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Review article

Immune system-mediated cellular and molecular mechanisms in idiopathic membranous nephropathy pathogenesis and possible therapeutic targets

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ABSTRACT

Idiopathic membranous nephropathy (IMN) has recently attracted much attention due to the development of auto antibodies, anti-phospholipase A2 receptor and anti-thrombospondin type I domain-containing 7A on podocytes, the establishment of immune networks complexes in circulation as well as the development of autoreactive immune cells against kidney, in both innate and adaptive participants. The auto inflammatory responses in IMN leads to the dysfunction of glomerular cells to represent pathological status. T cells, as a crucial factor in the immune network, support B cell-related responses and develop inflammation and cytotoxicity. They have the most determining roles in the autoimmune diseases. Activation of T cells occurs just before their infiltration in kidney. This process is definitely accompanied by costimulatory factors and cytokines, in order to develop and increase the number of these cells. In addition, altered B cell signaling network by the B cell receptor and co receptors such as B cell-activating factor receptor (BAFFR) stimulates the autoimmune-related pathogenesis. Autoantigens exposure and kidney infiltration of naive T cells lead to their local development. Furthermore, losing peripheral immune tolerance towards kidney antigens, will result in IMN. The growing findings about different immune system factors, cells and molecular mechanism have also revealed new pathways of pathogenesis and diagnosis approaches, such as personalized medicine in MN patients. This review aims to discuss the recent findings in adaptive immune cells, and distinguishes between intact and undone researches about pathogenesis and molecular signaling pathways of immune system in MN disease.

1. Introduction

Membranous nephropathy (MN) is an immune-related disease that is the most ordinary reason of idiopathic nephrotic syndrome in nondiabetic adults. Around 20% of cases, are correlated with different conditions such as malignancy, systemic lupus erythematous, drug reactions and infection, while the remaining 80%, which are primary, are mediated by specific nephrogenic autoantibodies [1–4]. Idiopathic membranous nephropathy (IMN) is a kidney-specific, autoimmune glomerular disease that are diagnosed with proteinuria and unique pattern of injury in glomeruli. Autoimmune pathogenesis of MN came to birth by Heymann experience in rats with developed nephrotic syndrome following immunization with kidney suspension and Freund's adjuvants [5]. It took 43 years to the first description of human alloimmune IMN mediated by maternal antibody against neutral endoproteinase (NEP) in an infant of a congenitally NEP deficient mother. This experience established the role of autoantibodies in MN pathogenesis in humans and opened a new area for recognition of potential target antigens in IMN [6]. The major breakthrough in this field was achieved by the introduction of two podocyte transmembrane glycoproteins, the M-type phospholipase A2 receptor 1 (PLA2R1) and thrombospondin type-1 domain-containing 7A (THSD7A) [7,8]. Both of these autoantigens could trigger IgG4-predominant antibody response [9]. IMN is mostly developed by anti-PLA2R1 (85%), anti-THSD7A (3%–5%), or by undetermined mechanisms (10%) [1,2,10–14]. Large extracellular region of PLA2R1 is consisted of a cystein-rich domain

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(CysR) and eight different C-type lectin domains (CTLD1–8) [15]. The CysR domain acts as the dominant epitope of the PLA2R1 and is probably related with the early and stable stage of disease [16]. Other two independent PLA2R1 epitopes including CTLD1 and CTLD7 have been presented as targets for anti-PLA2R1 antibodies and associate with the poor outcome of the disease. Furthermore, it has been shown that anti-CTLD1 and anti-CTLD7 antibodies disappear in the remission phase and reemerge in the relapse phase of the disease [17]. These finding indicate that epitope spreading is able to be happened during the time towards CTLD1 and CTLD7 that causes poor prognosis as well as decrease in therapeutic responses [18]. It was mostly suggested that autoimmune responses are initiated as a result of the outside epitope (CysR domain) of the PLA2R1. Inflammation and tissue injuries trigger a chain of secondary response via processing and presenting inaccessible or inner epitopes (CTLD1 and CTLD7) [18–20]. It has recently been demonstrated that other intracellular antigens, as autoantibodies targets in MN, comprise aldose reductase, superoxide dismutase, and α-enolase. A number of these targerts including aldose reductase and superoxide dismutase are known as neoantigens, because of their over-expression on the injured podocytes [20]. They also interfere in immune complex formation. Probably, developing humoral immune response leads to intermolecular epitope spreading and subsequently presentation of these antigen as the secondary targets [21].

The introduction of the anti-PLA2R and anti-THSD7A autoantibodies facilitated the paradigm shift in this disease from histological to pathophysiological pattern and empirical treatment to targeted intervention at preventing antibody production [7,8]. T cells, as crucial players in immune response, are able to support the release of cytokines, promotion of B-cell and the recruitment of macrophages, neutrophils, natural killer cell (NK cell) and other subgroups of T helper cells. Immune homeostasis and tolerance are conducted by T cells. Lack of the tolerance causes autoantibody development, and triggers the inflammation. Ultimately, T cell-derived cytotoxicity leads to tissue damage, precisely in kidney as IMN (Fig. 1) [22]. T cells contain several subclasses including T-helper 1 (Th1), T-helper 2 (Th2), T-helper 17 (Th17), follicular helper T cell (Tfh), T-regulatory cells (Treg), regulatory type 1 cells (Tr1) and potentially distinct T-helper 9 (Th9) [23]. On the other hand, B cells, as prominent inducers of immune responses in autoimmune diseases, develop autoantibodies and play the role as antigen presenting cells (APC) [24].

Cooperation of many factors such as genetic, epigenetic, environmental and immune regulatory system lead to the loss of immune system tolerance against autoantigens and the appearance of autoimmune diseases. B and T autoreactive cells, auto antibodies, immune complex and cytokines are produced following this process. Different findings have revealed impaired immune system in IMN diseases. Promoted findings of molecular biology of immune cells in patients with IMN also provide opportunity for the detection of specific treatment targets. In this context, the variation in circulatory T- and B-cell population has attracted attention. This review will focus in the Immunopathogenesis of IMN along with presenting prominent visions for the future studies on therapeutics and IMN diagnosis.

2. $CD4^+$T cell

2.1. TH1 and TH2 cells

APC-related autoantigen presentation to $CD4^+$ T cells causes activation and differentiation of these cells to certain subsets including TH1 and TH2 cells mainly due to primary signaling pathways [22]. These pathways are usually influenced by environmental cytokines which mediate glomerulonephritis formation [22]. TH1 specific cytokine profiles induce macrophage, cytotoxic T cell activity, B cell differentiation into plasma cells for promotion of immune globulin subclass production as well as the establishment of delayed-type hypersensitivity response. IFN-γ and IL-12 are the important cytokines that induce TH1 cells differentiation [25].

TH2 mediates the release of certain interleukins including IL-4, IL-5, IL-10, IL-13, as well as the promotion of IgG and IgE generation to facilitate immune response networks. IL-4, as the signature cytokine of T cell is able to induce the expression of GATA3 via STAT6/JAK signaling pathway [26,27]. STAT4 and STAT6 are pivotal proteins in TH1 and TH2 cells signaling pathways, respectively. Also, they are considered as potential therapeutic targets for autoimmune diseases [28]. Decreased serum IFN-γ/IL-4 ratio following upregulation of $CD4^+/CD8^+$ ratio in IMN patients also suggests possible correlation of TH2 and IgG4 dependent immune responses in IMN pathogenesis. Additionally, some evidences have confirmed TH2- related IgG4 (IgG1 in murine), as dominant autoantibody in IMN [29–31].

The *WSX-1_/_* MRL/*lpr* mice model, which is considered as an equivalent model for human MN, also represented decreased TH1-related immune response due to the aberration of immune response towards TH2-related responses. Additionally, IgG1 deposition (IgG4 in human) in glomeruli, augmentation in the levels of IgG1, IgE, IL4, and decreased level of IFN-γ in mice serum, were also described as the main interfering factors [32]. Whereas Zhang et al. [33] revealed that level of IFN-γ and IL-2 elevated to in IMN compared healthy control [33]. Furthermore, the comparison among lupus nephritis, membranoproliferative glomerulonephritis, Henoch-Schonlein purpura nephritis, IgA nephropathy revealed that the amount of peripheral TH1/TH2 cells were significantly lower and the level of $IL-4^+$ cells was higher in IMN group. Also, the number of TH2 cells was significantly correlated with urinary proteins suggesting the possible role of TH2-derived IL-4 in podocytes damage. In spite of the B cells stimulation by the high level of TH2 cytokines for producing of TH2-related IgG subclass (IgG4), no direct relation was found between the IL-4 and IgG levels. This surprising finding is supported by decreased concentration of IgG following urinary excretion [34,35]. In childhood IMN, the IgG4 level is also significantly increased in serum and glomerular deposit; however, in childhood secondary MN, IgG1, IgG2, and IgG3 deposits have been reported as the dominant immunoglobulin deposits. $CD4^+$ T cells mostly tend to be differentiated into the TH2 cells providing IMN pathogenesis as the prominent factor [36].

TH2-derived IL-10 is responsible for controlling immune tolerance through a) repression of NK and TH1 cells, b) suppression of MCH2 complex expression in APCs and c) suppression of APC-dependent T cell proliferation [22,37]. IL-10 and IL-10-depended signaling networks play a key role in regulation and maintenance of normal kidney function which is surprisingly increased in IMN [38]. This paradox is describable through its dual role for activation, expansion and differentiation of B-cells. Additionally, IL-10 triggers mesangial cell expansion and leads to impaired glomerular function. Upregulation and downregulation of IL-10 and IL-2 are probably connected with impaired cell-mediated immunity in IMN, respectively [38,39].

2.2. Follicular helper T (TFH) cells

Follicular helper T (TFH) cells as $CD4^+$T subsets have a potential role in the regulation of plasma cells and also memory B cells production. Regulation and expansion of TFH cells are controlled via expression of programmed cell death protein 1 receptor (PD-1 receptors), C-X-C chemokine receptor type 5 (CXCR5), inducible T cell co-stimulator (ICOS), as well as IL-21 release [40–42].

IL-21 is able to stimulate and promote the differentiation of TFH by inducing B-cell lymphoma 6 (BCL6) and MAF (v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)) molecules [43,44]. TFH cells differentiation interacts with APCs such as dendritic cells and induced B cells in lymphoid tissues [45]. Dendritic cells, via IL-6, IL-12 and IL-27 release, and B cells, through IL-6, initiate STAT3 pathway which triggers transcription factors expression such as BCL6, MAF, BATF (basic leucine zipper transcriptional factor ATF-like) and IRF4 (interferon-regulatory factor 4) [46]. Mentioned transcription factors

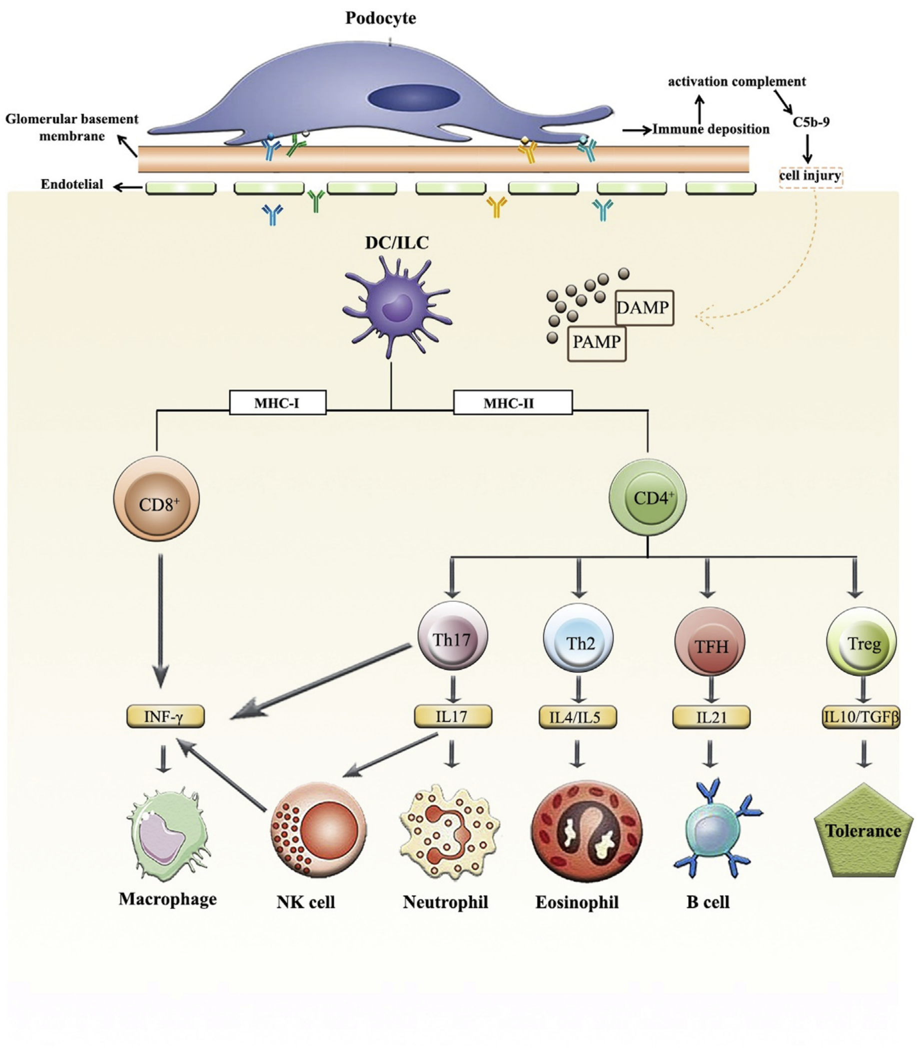

Fig. 1. Procedure involved in IMN promotion. Deposit of immune complex in the GBM causes complement activation and the commencement of disruption events which results in damage-associated molecular patterns (DAMP) and pathogen-associated molecular patterns (PAMP) release. The recognition of these molecules is mediated via Toll-like receptors on innate immune cells such as innate lymphoid cells (ILCs), dendritic cells and certain kidney cells. This recognition consequently activates these cells as antigen-presenting cells (APCs). Activated APCs trigger differentiation of signaling pathways in T cells in IMN patients. These T cells include T-helper2 cells, Thelper17 cells, T regulatory cells, and T follicular cells. Ultimately, the released cytokines support these procedures and induce the production of another group of cytokines such as IFN-γ which is crucial for macrophages induction. TH17 cells stimulate natural killer (NK) cells and neutrophils via IL-17 release. TH17, TH2, and T follicular helper (TFH) cells induce B cells for antibodies production. TH2 cells via IL-5 and IL-4 production, activate eosinophils. These factors and cells cooperate with each other to create inflammatory responses causing renal function impairment and tissue damages; IMN, idiopathic membranous nephropathy; GBM, glomerular basement membrane; DAMP, damage-associated molecular patterns; PAMP, pathogen-associated molecular patterns; ILC, innate lymphoid cells; APC, antigen-presenting cells; IFN-γ, interferon gamma; NK, natural killer; TFH, T follicular helper.

promote expression of CXCR5, ICOS genes, IL-21 and PD-1 that are needed for TFH cells formation. Cytokine-related stimulation of STAT1 might also be cooperated in this process [46]. Co-stimulatory ICOSL on dendritic cells and B cells are essential for upregulation of BCL6, MAF, BAF, IRF4 and are involved in optimal TFH cells generation [47].

TFH cells dysregulation has also been indicated in several autoimmune diseases including lupus erythematosus, primary cutaneous CD4$^+$ small/medium-sized pleomorphic T cell lymphoma and angioimmunoblastic T cell lymphomas [48,49]. Existence of T cells subsets (comprising TFH cells) in kidney has been documented in some studies [50]. A recent study demonstrated a significant increase in the number of TFH cells, naïve B cells and plasma cells in IMN patients, suggesting a possible correlation between the frequency of these cells and the progression of histopathological manifests [33]. The serum levels of IL-2, IL-4, IL-10, IL-17A, and IFN-γ were also significantly upregulated in IMN patients compared to healthy controls [33]. Percentage of circulating CD138$^+$CD19$^+$ plasma cells, CD4$^+$CXCR5$^+$IL-21$^+$ TFH cells, and serum level of IL-21 were significantly decreased following the treatment [33]. These findings show that there is correlation between the level of dysregulated cytokines and the progression of the disease. Following the treatment, the serum level of IL-4 and IL-10 elevated; however, no significant changes have been reported in the level of IL-2, IL-17A, and IFN-γ. It is also suggested that TH1 and TH2 pro-inflammatory responses mediate IMN pathogenesis which may promote anti-inflammatory responses of TH2. On the other hand, TH2 negative feedback is able to decrease pro-inflammatory responses [33]. The differentiation of TFH is connected with the function of inducible T cell costimulatory (ICOS), through BCL6 induction, which subsequently promotes CXCR expression to navigate cells into the germinal centers. Furthermore, programmed cell death-1 (PD1) acts as an immune system suppressor, via inhibition of CD3/CD28-stimulating receptor which stimulates PI3K pathway [51,52].

Therefore, ICOS$^+$ TFH and PD1$^+$ TFH cells probably act as activators and suppressors of the immune system, respectively [51,53–55]. The number of total ICOS$^+$ and PD-1$^+$ TFH cells and the ratio of ICOS$^+$/PD-1$^+$ TFH cells also increased in IMN patients. No correlations were observed between serum concentration of the IL-21 and IMN progression, while, a direct association between TFH cells (CD4CXCR5IL21$^+$) intracellular IL-21 and IMN development was reported [56]. The acceptable reason for the mentioned finding is that in addition to TFH, other immune cells including CD4$^+$ T cells and NKT cells, were likely to participate in the development of IL-21 in serum [57,58]. It has also been proposed that THF cells are capable to mediate the IMN pathological mechanisms through differentiation of naïve B cells into plasmablasts and increase the generation of IgG4 in IMN. In addition, the standard treatment restricts the differentiation of TFH cells in IMN. Altogether, the ratio of ICOS+/PD-1+ and the level of IL-21 could be considered as a sensitive marker for the assessment of IMN development [56]. Studies on TFH cells in IMN are not sufficient such as other autoimmune diseases.

2.3. TH17/T regulatory cells

T regulatory cells participate in immune response regulation by the inhibition of CD4$^+$, the proliferation of CD8$^+$ T cells, the suppression of B cells, NK cells, macrophages, and the activation of dendritic cells via releasing TGF-β and IL-10 [59].

Naturally, thymus-related Tregs (tTregs) cells conserve Foxp3 development and survival in IL-2 and transforming growth factor-b (TGF-β)–associated manner [60]. In the presence of a various inflammatory situations such as injury, autoimmunity and transplantation, tTreg cells are able to be differentiated peripherally towards different effector Treg subclasses containing T helper 1 Treg (TH1-Treg), T follicular helper Treg (TFH-Treg), T helper 17 Treg (TH17-Treg), T helper 2 Treg (TH2-Treg) and tissue Tregs [61,62].

Effector Treg cells express B lymphocyte–induced maturation protein-1 (Blimp-1), Foxp3 and IL-10 in common. Blimp-1 is a master transcription factor and prominent for Treg cells function, which regulates B-cell and T-cell differentiation and function [63]. Beside different tolerogenic conditions and accumulation of retinoic acid or TGF-β/IL-2 naive CD4$^+$, non-Foxp3 T cells differentiate towards peripherally Foxp3$^+$-related Treg cells through stimulating the Foxp3, *in vivo* [64]. Foxp3-expressed Treg cells display different repressive functions such as direct cell interaction between suppressor and effector T cells, and subsequently the expression of IL-35, TGF-β and IL-10. Furthermore, CD4$^+$ non-Foxp3$^+$ T cells in presence of IL-10 and/or IL-27, differentiate towards CD4 type 1 Tregs, and subsequent, over express a IL-10 and coexpress lymphocyte activation gene 3 (LAG-3), CD49$^+$ [64]. TGF-β and IL-2 are introduced as critical factors to trigger Treg cells differentiation. Stimulation of Sma- and Mad-related protein (SMAD)2 and SMAD3 through TGF-β pathway causes interaction between these transcription factors and Foxp3 locus, followed by express the Foxp3 gene [65,66]. IL-2 signaling pathway induces STAT5 to produce Foxp3 which is crucial for Treg cell hemostasis [66].

TH17 cells are a distinct subset of CD4$^+$cells which are characterized by the expression of IL17 and RORγt as a major transcription factor and are promoted by IL6, TGF-β, IL-23, IL-1 and IL-21 (TFH mediated cytokine) towards differentiation and expansion and cytokine production [67–69].

Th17 cells participate in autoimmune diseases by releasing factors such as IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL- 21, IL-22, IFN-γ, and tumor necrosis factor (TNF)-α [70,71]. TGF-β is prominent for the development of both Treg cells and Th17 cells through the expression of FoxP3 and RORC [72]. Nevertheless, without any inflammation, FoxP3 suppresses RORC and develops T regs cells. Inflammatory cytokines, including IL-6, IL-21 and IL-23, trigger signaling pathways, which ends up to STAT3 phosphorylation, releasing RORC from the repression of FoxP3 and originates Th17 programming [73]. STAT3 in combine with IFN regulatory factor 4 (IRF4), stimulates RORC production.

Binding of STAT3, RORC and Runx1 to the promoter regions of the *IL-17*, *IL-21*, *IL-22* and *CCL20* genes causes expression of mentioned factors. TH17 differentiation can be suppressed through IFN-γ, IL-2 and IL-27 via activation of STAT5 and STAT1 and subsequently repression of STAT3 [74]. IL-17 releases from local TH17 cells straightly on mesangial and tubule epithelial renal cells and subsequently stimulates these cells to express CCL20 and CXCL5. TH17 cells via recruitment of CCL6-CCL20, migrate into kidney and trigger signaling pathways which lead to impairment of kidney cells [75].

In addition of developing a self-sustain environment, TH17 cells agitate migration of other CCR6-producing leukocytes such as Treg cells into kidney which probably a self-limiting function of the TH17 cells.

TH17 augment inflammation, promote B-cell stimulation and loss of tolerance [68]. Pathogenic TH17-related immune responses are the results of CXCL5 overexpression via kidney tubular cells. Mentioned cytokine, absorbs neutrophils towards the kidneys and originates tissue damage [76]. Despite the fact that there are rare studies on the TH17/Treg cells in IMN, evaluation of other autoimmune diseases revealed the prominent role of these cells. A recent study revealed that upregulation of IL-17 induces pro-inflammatory profile cytokines (IL-6, TNF-α, IL-1β), chemokines (CCL2 and CXCL2), and pro-fibrotic genes (TGF-β and fibronectin) in kidney by the recruitment of certain mechanisms (recruitment Act1, triggering the NF-κB pathway) [77].

The produced IL-17 by kidney infiltrated TH17 cells lead to tissue damages through induction of mesangial and tubule epithelial cells for the expression of CCL20 and CXCL5 which are bound to CCR6 and CXCR2 on TH17 and neutrophils, respectively [77].

They also inhibit tissue necrosis; however, in strong responses the tissue damages are unavoidable. Hence, TH17/T reg balance is vital for preserving immune tolerance, immune hemostasis and inflammation control [78,79]. Despite the fact that the role of Th17/T reg cells is recognized in autoimmune diseases but there are not sufficient studies on these cells in PMN. A clinical study has reported a decreased and increased percentage of peripheral Treg and TH17 cells in IMN compared to healthy control group. Additionally, increased concentration of IL-17 and TNF-α, and decreased concentration of TGF-β have also been reported in IMN patients. Moreover, the treatment by rituximab leads to Treg cells number increase which is interrelated with the clinical outcomes including the proteinuria reduction [31,80].

3. CD8$^+$ cytotoxic Tcells

The important role of CD8$^+$ cytotoxic T cells as an inducer of glomerular damage has been shown in Heymann nephritis (HN) [81]. Data revealed the permanent decrease in the frequency of CD8$^+$ T cells following adult thymectomy and CD8 mAb treatment, leading to proteinuria progression suppression in HN. CD8$^+$T cells may also trigger cytotoxicity through a granule perforin pathway for glomerular endothelial cell (GEC) damage and proteinuria induction. In this study, also there were no differences in glomerular deposition of IgG and C3 between control and treated HN groups. In fact, stimulated CD8$^+$ T-related B cells showed a milder response to Fx1A compared to stimulated CD4$^+$ T cell-related B cells [81]. An acceptable mechanism for the activation of CD8$^+$ T cells in HN is the stimulation of B cells in draining lymph node following TH1 and TH2 CD$^+$4 cells activation. Autoantibody production forms immune complex deposits on GEC and activates MHC1-mediated antigen presentation to the CD8$^+$ T cells. This reaction may need to recruit TH1-related immune response [82–84]. It is necessary to mention that the GEC has the ability to express both MCH1 and MCH 2 proteins [81,85–87]. Furthermore, glomerular macrophages which are related to stimulated CD4$^+$ and CD8$^+$ T cells, can participate in glomerular damage by cytotoxic substance production [88–91]. Moreover the CD8$^+$ T cells recruitment has also been suggested for proteinuria development in the final stage of the diseases [81].

3.1. CD8$^+$ regulatory T cells

CD8$^+$ regulatory T cells (CD8$^+$ Tregs) as a sub-population of CD8$^+$ T lymphocytes, efficiently regulate immune responses to display immunosuppressive functions via the development of several cytokines and chemokines including TGF-β, IL-16, IFN-γ, IL-10, and chemokine (C– C motif) ligand 4. CD8αα+ T cell receptor (TCR)-αβ+ Tregs as novel subsets of CD8$^+$ Tregs are able to recognize major histocompatibility complex class Ib (MHC Ib) molecules Qa 1 (or HLA-E in humans) at the surface of stimulated T and B lymphocytes and dendritic cells which represent a cytotoxic effect against antigen overactive CD4$^+$ T cells. The immune regulation function of Qa-1-restricted CD8$^+$ Treg has been confirmed in several murine models of autoimmune diseases, such as Type I diabetes, herpes stromal keratitis and experimental autoimmune encephalomyelitis (EAE) [92–94]. Protective function of T-Cell Vaccination (TCV) has also been revealed in several autoimmune diseases [95]. For preparation of TCV, CD4$^+$ T cells were extracted from renal tubular antigen (Fx1A)–immunized rat, and were stimulated *in vitro* for expressing the MHC class Ib molecule Qa-1. T cell-vaccinated HN rats were able to restrict HN via the stimulation of autoreactive CD4$^+$T cell expressing Q-1 and subsequently the activation of Qa-1–mediated CD8$^+$ Tregs [96].

HN + TCV also demonstrated the downregulation of inflammatory cytokines including IFN-γ and IL-6 in splenocytes compared to the control group. In contrast, the level of anti-inflammatory cytokines such as TGF-β and IL-10 elevated in HN + TCV. However, IL-21 upregulation was not significant in rat's spleen. On the other hand, there was no significant variations in the percentage of CD4$^+$ Foxp3+ T cells and the level of Foxp3 expression in both groups. This indicates that these cells did not exhibit a protective role in HN + TCV group. TVC also restricts Qa-1–expressing CXCR5+ TFH cells in development HN cases. As a matter of fact, mentioned results suggest that TCV and CD8+Tregs can be considered as therapeutic choices for IMN [96].

3.1.1. B cells

B-cell dysregulated immune response is believed to modulate pathogenesis of autoimmune diseases establishment due to neglected self-antigen presentation, auto-antibody production, and impaired cytokine secretion [97]. CD20 is considered to be expressed in all linages of B cells except for plasma cells [98,99]. CD20 is able to provoke proliferation and differentiation of B lymphocytes, as well as the regulation of immune system function [100]. Recent findings revealed that anti-CD20 antibodies are effective immunosuppressants which are capable of repressing the B cell proliferation and pathogenic antibody development in IMN [101].

In IMN cases, the percentage of B lymphocytes and regulatory T-cells have been reported to be significantly higher and lower than the control group, respectively. However, there are no correlations between the level of B lymphocytes, proteinuria, and serum albumin in IMN [31,102]. Deposited sub-epithelial immune complex in kidney triggers the complement pathway activation, causing development of C5b-9 attack in podocyte for tissue damage and proteinuria [101]. IgG4 is also a dominant deposited immunoglobulin subset in IMN [103]. TH2-derived IL4 promotes IgG subclass (IgG4) production.Subsequently, deposition of subepithelial auto antibodies, leads to trigger complement pathways and generation of the membrane attack complex (MAC, C5b-C9) [14,104]. MAC is main causes to sub epithelial podocyte injury by stimulation of transcription factors, which are involved in fibrosis, cytoskeletal podocyte rearrangement and induces overexpression of nephritogenic molecules including reactive oxygen species (ROS), vasoactive molecules, proteases and proinflammatory cytokines [105]. In spite of hetero-divalent structure, IgG4 reveals itself as amonovalent, non-cross- link antibody which is notable to develop enormous immune complexes. Hypoglycosylated anti-PLA2R IgG4 complexes induce complement via mannose binding lectin (MBL) pathway. Because of incapability of binding to C1q, IgG4 does not stimulate classical pathway, but triggering alternative pathway seems to be possible [106]. Regulation of IgG4 production is achieved through Th2 cytokines (IL-4 or IL-13), and antigen, related to an IgE response, may be suitable for IgG4 stimulation. IgG4 production seems to happen independent from IgE response (via exposure to Treg mediated IL-10, which subsequently decrease IgE expression [107]. Anti-CD20 monoclonal antibody rituximab targets the B-cell surface antigen CD20 and suppresses auto-antibodies generation (mainly IgG4) then decreases glomerular IgG4 and C3 staining. following this, improves the outcome of IMN [18]. Deposition of IgG4- PLA2R/THSD7A complex can be confirmed via immunofluorescence microscopy with proper antigen improvement procedures in glomerular. Immunofluorescence microscopy ordinarily shows diffuse, identical and granular deposits of IgG4 along the outward faces of capillary walls that is a golden method for diagnosis of PLA2R/THSD7A-mediated IMN [10]. Circulating anti-PLA2R antibodies is evaluated with enzyme linked immunosorbent assay (ELISA) [108]. Hence PLA2R autoantibodies(predominately IgG4) can be used to detect disease activity and development, also to monitor response to immunosuppressive therapy.

The significant role of complement response (precisely C5b-9 attack complex) in renal dispose makes it a suitable target for therapeutic approaches in IMN patients [10,100]. Moreover, CD40, as a critical receptor on B cells and antigen–presenting cells is demanded for the T cell stimulation and B cell differentiation [109]. In a study based on blocking CD40-CD154 costimulatory pathway, by CD40 DNA vaccine in HN, vaccinated rats with scDEC presented lower levels of proteinuria and protection against progressive HN. Additionally, it has been reported that CD40 DNA vaccines can drive major considers as novel therapeutic methods for the restriction of the HN progression via dendritic cells targeting [110].

3.1.2. Macrophage

Antibody deposition related cell injury releases apoptotic and necrotic substances which stimulate innate immune cells that distinguish particle via pattern recognition receptors (PRRs) [22]. Prominent materials of innate system, which induces the adaptive system is consisted of apoptotic debris, type 1 interferon, other cytokines and MHC II in autoimmune diseases [111].

Monocytes (Mo) and macrophages (M#) are the prominent cells of innate system which present a role in the regulation of the beginning, progression, and perseverance of several inflammatory disorders. On the other hand, these cells mediate tissue regeneration and immune regulation [112]. It was demonstrated in a number of studies that a fundamental relationship exists between the number or stimulation of these cells and the autoimmune disorder progression [112].

Recently, monocytes are divided into two main phenotypes: M1 monocytes produce IL-12 and tumor necrosis factor (TNF-a) that promote local inflammation and TH1 immune responses, while, M2 monocytes modulate the immune system, repair tissue, and also stimulate TH2 immune response via releasing IL-4 and IL-10. Human peripheral blood M1 and M2 monocytes differentiate into M1, M2 macrophage in the tissue [113–115].

M2 monocytes are recognized by CD14$^+$ (highly expressed on monocytes), CD163+ (classical marker of M2 cells) and CD206 + CD115+, while, there is no specific markers for M1. Accordingly, M1 promotes TH1 immune responses and M2 stimulates TH2 immune responses [116]. Positive correlation has been demonstrated among CD14 + CD163 + CD206 + M2-like monocyte number with the 24 h urine albumin, serum PLA2R levels, intracellular IL-10 concentrations as well as progression of disease in IMN patients. Several lines of evidence have shown that stimulated M2 cells suppress inflammatory process and develop fibrosis in renal diseases [117]. Macrophage migration in tubuleinterstitium injury is a common finding in the pathological course of IMN early phase. Peripheral CD14 + CD163 + CD206 + M2-like monocytes are stimulated via IL-4 and IL-13 from Th2-type immune responses and are attracted through such damages towards renal tissues in IMN [117]. Overexpression of pro-inflammatory genes including, monocyte chemoattractant protein-1 (MCP-1) and osteopontin (OPN) by tubulointerstitium represents the prominent role in this migration. Despite the protective role of M2 monocytes, they are able to release fibronectin which interferes renal fibrosis at the end stage IMN. Altogether, M2-like monocytes and mentioned chemoatractin proteins potentially can be considered as a sensitive indicator for IMN progression [118,119]. Nevertheless, insufficient evolution has been presented on the correlation of monocyte phenotypes in IMN progression. Accordingly, study of the roles and mechanisms of innate system is unknown in IMN. Hence, this system requires more detailed analyses via using the cell culture and the murine model like other autoimmune diseases.

3.1.3. Candidate molecules for targeted therapy

T cell receptor stimulation by APCs leads to naïve CD4$^+$ T cell differentiation into the active subsets with the ability of cytokine production under recruitment of environmental cytokines (IL-2, 1L-4), signaling pathways (MAPK, Ca^{2+}–calcineurin) and transcription factors (STATs, T-bet) [122].

APCs exposure to T cells along with recruitment of costimulatory receptors (including CD28) and co-receptors (such as CD4+ or CD8+ which interact with MHC class II or MHC class I complex, repeatedly) leads to phosphorylation of immune receptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic domains of CD3 subunits by lymphocyte-specific protein tyrosine kinase (LCK). LCK is a member of the Src family which interacts with intracellular domains of $CD4^+$ and $CD8^+$ [123]. Additionally, exposure of APCs to T cells also leads to an interaction between LCK and intracellular domains of CD4 and CD8, along with engagement of this cluster with the TCR. The mentioned complex induces phosphorylation of immune receptor tyrosine-based activation motifs (ITAMs), in the cytoplasmic domains of CD3 subunits. Phosphorylation of ITAMs provokes the protein tyrosine kinase ZAP70 for LAT phosphorylation (a transmembrane adaptor protein linker for activation of T cell). The activated LAT stimulates certain master signaling pathways including mitogen-activated protein kinase (MAPK), Ca^{2+}– calcineurin, and nuclear factor-κB (NF- κB) [124,125].

B cell receptor (BCR) complex contains a membrane-tethered IgM antibody which is associated with membrane bound protein CD79a/CD79b [126]. Antigen-mediated ITAM stimulation which is located in cytoplasmic side of CD79a/CD79b, is phosphorylated by Lyn1 (Src family kinases) and spleen tyrosine kinase (Syk). Subsequently, the phosphorylated ITAM stimulates the signalosome [127]. Signalosome contains various kinases and adaptor proteins, such as Syk, Bruton tyrosine kinase (Btk), Lyn, guanine exchange factor Vav proteins, adaptor proteins Grb2 and B-cell linker [128]. SYK induces phosphorylation of CD79a/CD79b and Lyn via interactions among CD19 and further costimulatory factors causes BCR amplification maintenance. Overall, mentioned cascades trigger three signature pathways including PI3K, PLC-γ2 and Btk (Fig. 2) [129].

B cell-activating factor receptor (BAFFR), binds to its ligand, B cell-activating factor (BAFF) on B cells and triggers survival and maturation of signaling networks through recruitment of the nuclear factor κB cascade. Interaction between BCR and BAFFR signaling network leads to PI3K mediated B cell survival following CD19 phosphorylation [24].

As a whole, the identification of molecular abnormalities in IMN-related immune cells may present effective strategies for IMN therapy and diagnosis.

Activators of transcription and signal transducers (STATs) are also important transcription factors which induce the activation and differentiation of T cell subsets, as well as the regulation of B cells differentiation via cytokines and Janus kinases (JAK) cooperation [130]. JAK-induced STATs phosphorylation leads to STAT dimerization, and provokes the transcription of related genes. STATs likely induce tissue fibrosis via TGF-β upregulation [77]. Furthermore, IL-4 stimulates STAT6 and recruits GATA binding protein 3 (GATA3) for promoting TH2 cell differentiation [131]. IL-12 also stimulates STAT4 for TH1 development [132]. GATA3 promotes TH2 differentiation, stimulates IL-4 expression and inhibits production of IL-12 receptors and INFγ in naïve CD4+ cells [133]. INF-γ is another important cytokine for the induction of TH1 cells differentiation, which triggers STAT1/JAK signaling pathway [132]. T-bet is also another transcription factor which is expressed via this pathway [134] T bet, regulates INF-γ expression, upregulates b2 chain of IL-12 receptor, and also inhibits TH2 immune responses through suppression of GATA3 DNA binding [135,136]. STAT3 pathway is also induced by the cooperation of IL-23, IL-6, IL-21, IL1-β, and TGF-β for the promotion of TH17 or TFH cell differentiation [137,138]. RORγt is known as the prominent transcription factor in TH17 cells [139]. IL2/STAT5 signaling axis also leads to the differentiation of Treg cells, via recruitment of TGF-β [140]. Foxp3 is the master transcription factor of this pathway, for restricting the TH1 and TH17 cell functions. In this regard, inhibition or activation of the target

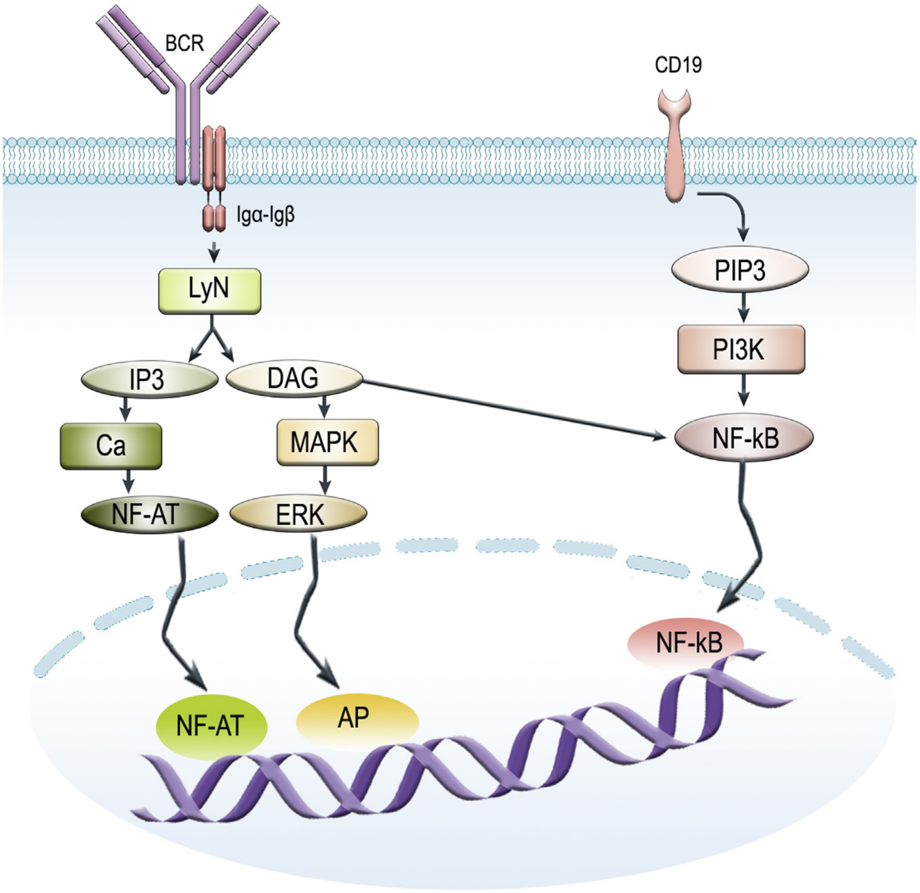

Fig. 2. Major BCR signaling pathways overview. BCR via recruitment of various adaptors and molecules induce downstream signals. The BCR complex leads to major specific outcomes, such as proliferation, differentiation into plasma cells or memory B cells, survival, tolerance and apoptosis. There are three master mechanisms that can be assumed in BCR signal transduction, such as: nuclear factor- κB (NF- κB), MAPK, and Ca2+signaling pathways. Induction of Ca2+–calcineurin pathway causes migration of nuclear factor of activated T cells (NFAT) toward nucleus. NF- κB signaling is also triggered through two major pathways such as PI3k-AKT and MAPK pathways. These pathways lead to translocation of NF- κB transcription factor. MAPK pathway induces activator protein 1 (AP-1) activation to start effector gens transcription in B cells as well. It is necessary to mention that all of signaling pathways and effector molecules are not illustrated in this figure; BCR, B cells receptors; NF- κB, nuclear factor-κB; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cells; PI3k, phosphoinositide 3-kinases; AKT, protein kinase B; AP-1, activator protein 1.

of rapamycin (mTOR) pathway is vital for all these procedures [132,137].

mTOR is a serine/threonine kinase that regulates proliferation and survival procedures in cells [141]. A rapid glance at stimulating mechanisms of mTOR confirmed PI3K/AKT or MAPK as upstream stimulatory pathways [142]. Differentiation of TH17, TH1 and double negative T cells are also related to mTOR1. On the other hand, mTOR2 presents a vital role in the differentiation of TH2 and TFH cells which is regulated via SOCS5. It has been shown that mTOR1 and mTOR2 activation causes impaired Treg cell expansion [143,144]. On the other hand, mTOR inhibition in autoimmune nephropathy mice models decreases migration of T cells and B cells and shifts TH17 cells differentiation towards Treg cells and suppresses glomerular nephritis. Mentioned mechanisms support therapeutic application of this inhibitory molecule in autoimmune nephritis [145,146].

Rho-associated protein kinase (ROCK), a serine/threonine kinase, is another important protein involved in TH17 differentiation signaling pathway. ROCK stimulates IRF4, which is known as an enhancer for the transcription of IL-17 and IL-21 in T cells [147,148].

PPA is also obligatory for the differentiation of T reg cells via mTOR inhibition [149]. Furthermore, it upregulates the IL-17 and INF-γ and down regulates IL-2 [149–151]. It seems that PPA2 has a distinct effect on T reg cells and effector T cells. Additionally, PPA2 stimulates ROCK function and subsequently mediates IRF4 and IL-17 promoter interaction in T cells [150]. It suggests that PPA may have various effects on the action of T cells (Fig. 3).

4. Conclusions

As it has been mentioned in the previous studies, various factors participate in the formation and promotion of IMN diseases. The majority of findings indicate that, the origin of this disease is related to the adaptive and innate immune cells and subsequently to their functions in kidney. It seems that despite the important role of immune system in IMN pathogenesis, the evaluation of T and B cell population is insufficient and controversial (Table 1). T cells play a crucial role in immune system responses control. Any impairment in the function of these cells influences the stability of peripheral tolerance and leads to the production of autoantibodies by B cells [22].

Following autoantigen presentation by APCs to immune cells including T cells, these cells are stimulated and committed to release cytokines (such as IL-2, IL-4, INF-γ) and differentiate into various subsets via expression transcription factors (STATs, RORγ, GATA3) (Fig. 4). On the other hand, these cells present cytotoxicity specification before infiltration to kidney; however, after infiltration they might promote and augment immune response. Moreover, podocytes via releasing cytokines such as IL-23 or producing costimulatory proteins stimulate CD4$^+$T cells after infiltration in kidney. Increased number of TH2 cells induce B cells towards plasma cells via cytokines (IL-4, IL-10) production in IMN. Antibodies deposition in sub-epithelial cells, triggers complement activation and generation of the MAC that causes subepithelial podocyte injury and proteinuria. Although, TH2-derived IL10 is responsible for the control of immune tolerance, but the overexpression of IL-10 interferes with activation, expansion and differentiation of B-cell, additionally, triggers mesangial cell expansion which are probably connected to impaired cell-mediated immunity in IMN. Furthermore, crucial role of B cells in IMN pathogenesis has been revealed via the presence of sub-epithelial autoantibodies deposition and circulating immune complexes. Also, prominent role of B cells has been presented via increased IL-21-related TFH cells in the pathogenesis of this disease. Th17 cells produce main cytokines for the stimulation and attraction of neutrophils, also target non-immune cells, such

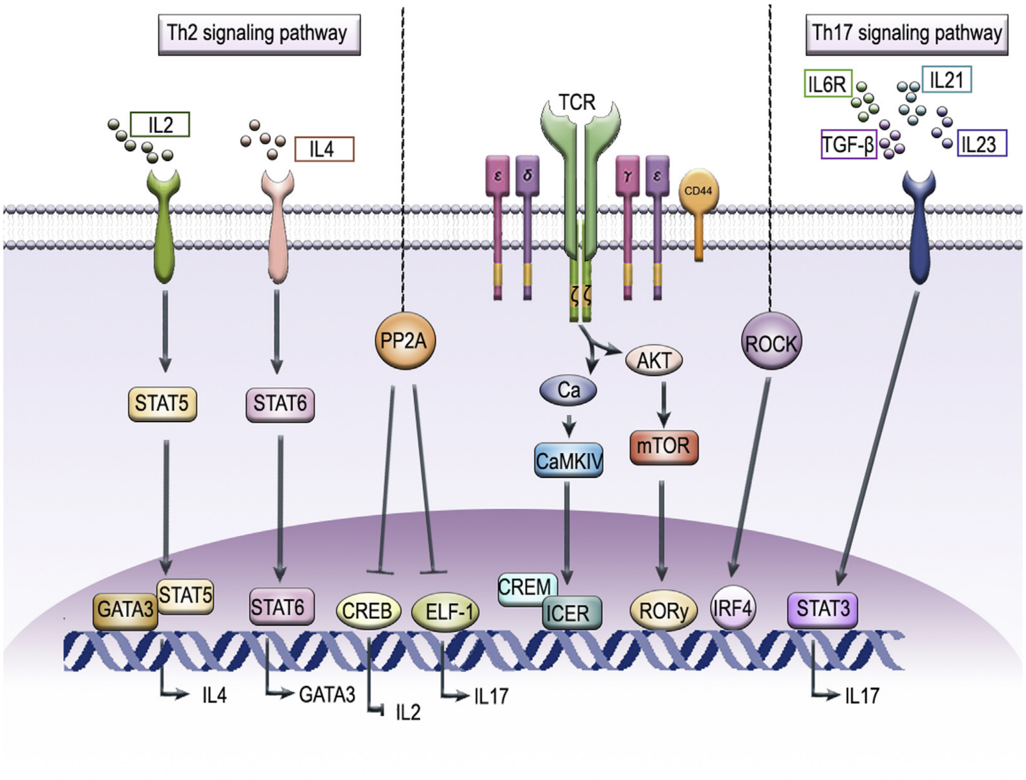

Fig. 3. Molecular pathways mediating T cells differentiation and cytokines production. Chemokines and cytokines are prominent factors which are overexpressed in autoimmune nephritis. IL-6, IL-23, IL-21 and transforming growth factor β (TGF-β) triggers signaling pathways via STAT3/JAK activation in their downstream, for IL-17 and BCL6 expressing induction. IL-17 and BCL6 maintain the inflammation and stimulate B cells in auto immune responses. According the previous studies, these procedures could be considered in MN. In autoimmune diseases, T cells are distinguished via impairment of signaling pathways including activated PI3K-Akt-mTORC1, factors like Rho associated protein kinase (ROCK), protein phosphatase 2A (PP2A), and calcium/calmodulin kinase IV (CaMKIV). Increased cytoplasmic Ca2$^+$ leads to CAMP Responsive Element Modulator (CREM) and inducible cAMP early repressor (ICER) binding to IL-17 and IL-2 promoters. These two enhancers induce IL-17 and IL-2 expression. Phosphatase 2A (PP2A) activation via suppression of cyclic AMP-responsive element-binding protein 1 (CREB), inhibits IL 2 expression. Cooperation of PP2A and ROCK also stimulate interferon regulatory factor 4 (IRF4) as IL-17 transcription factor. On the other hand, ELF-1 causes IL-17 expression induction; TGF-β, transforming growth factor β; STAT3, signal transducer and activator of transcription 3; JAK, janus kinase; BCL6, B-cell lymphoma 6; MN, membranous nephropathy; PI3K, phosphoinositide 3-kinases; Akt, protein kinase B; mTORC1, mammalian target of rapamycin complex 1; ROCK, Rho associated protein kinase; CaMKIV, calcium/calmodulin kinase IV; PP2A, protein phosphatase 2A; CREM, CAMP responsive element modulator; ICER, inducible cAMP early repressor; PP2A, phosphatase 2A; CREB, cyclic AMP-responsive element-binding protein 1; IRF4, interferon regulatory factor 4.

Table 1

Effects of immune cells in IMN diseases progression.

Cell	Phenotype	Contributing factors to autoimmune nephritis	Variation factors in MN	Refs
TH1 cells	IL-2 + TNF-β + IFN-γ +	IL-2, IFN-γ and lymphotoxin,	TH1 cells ↓ IFN-γ ↓ IL2 ↓	[29–32,34,35,38,120]
TH2 cells	IL-4 + IL-5 + IL-10 + IL-13 +	IL-4, IL-5, IL-6, IL-10	TH2 cells ↑ IL4, ↑ IL10 ↑	[29–36,38,104],
TH17 cells	RORγτ + CCR6 + IL-23R + IL-1R1 +	IFNγ, IL-17, IL-21, IL-22	TH17 cells ↑ IL17A ↑ TNF-α ↑	[33,80,120]
Treg cells T	CD4 + CD25 + FOXP3$^+$	IL-10, TGF-β	Treg cells ↓ TGF-β ↓	[31,80,121]
TFH cells	CXCR5$^+$PD-1$^+$ICOS$^+$ BCL6$^+$	IL21,IL6, IL12,1L4,IL10	TFH ↑ ICOS ↑ PD-1 ↑ IL21↑	[33,56],
CD8$^+$ T cells	CD45 + ,CD3 + , CD8 +	perforin, granzymes B, INFγ, TNF-α	CD4$^+$/CD8$^+$ T cells ↓	[31,104,121]
B cells	CD45 + , CD19 + , CD20 + , CD24 + , CD38$^+$, CD22$^+$	IL-10, TGF-beta, Ig	B cell ↑ IgG4 ↑	[31,33,102], [104,117],
M2-like monocytes	CD14 + CD163 + CD206 +	ROS IFNγ, IL-1β, IL-6, TNF Metalloprotease 9	M2-like monocytes ↑	[117]
NK cells	CD3 − NKp46 + CD226 + CD69 + CD11b + CD43 + T-bet +	IL-17, IFNγ, TNF Perforin, granzyme B	NK cells ↓	[31],

TNF-β, tumor necrosis factor; IFN-γ, interferon gamma; RORγ, RAR-related orphan receptor gamma; CCR6, C–C chemokine receptor type 6; FOXP3, fork head box P3; Treg cells, regulatory T cells; TGF-β, Transforming growth factor beta; CXCR5, C-X-C chemokine receptor type 5; PD-1, Programmed cell death protein 1; ICOS, inducible T-cell co-stimulator; BCL6, B-cell lymphoma 6; TFH, T-follicular helper; Fas, first apoptosis signal; ROS, reactive oxygen species; NK, natural killer cell; Ig, immunoglobulin.

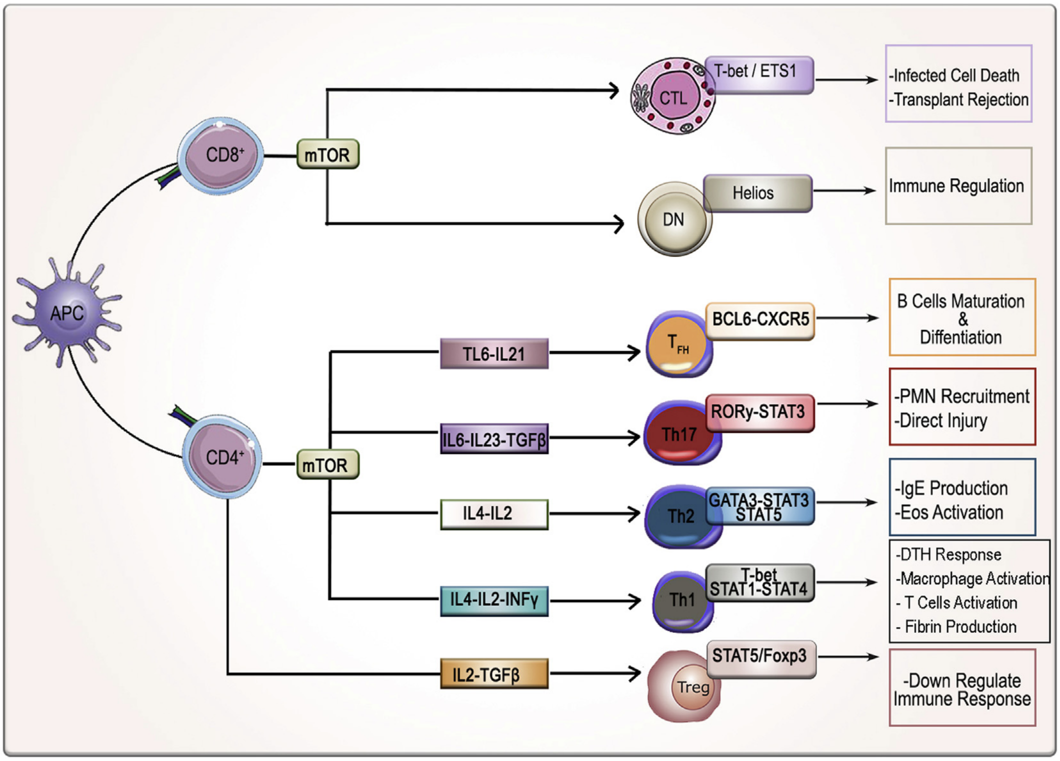

Fig. 4. Differentiation of T helper cell subsets. Antigens presentation to CD4$^+$T (MHC2) or CD8$^+$T (MHC1) cells, cause to differentiate of these T cells to their subsets. Naïve CD4$^+$ T cells differentiate into T helper 1 (TH1), TH2, TH17, regulatory T (T regulatory), and T follicular helper (TFH). On the other hand, naive CD8$^+$ T cells can be modified into cytotoxic T lymphocytes (CTL) and double negative (DN) T cells. T cells modification depends on the environmental cytokines, inducing specific signaling factors and transcription factors. In this figure, significant cytokines, factors with the crucial role in differentiation pathways control and transcription factors are illustrated; MHC, major histocompatibility complex; APC, antigen-presenting cell; TFH, T follicular helper; CTL, cytotoxic T lymphocytes; DN, double negative; BCL6, B-cell lymphoma 6; CXCR, C-X-C chemokine receptor type 5; RORγ, RAR-related orphan receptor gamma; STAT, signal transducer and activator of transcription; GATA3, GATA binding protein 3, IFN-γ, interferon gamma.

as endothelial cells, epithelial cells, and fibroblasts to stimulate proinflammatory substances. Th17 cells regulate autoantibody production as well that can be considered in IMN pathogenesis. Increased Th17 cell by accumulating mentioned process might promote IMN pathogenesis. Treg cells may suppress the proliferation or cytotoxicity of different immune cells, at the same time initiate the generation of factors including IL-10, IL-35, and TGF-β directly and indirectly. Treg promote the production of the other local regulatory cells through this process. Reduced Treg cells breaks the autoimmune system tolerance, augments inflammation and product autoantibodies elevating the IMN outcome.

$CD8^+$T cells may also promote glomerular endothelial cell (GEC) damage and proteinuria induction via stimulation of cytotoxicity and macrophages. Th2 cell related cytokines such as IL-4 and IL-13 has prominent role in inducing peripheral M2-like monocytes in IMN. On the other hand, M2 like monocytes via releasing IL-10 and other factors induces mesangial cell expansion and glomerular function defect. IL-10 upregulation is probably associated with damaged cell-mediated immunity in IMN. However, published studies about numbers and functions of immune system in IMN are contradictory and the definitive role of these system in IMN remains unclear.

Any variation in T and B cells molecular factors supports initiation of autoimmune diseases. In addition, malfunction in signaling factors of immune system including STAT3, ROCK, mTOR and CaMKIV leads to initiation of autoimmune diseases through influencing immune responses. Several of these factors regulate kidney cell function and have recently been considered as potential therapeutic targets for IMN.

Declaration of competing interest

The authors declare no conflict of interest.

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