Autoimmunity Reviews 18 (2019) 306–311

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Innate immune-responses and their role in driving autoimmunity

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A B S T R A C T

Autoimmunity and autoimmune diseases were always considered to be driven mainly by adaptive immune responses, namely by auto-reactive B and T cell over-activity. The continuous stimulation of dendritic cells by autoantigens increases B cell activity, driving auto-reactive B cells to increase the production of auto-antibodies and of pro-inflammatory cytokines. On the other hand, a subset of dendritic cells is established being of tolerogenic properties thus becoming important in maintaining self-tolerance. However, early innate immune responses are continuously appreciated to be highly important in the development of immune-mediated inflammation in general and autoimmunity in particular. The innate immune system is a complex network of structured cells/proteins such as antigen presenting cells (macrophages and dendritic cells), the complement cascade, and many receptors/cytokines/proteins. Of these, one may mention the high expression of toll-like receptors 7 and 9 in antigen presenting cells, and B cells of systemic lupus erythematosus patients contributing to the expansion of auto-reactive B cells. C-reactive protein (CRP) and C1q are crucially important for efficient uptake of apoptotic cells. However, CRP is appreciated to have a role in maintaining anti-inflammatory responses and in altering autoimmunity. Natural killer cells (NK) are responsible for cytotoxicity responses but some of them (mainly CD56high), are important in maintaining peripheral self-tolerance, thus considered to be immune-regulatory cells. In this review we will cover most of the new data on innate immune system and discuss its importance in the development of autoimmunity. New treatments were developed following our better understanding of these pathways, the targeting of which, opened new therapeutic avenues in treating autoimmune diseases.

1. Introduction

1.1. Dendritic cells (DCs) and autoimmunity

Ralph M. Steinman received his Nobel Prize for the discovery of dendritic cells (DCs) identified to bridge innate and adaptive immunity. His identification of DCs, established innate immune responses to be a leading player in the initiation of autoimmune diseases. The origin of human macrophages and DCs, their precursors in bone marrow, the different pathways of their differentiation (such as to plasmacytoid DCs), and finally, how they migrate to peripheral lymphoid organs, remain to be elucidated [1]. DCs are front players in promoting imbalanced active immune responses, leading in individuals with genetic predispositions to the development of autoimmune diseases. On the other hand, DCs are responsible to the modulation of inhibitory responses against self-antigens and the maintenance of self-tolerance. When DCs fail to achieve their tolerogenic properties due to the increased ratio of activating/inhibitory receptors on their surfaces, they induce T cell activation and other immune-mediated inflammatory responses [2,3]. Over-activity of DCs is linked to the increased expression of molecules such as CD86, CD80 and TLRs, defining by that their immunogenic phenotype. T cell activation begins with antigen presentation by DCs and the formation of stimulatory immunological synapse (IS), including co-stimulatory molecules such as ICAM-1/LFA-1 and CD28/B7-1. When these molecules are targeted by monoclonal antibodies such as anti-CTLA-4, anti-LFA-3-Ig and anti-CD3, effective engagement between DCs and T cells is prevented and T cell activation is down-regulated. In healthy individuals, Th17 cells increase CD11c, CD86 and CD80 expression on DCs; however, this capacity was shown to be more potent in patients suffering from immune-mediated diseases. In this respect, blocking cell-to-cell contact and/or neutralization of IL-17 reduces the expression of CD80 and CD86. These results indicate that DC differentiation and activation is increased by a positive feedback loop between IL-17 and DCs [4,5]. Plasmacytoid dendritic cells (pDCs) are considered the major source of increased IFN-α in systemic lupus erythematosus (SLE) and anti-phospholipid syndrome (APS) and are regulated by microRNAs such as miR-361-5p, miR-128-3p, and miR-181a-3p. In a recent study, the expression of these microRNAs was found to be down-regulated in both SLE and APS as compared with healthy individuals. A further decrease of microRNAs was noticed when these pDCs were stimulated with TLR-7, in correlation with a high IFN-α signature. Being involved in pDCs activation in SLE microRNAs may become a therapeutic target in order to lower IFN-α signature [6]. In another study, the IFN-α producing capacity of pDCs from patients with SLE and healthy individuals was assessed following their stimulation with TLR-7 compared to that with TLR-9. The IFN-α producing capacity of pDCs was notably increased when stimulated with TLR-7 agonist in SLE compared to in healthy individuals. However, when pDCs were

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https://doi.org/10.1016/j.autrev.2018.10.005
Received 10 October 2018; Accepted 31 October 2018
Available online 11 January 2019

stimulated with TLR-9 the capacity of producing IFN-α was reduced. Increased IFN-α production by lupus pDCs was shown to correlate with disease activity and serum IFN-α level. The exposure of pDCs of SLE patients to IFN-α enhanced IFN-α production of TLR-7 stimulated pDCs, but reduced that of pDCs stimulated with TLR-9 agonist. In addition, TLR-7 localization was enhanced in late endosome/lysosome compartments in pDCs from SLE patients, contributing to the pathogenesis and severity of SLE [7,8].

1.2. DCs and phagocytosis

The process of apoptosis includes the formation of apoptotic blebs on cells surfaces. Later nuclear components separate from dying cells and are released into the circulation. Apo blebs exist early in the process of apoptosis and characterized by being AnxA5 (pos) PI (neg), or late apo-blebs and then identified as AnxA5 (pos) PI (pos). Both forms of blebs are efficiently phagocytosed by normal DCs. In SLE, blebs on apoptotic lymphocytes and leukocytes are loaded with auto-antigens, and when these auto-antigens are released they are continuously presented by DCs inducing increased auto-reactive T cell activation and the increased production of pro-inflammatory cytokines such as IL-6 and IFN-α [9]. In one study, the uptake of apoptotic blebs and apoptotic contents/bodies by DCs was assessed by flow cytometry and confocal microscope. It was found that DCs cleared apoptotic blebs more efficiently than clearing apoptotic cell bodies. When DCs were co-cultured with apoptotic blebs it resulted in increased CD40 and CD86 expression and also increased production of pro-inflammatory cytokines. In contrast to this, apoptotic cell bodies did not induce similar stimulatory effects [10,11]. Increased apoptosis and the well-established defective phagocytosis by macrophages and DCs are important events in the development of SLE. Players other than DCs such as C1q deficiency and insufficient natural IgM are also involved in the process of defective phagocytosis in SLE. The continuous activation and maturation of pDCs and myeloid DCs by modified auto-antigens result in activating auto-reactive T and B cells, leading to autoantibody production, inflammation and renal damage in SLE [12]. The expression of TAM receptor tyrosine kinases (a big family of receptors, such as Mer; Tyro3 and Ax1) on monocytes and macrophages are considered highly important for the phagocytosis of apoptotic cells. When measured on macrophages of patients suffering from SLE, their expression was significantly decreased compared to that of healthy controls. Opposite to their membrane expression, soluble Mer, Tyro3 and Ax1 were found to be increased when compared to healthy individuals. These findings are contributing factors explaining the deficient phagocytic abilities of macrophages and DCs in SLE which leads to prolonged exposure of nuclear auto-antigens to the immune system. In another study, the shedding of TAM receptors (Mer and Tyro3) from cell membranes was found to be increased and soluble Mer and Tyro3 levels were documented the highest in active SLE patients. These soluble receptors were particularly high in patients with lupus nephritis and increased titers of anti-dsDNA antibodies. Following therapy and clinical remission, the level of soluble Mer and Tyro3 decreased in parallel to the decrease in SLEDAI. Later, soluble Mer levels in plasma of SLE patients were also demonstrated to be increased in positive correlation with CD163 expressed on macrophages. Increased soluble Mer were again found in SLE patients with higher SLEDAI, anti-Sm, and Ro antibody positivity. Increased shedding of TAM receptors namely Ax1 was considered to be a result of increased ADAM metalloprotease-mediated cleavage of leukocyte Ax1. In this regard, it is suggested that the inhibition of ADAM is a potential therapeutic modality in SLE [13–16].

1.3. Tolerogenic dendritic cells

Normal immune-mediated responses are usually maintained by keeping a balance between stimulatory DCs (the professional antigen presenting cells, involved in activating naïve T cells to initiate a pro-inflammatory response against non-self-antigens) and tolerogenic DCs (tolDCs) the role of which is to maintain tolerance to self-nuclear components and suppress responsible effector T cells to immune mediated inflammatory conditions. When this balance is disturbed, tolDCs fail to regulate inflammation by allowing auto-reactive T and B cells to continuously produce pro-inflammatory cytokines and auto-antibodies followed by the development of autoimmune diseases. When DCs ingest efficiently apoptotic cells, they produce only limited amounts of pro-inflammatory cytokines and therefore they fail to prime effector T cells. Namely, the binding of apoptotic cells to the receptor CR3 (CD11b/CD18) on human monocyte-derived DCs, reduces the secretion of pro-inflammatory cytokines. The ligation of CD11b on DCs was shown to limit the expansion of Th17 cells within the human memory CD4+ T cells, strengthening by that the tolerogenic capacity of DCs. The ligation of CD11b on healthy homozygous carriers of the rs11143679 (ITGAM) variant-a genetic susceptibility marker for SLE, strongly decreased the secretion of Th17. These findings underline the important role of tolerogenic DCs and the therapeutic potential of targeting CD11b in SLE and other autoimmune diseases [17]. Normal immune homeostasis is achieved when proper differentiation conditions mediate the potential of reprograming DCs in an antigen-specific fashion and turn them to become tolerogenic to self [18]. The development or failure of tolDCs was shown to be in part the result of the expression ratio of the activating FcγRIII or the inhibitory FcγIIb. Recent studies were able to demonstrate the capacity of tolDCs to induce interleukin (IL-10)-secreting regulatory B cells or the reprograming of auto-reactive CD4+ T cells. The exposure of macrophages to anti-inflammatory cytokines such as IL-10 may lead to their differentiation into regulatory M2c (CD14highCD16 + CD163 + Mer+) macrophages. The development of tolDCs is down-regulated when Th pro-inflammatory cytokines are increased and macrophages are mature [19,20]. The prolonged exposure to IFN-γ and IL-4 promotes increased apoptosis and inhibits M2c differentiation leading to impaired phagocytosis and accumulation of apoptotic cells and persistence of inflammation. On the other hand it was reported that in the presence of IL-17, macrophage survival is increased and M2c differentiation is enhanced, enabling efficient clearance of apoptotic cells and the development of anti-inflammatory status [21]. Tolerogenic DCs are a promising therapeutic candidate for suppressing auto-reactive T cells in autoimmune diseases such as SLE and RA. In this respect, human monocyte-derived tolDCs were isolated from RA patients by applying a combination of immune-modulatory agents. The phenotype of these tolDCs was characterized by having reduced co-stimulatory molecules, low production of pro-inflammatory cytokines and low ability of stimulating autologous antigen-specific T cells compared to tolDCs that were derived from healthy controls. These cells were also characterized to have high expression of TLR-2 and were able to suppress mature DC-induced T cell proliferation and the production of IFN-γ. They were considered to be stable, highly tolerogenic and therefore a promising therapeutic tool for RA. In a recent study, tolDCs generated from SLE monocytes were also shown to have a stable immature/tolerogenic phenotype and of suppressive abilities of effector CD4+ T cells, thus making them suitable for an antigen-specific immunotherapy for SLE. Both in-vitro and in-vivo studies have shown that NF-kB blockade on DCs and Fcγ modulation induce a significant increase of the tolerogenic capacity of DCs supporting the notion that both are considered as therapeutic targets to induce or restore self-tolerance and decrease inflammation in autoimmune diseases [19,22,23].

2. CRP and autoimmunity

C-reactive protein (CRP) is synthesized in the liver as a result of several stimulations, e.g. interleukin (IL)-6 and IL-1, and as such is considered to be a classical acute-phase protein. CRP level is acceptably correlated with the severity of inflammation making it a reliable marker for follow-up after infections/inflammation and response to treatment

[24,25]. Focusing on the interaction between CRP and the complement system it was shown that one of the main functions of CRP is its interaction with C1q resulting in the activation of the classical complement cascade. On the other hand, it was also found that CRP is able to interact with the regulatory complement protein, namely, factor H, decreasing by that the generation of the active membrane attack complex [26]. Thus, it is hypothesized that this interaction may limit tissue damage at sites of inflammation and decreases the chemo- attractant ability of the C5a. In a mice model of lupus nephritis (NZB X NZW F1 female mice -NZB/W) CRP was shown to induce a long-lasting protection from nephritis; delay the onset of proteinuria and to prolong survival rates of these mice [27]. This is achieved by the binding of CRP (even at low levels of 1 μg/mL) to auto antigens thus, preventing their continuous presentation to the immune system and thereby preventing the generation of autoantibodies. SLE patients have usually low levels of CRP, despite disease exacerbations and tissue inflammation. In this case it is suggested that elevated CRP could serve a marker for infections in SLE (as opposed to a flare of disease) [24]. It is not known at this stage, what are the factors or inhibitors that are responsible for the altered synthesis of CRP in SLE. Long term exposure of the immune system to low amounts of CRP is hypothesized to modulate the natural history of autoimmune diseases and prevent the generation of pathogenic autoantibodies. In a recent study, it was demonstrated that when a single injection of 200 μg of CRP was injected into NZB/W mice it delayed the onset of proteinuria and prolonged survival rates of these mice [28]. Furthermore, when NZB/W mice in which high grade of proteinuria were present and were treated with CRP injections, one could see a complete and long lasting reversal of this proteinuria. One of the possible mechanisms of the anti- inflammatory effects of CRP is the ability of CRP in the presence of LPS to enhance the production of the anti-inflammatory cytokine, IL-10. The above finding was found both in vivo and in bone-marrow macrophage cultures from normal mice, were IL-10 has been shown to protect mice from endotoxin lethality [24]. The other possible explanation of CRP induced protection could be mediated by the increased induction of immune-regulating cells, such as T regulatory. These recently rediscovered cells are long lived and are capable of suppressing inflammation [24]. They are induced following the activation of naïve T cells and in the presence of high levels of IL-10 cytokine-milieu. In another study, the addition of CRP to PBMC's culture was able to inhibit the expression of CD209, the co-stimulatory molecules CD40 and CD86, thus suppressing the differentiation to DCs. This inhibition was shown to be in correlation with the timing of this addition. Earlier addition of CRP was associated with a stronger inhibition. Moreover, CRP reduced the expression of CD205 and CD206- antigen uptake molecules, which resulted in reducing the endocytosis properties of DCs. In addition, CRP also reduced the maturation marker of DCs (CD83), decreased the expression and secretion of pro-inflammatory cytokines from these DCs (e.g. IL6, 8, 12, TN alpha MIP and so on). Also, dendritic cells treated with CRP demonstrated inhibitory effects on T cells proliferation. [29]. Thus, it seems that the main role of CRP in autoimmune diseases is to maintain anti-inflammatory responses rather than promoting auto-antigen clearance or affecting their presentation.

3. C1q and autoimmunity

The complement system is the humoral arm of the innate immune response that is responsible, among other effects, for the efficient clearance of immune complexes and their degradation by effector immune cells. The classical pathway of compliment activation is believed to be pivotal in innate-immune pathogenesis and has been most widely studied in the context of SLE. The C1 complex binds to the Fc region of the IgG antibodies of immune complexes following this boundary- the bound C1 complex cleaves C4 and C2 in order to form a C3 convertase which in turn can cleave C3 into C3a and C3b. The later facilitates opsonization and the clearance of the immune complexes [30,35]. C3 convertase also generates other constituents of complement system, such as C5a which is a chemotactic factor that can attract and recruits inflammatory cells such as neutrophils, eosinophils, monocytes, and T lymphocytes to the inflammatory site.

Rare genetic deficiency of C1, either occur as a mutation where no protein is present or a mutation where C1q is nonfunctional, can result in a tendency to develop SLE mostly due to the diminished capacity to clear immune complexes [35]. Low C1q levels are also seen not only as the result of genetic mutation but also as a result of over-use which is associated with active disease [35]. It was demonstrated in auto-immune diseases, especially in SLE that patients might develop autoantibodies to C1q. The reason for this is that following the binding of C1q to an immune complex, its conformation is changing thus it results in the exposure of new antigenic sites [35]. It was demonstrated in SLE patients that there is a positive correlation between the presence of antibody against C1q and disease activity (SLEDAI score)- nephritis, dermatitis, hypo-complementemia, dsDNA antibodies, and circulating immune complexes. It was also found in this research that the concentration of autoantibodies to C1q in the glomeruli was greater than those that were found in the serum, thus it was postulated that these depositions might contribute to the pathogenesis of lupus nephritis [31]. In addition, it was also found that the presence of both hematuria and anti-C1q antibodies potentially correlate to active inflammation of the kidneys in lupus patients [33]. In earlier studies in SLE patients it was showed that six months prior to the appearance of clinical renal signs, there is increment of serum titers of C1q-autoantibodies. [32] Moreover, it was demonstrated that while there is increment in anti-C1q antibodies in active renal disease, this level decreased to normal or near normal values following treatment-induced remission [35]. The appearance of both anti-C1q and anti-dsDNA in the same patient increased the possibility of renal disease activity and poor renal outcomes [34]. This phenomenon might be used as an important biomarker for predicting a renal involvement in the progression of SLE disease [32].

4. Toll-like receptors and autoimmunity

The 2011 Nobel Prize was awarded to Bruce A. Beutler and Jules A. Hoffman for their discoveries on toll-like receptor (TLR) activation of innate immunity [36]. Toll-like receptors are innate pathogen recognition receptors shown in earlier studies to be responsible for the recognition of pathogen-molecules such as viral particles, bacteria, and drive the initiation of relevant immune responses. Later TLRs namely, TLR-7, 8 and 9 were recognized being linked to the detection of host RNA and DNA and the development of autoimmune diseases [37]. The expression of TLR-9 by RT-PCR and immunohistochemistry in renal biopsies of SLE patients compared to renal biopsies of healthy individuals was studied in relevance with a role of its genetic polymorphisms. A significant genotypic and allelic association was found between TLR-9-rs 352,140 and SLE nephritis. TLR-9 transcript was notably higher in SLE renal biopsies when compared to that of controls. Increased histochemical expression was found to be in the tubule-interstitial parts of involved SLE renal tissues. This was a further prove that TLR-9 is a susceptible gene to lupus nephritis supporting his role in the pathogenesis of SLE [38]. In a very recent study, TLR-9 was reported to be of high importance in the induction of B lymphocyte stimulating factor (BLyS)-induced SLE in mice. Aiming to assess the role and blood levels of BLyS and TLR-9 in a mice model of SLE, mice were divided into 3 groups: 1. Control mice received intraperitoneal injections of normal saline; 2. Mice in the BLyS inhibition group received anti-BR3 monoclonal antibodies; 3. Mice in the TLR-9 inhibition group received anti-human TLR-9 antibodies. TLR-9 mRNA, BLyS, IL-10, anti-dsDNA antibody titer, and C3 and C4 levels were all assessed, and found to be significantly increased in the control mice compared to that of both inhibition groups. This suggests that TLR-9 signaling is important in the regulation of BLys induced inflammation in SLE [39]. Furthermore, the recognition of self-nuclear antigens by endosomal TLRs in

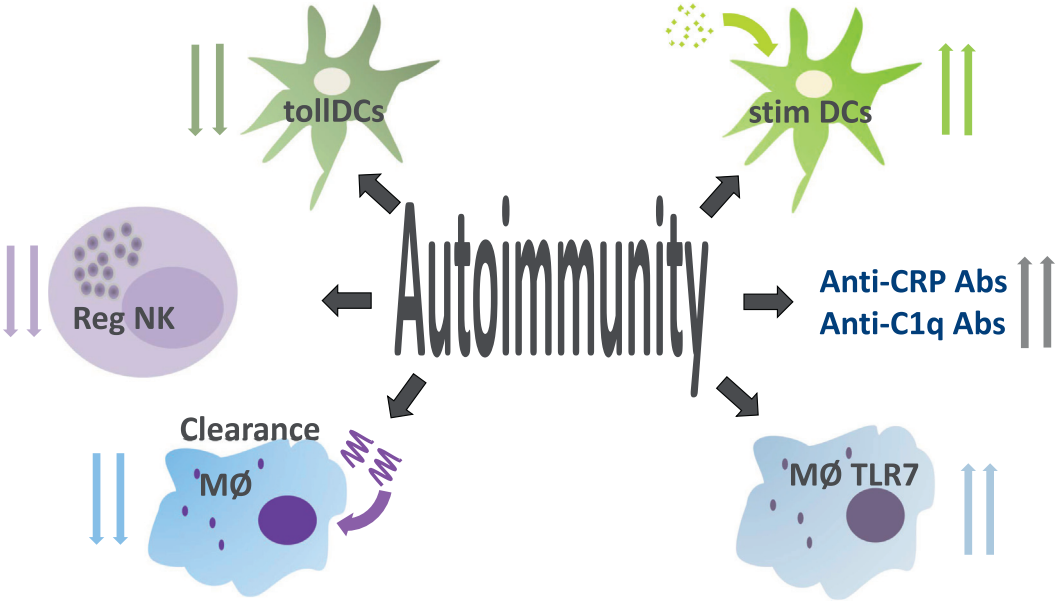

Fig. 1. The different pathways of innate immune responses leading to autoimmunity.

pDCs and B cells is a crucial step in the development of SLE, namely, the production of relevant autoantibodies and increased amounts of IFN-α. TLRs were shown to recognize non-coding RNA, SSA/Ro, thus contributing to the occurrence of asymptomatic SLE in pregnant mothers and to neonatal lupus. This was noticed to be in association with the production of anti-Ro60 antibodies and the development in some children characteristic rash and heart block [40]. Toll-like receptor-7 mediated DC activation, autoantibody production; lympho-proliferation and inflammatory damage are continuously observed in murine models of SLE. In this respect, X-chromosome consisting of 16 genes including TLR-7 was found to clearly mediate the autoimmune phenotype via the duplication of TLR-7 supporting its involvement in the genetic risk of SLE. The presence of genetic abnormalities leading to defects in the elimination of apoptotic cells, are shown to be responsible factors in the production of autoantibodies against nucleic acid-proteins such as chromatin and the envelope glycoprotein gp70 of endogenous retroviruses. Here also, TLR-7 and 9 were found to be involved in the regulation of autoimmune responses against endogenous retroviral gp70 elucidating by that the molecular role of these TLRs in the development of autoimmune diseases [41,42]. Accumulating evidence supports the notion that TLR9 and TLR7 may have a pivotal role (both pathogenic and protective) in the development of SLE in murine models. Aiming to address this concept, the production of relevant autoantibodies and the development of lupus nephritis was evaluated following the deletion of TLR9 and TLR7 in C57BL/6 mice. TLR9-deficient mice displayed enhanced production of anti-nuclear autoantibodies, anti-retroviral gp70 antigens and developed severe lupus nephritis. In addition, increased disease severity was found to be associated with increased expression of TLR7 and TLR7-dependent DC and B cell activation. SLE exacerbation in TLR9-deficient mice was improved by the deletion of TLR7, indicating that TLR7 has a pivotal role in autoimmunity and that increased activity of TLR7 is a dominant factor in the development of SLE. In a very recent study and in relevance to the above, TLR-/- mice were again shown to have enhanced autoimmune responses, increased immune complex deposition, DC and T cell renal infiltration. These findings were shown to take place in parallel with increasedTLR7 expression. This suggests that TLR9 is protective during TLR7-induced autoimmunity. Putative therapeutic strategies should manipulate TLRs accordingly [43,44].

5. Natural killer cells and autoimmunity

Natural killer (NK) cells are granular lymphocytes traditionally identified as part of the innate immune system. Classically, it is responsible in defending the body against microbes and cancer cells. Natural Killer cells are primarily developed in the bone marrow during adult life and then migrate to various peripheral organs. This process is controlled by a network of adhesion molecules such as integrins, selectins and chemokines, thus developed into tissue-specific NK cells. Upon micro-environmental changes during infectious diseases or immune-mediated inflammation, NK cell subsets infiltrate local pathological tissues where they induce their relevant functions. In general NK cells are defined as CD56 + CD3- though CD56 + CD3 + can function as NK-like T cells occasionally demonstrating several NK cell markers. CD56dim cells in peripheral blood constitute 90% of all NK cells being mature and mostly responsible for cytotoxicity responses. In contrast, CD56high cells are mostly immature and involved in cytokine production with little cytotoxic functions. Though autoimmune responses are adaptive in principle, NK cells appear to play a crucial role in the induction of immune-mediated responses or the maintenance of peripheral self-tolerance. Recent data focuses on the involvement of NK cells in the pathogenesis of many inflammatory immune-mediated diseases being of both protective and pathogenic properties. In diseases such as in psoriasis and RA, CD56high NK cells are reported to be immune-regulatory. They accumulate in inflamed tissues of these diseases such as the skin and synovial membranes, shown to be of impaired function and protective. In different inflammatory arthropathies such as in spondyloarthritis, NK cells are shown to express killer immunoglobulin-like receptors (KIRs) superfamily, considered responsible for the production of pro-inflammatory cytokines, the development of bone damage and DC activation, thus, modulating the susceptibility to this group of diseases [45–47]. Different KIRs and their corresponding specific HLA-C ligand phenotypes play role in defining susceptibility or resistance to infections or autoimmune diseases. In this respect, inhibitory KIRs were assessed in patients with reactive arthritis. KIR2DL2 and KIR2DL5 were found significantly lower than that in healthy controls. The expression of more than seven inhibitory variants of KIR genes was proved to be protective. However, the activating KIR2DS1 alone or in combination with HLA-C1 genotype was noticed to be present in association with susceptibility to reactive arthritis. This indicates that the imbalance between inhibitory and activating KIRs may

affect NK and T cell functions and the extent of innate immune responses in immune-mediated diseases [48]. The protective ability of NK cells was also demonstrated in a mice model of allergen-induced airway hyper-reactivity (AHR). In this model, the protective ability of CD4- CD8- double negative (DN) NK T cells was attributed to their high expression of CD38 and high production of IFN-ɣ. They were shown to suppress CD4+ effector T cell proliferation in a contact-dependent mechanism. A prior exposure of these mice to influenza virus was a contributing factor in increasing this protective function of NK cells against the development of allergic asthma [49]. Innate immune cells are front players in regulating immune responses in both the liver and the gut system. Innate-like and adaptive T cells are involved in responding and eliminating gut microbes but also in maintaining tolerance to gut-derived antigens. There are two subsets of reactive CD1d-restricted NKT cells, the one is invariant NKT (iNKT) and the second is type II NK cells, both present in humans. Due to their different properties in producing pro- or anti-inflammatory cytokines it is well defined that iNKT cells are considered to be pathogenic whereas type II NK cells are protective. A well-defined understanding of these regulatory pathways will lead to the introduction of novel therapies against liver and gut inflammatory diseases [50].

6. Conclusions

Innate immune responses are the starter of all adaptive immune responses, both in normal immunity and autoimmunity. It maintains a proper homeostasis keeping the balance between pro- and anti-inflammatory immune responses [51]. In this review we updated the recognition of innate immunity as a regulatory arm (Fig. 1), the responses of which are crucial for maintaining self-tolerance.

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