiting Syk (which can be detected in leukocytes within renal lesions in patients with AAV-related renal disease) resulted in reduced ANCA-induced neutrophil responses *in vitro*, and was an effective treatment for MPO-AAV in a rat model [319].

3.6. IgG4-related disease

IgG4-Related Disease (IgG4-RD) is an immune-mediated systemic disease characterized by fibroinflammatory lesions that can occur at

nearly any anatomic site, the most common manifestations being autoimmune pancreatitis, sialadenitis, dacryoadenitis, and IgG4-related retroperitoneal fibrosis [320,321]. Because of its recent recognition as a distinct disease and its protean manifestations, it's very difficult to have a clear idea of IgG4-RD true prevalence, but in Japan, the overall prevalence of IgG4-related autoimmune pancreatitis (which is only one of several organs potentially affected by the disease) has been estimated at 2.2 per 100,000 individuals [322]. As indicated by the name of the disease, IgG4 are important in IgG4-RD (some patients having highly increased serum IgG4 levels, and detecting increased proportion of IgG4-positive resident plasma cells being a significant element for the diagnosis) [323], however, there is no clear evidence for their direct pathogenicity [324].

Studies investigating the role of Fc Receptors in IgG4-RD are scarce, probably because IgG4 are often thought not to be able to bind to any FcγR, whereas it has been demonstrated that they can bind to the high affinity FcγRI, but also to FcγRIIA, FcγRIIB, FcγRIIC, and FcγRIIIA [325]. So, one study has been looking at IgG4 glycosylation profiles in IgG4-RD and reported decreased galactosylation, as seen in several autoimmune and chronic inflammatory conditions. There was also an increase in IgG4-specific Fc fucosylation in patients when compared to controls, but the potential consequences of these changes in terms of effector functions remains to be investigated [326]. Of note, a study in 83 patients with chronic periaortitis (which is associated with IgG4-RD in 20–60% of the cases) identified an association between the SNP rs1801274 of the FCGR2A gene and the disease, however the association was stronger in patients with normal IgG4 levels [327].

As mentioned in RA and SLE, a phase-II trial evaluating obexelimab (the anti-CD19 monoclonal antibody whose Fc has been specifically engineered to bind FcγRIIb) in IgG4-RD (NCT02725476) has been completed, and initial results are encouraging [328].

4. Adverse FcR engagement in autoimmune hematological disorders

4.1. Immune thrombocytopenia

Immune thrombocytopenia, also known as idiopathic thrombocytopenic purpura (ITP), is a primary hemorrhagic disorder [329], whose approximate prevalence is 10 per 100,000 individuals. It is characterized by thrombocytopenia and bleeding resulting from immune-mediated platelet destruction in the spleen and liver [330]. The immunological nature of ITP is established: patients produce autoantibodies targeting glycoproteins (GP) expressed on the surface of platelets [331] and inducing numerous FcγR- and non-FcγR-mediated pathogenic effects [332]. Among the FcγR-dependent mechanisms, FcγR-mediated phagocytosis of opsonized platelets, mainly by splenic macrophages, seems to be a key element in the disease which is well illustrated by the potentially curing effect of splenectomy [330,333]. This is also supported by the association between higher-affinity-inducing FcγR polymorphisms and ITP occurrence [334].

Evidence that platelet FcγRIIA, the only class of FcγR expressed on platelets, contributes to ITP pathology is less clear. However, a specific form of ITP involves the production of autoantibodies targeting platelet GPVI, which is noncovalently complexed with the FcR γ chain, resulting in bleeding symptoms because of the anti-GPVI-positive patient's platelets inability to become activated by or react with collagen [335].

Regarding treatments, IVIg are used as a first line therapy for patients with severe ITP. As aforementioned, their role is incompletely understood, but IVIg are thought to interfere with FcγR-mediated platelet clearance by competitive binding to splenic phagocytes' FcγR [50], and saturate the FcRn recycling receptor for IgGs [336]. Other ways of competing with the pathogenic anti-platelets autoantibodies binding to their Fc receptor have been used or are being evaluated in ITP [337]. More recently, a Syk (which is necessary in the FcR-induced cytoskeletal rearrangement leading to phagocytosis) inhibitor has been approved for

the treatment of chronic ITP [338].

4.2. Autoimmune hemolytic anemia

Autoimmune hemolytic anemia (AIHA) is an apparently simple autoimmune disease, where autoantibodies directed against red blood cells induce their destruction, causing anemia. However, it has always been a clinically heterogeneous disease, ranging from mild and compensated to life-threatening anemia [339]. It is now known that this is due to variations in autoantibodies' thermal amplitude, isotype and ability to induce complement cascade activation, as well as to different bone marrow capacity to compensate. AIHAs may be primary or secondary, *i.e.*, associated with autoimmune diseases, lymphoproliferative diseases, solid tumours, infections, immunodeficiencies, transplants, and drugs, which complexify their management [340].

Warm AIHA represents 60–70% of all forms of AIHAs, and is classically mediated by IgG autoantibodies targeting proteins of the Rhesus system, weakly able to activate the complement, and whose optimal temperature of reaction is 37 °C. The opsonized red blood cells end up being modified, subsequently becoming spherocytes, and eventually cleared (mainly in the spleen) by monocytes and macrophages *via* FcγR-dependent phagocytosis (which can be induced by the activating FcγRI, FcγRIIa, and FcγRIIIa) [341,342]. Monocyte FcγR expression has been historically reported to be increased in patients with AIHA, and glucocorticoid administration was associated with a dose-dependent decrease [343]. In AIHA, inhibition of IgG-mediated phagocytosis by IVIg is mainly dependent on their capacity to directly saturate FcγRI and FcγRIIa, whereas no inhibitory role could be ascribed to FcγRIIb in human macrophages, contrary to what has been described in other diseases [54]. More specific treatments targeting kinases involved in FcγR downstream signalling, namely Btk and Syk inhibitors, are being evaluated in phase II and phase III clinical trials and could represent interesting therapeutic options in warm AIHA in the near future [344,345].

Interestingly, warm AIHA has been associated with an increased risk for thromboembolism, whereas classical risk factors are frequently absent in these patients [346]. Hemolysis by itself is likely to be an independent risk factor for thrombosis, as this increased risk for thrombosis is present in multiple hemolytic diseases, but other specific mechanisms are certainly involved. In line with this, it has been recently described that red blood cells coated with anti-(α -Rh(D) antibodies required FcRn to induce Tissue-Factor-activity in monocytes [347]. Hence, blocking FcRn, as reviewed elsewhere [47], could be an interesting therapeutic option in warm AIHA, and is being evaluated in clinical trials [3,345,348].

5. Adverse FcR engagement in prothrombotic autoimmune disorders

5.1. Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is the main prothrombotic autoimmune disease, whose key features are recurrent venous and/or arterial thrombosis and obstetrical complications [349]. It is frequently associated with SLE (40% of SLE patients have APS), and its approximate prevalence is 40 per 100,000 individuals [350,351]. The humoral autoimmune response in the disease is targeting components of the cell membrane *i.e.*, phospholipids and/or their associated proteins, mainly β 2-glycoprotein-I (β 2GPI) [352]. Autoantibodies detected in APS have also been described in COVID and could be contributing to the prothrombotic state present in the disease [353].

In APS, because of the very nature of the autoantibodies' targets (*i.e.*, the cell membrane), it is understandable that Fab-related features have been receiving much attention. Moreover, historical results from an APS hamster model study reported that anti- β 2GPI monoclonal antibodies had the same prothrombotic effects with or without their Fc fragment

[354]. Conflicting results have been reported by another group, which described a FcγRIIa-dependent neutrophil activation by different monoclonal anti- β 2GPI antibodies [355]. The role of neutrophils and their NETs forming ability have been recently highlighted in APS, since serum samples from patients with APS, as well as their purified autoantibodies, seemed to be able to trigger neutrophils to release NETs [356]. Moreover, depleting neutrophils or dissolving NETs with DNase was protective in an APS mouse model [357]. However, here again, the Fc fraction of anti- β 2GPI autoantibodies was not required *in vitro* to induce NETosis [356]. More recently, FcRn, in conjunction with FcγRIIa, was found to be involved in the induction of the Tissue Factor-dependent factor Xa activity by IgG ICs containing IgG autoantibodies [347]. In this study, using ICs containing anti- β 2GPI autoantibodies, required FcRn to induce Tissue-Factor-activity in monocytes [347]. Hence, blocking FcRn could be interesting, not only to reduce ICs-mediated autoimmune disease activity, but also to lessen the risk of thromboembolic complications caused by these ICs [47,48]. Prior to that report, saturating the FcRn *via* IVIg treatment had been found effective in APS mouse models to inhibit the thrombogenic effects of APS *in vivo* and reduce the circulating autoantibodies levels [358].

5.2. Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is also worth mentioning in that section, despite its drug-induced character, because it is a prothrombotic autoimmune disorder characterized by the presence of anti-platelet factor 4 (PF4), which have recently been described in post-COVID vaccination thromboembolic complications [359]. Patients have circulating autoantibodies (predominantly IgG1 class) which can bind to distinct epitopes within PF4 and engage FcγRIIa on platelets as well as Fc receptors on monocytes, and induce thrombocytopenia as well as thrombosis [360,361]. Regarding the mechanisms behind thrombosis, it was demonstrated that anti-PF4/heparin complexes were able to induce Tissue Factor expression and the release of Tissue Factor-bearing microparticles by monocytes involved FcγRI [362], as well as FcRn engagements [347].

6. Conclusions

While undisputed, the role for antibodies and especially autoantibodies, in autoimmune and inflammatory diseases, is complex, multifaceted, and still partially known. The various FcRs, as the main mediators of antibody-dependent effector functions, have gained major interest during the recent years. Despite the multiple FcRs-related functions and interactions with antibodies Fc reported in this autoimmunity-focused review article, there are still a lot of unknowns and uncertainties. Gaining further knowledge in that field can lead way to the development of future therapeutic strategies.

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