B lymphocytes in renal interstitial fibrosis

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Abstract Fibrosis is defined as an excessive deposition of extracellular matrix (ECM), which leads to the destruction of organ structure and impairment of organ function. Fibrosis occurs not only in kidney but also in lung, liver, heart, and skin. Common pathways of fibrosis are thought to exist. Renal interstitial fibrosis is a complex process that involves multiple molecular signaling and multiple cellular components, in which B cells appear to be one of the emerging important players. B cells may affect fibrosis through cytokine production and through interaction with other cells including fibroblasts, macrophages and T cells. This review summarizes recent research findings of B cells in fibrosis and provides an insight of how the future therapeutics of fibrosis could be developed from a B-cell point of view.

Keywords Renal interstitial fibrosis · B cell · B lymphocyte · Inflammation

Introduction

Renal fibrosis consists of interstitial fibrosis and/or glomerulosclerosis, it is a common ending path of all progressive forms of diabetic and nondiabetic glomerular diseases (Meng et al. 2014). In renal allograft studies, the extent of

interstitial fibrosis is used to prognosticate the life of an allograft (Farris et al. 2011). Though it is not clear whether a causal relationship between fibrosis and chronic renal function loss exists (Mack and Yanagita 2015), a reciprocal correlation lies between kidney function and interstitial fibrosis extent (Farris et al. 2011). In the past decade, the supposition that fibrosis is irreversible was challenged by a study that showed, in patients with diabetic nephropathy, the progression of chronic lesions could be repaired on pancreas transplantation (Fioretto et al. 2006). The investigation of the mechanism of fibrosis is necessary for the development of effective therapeutics to halt or even reverse fibrosis.

Renal interstitial fibrosis is characterized by the excessive accumulation of extracellular matrix (ECM), and is usually associated with tubular atrophy (Racusen et al. 2002). One of the most important causes of renal fibrosis is intrarenal inflammation. Various types of kidney injury initially induce inflammation as a protective response (Meng et al. 2014). However, if the injury continues to exist, which seems to be the case in many progressive kidney diseases, the inflammation will promote interstitial fibrosis even when the original inflammation occurs in the glomerulus, as in glomerulonephritis-induced interstitial fibrosis. Other than immune factors, non-immune factors including advanced glycation end-products, reactive oxygen species (ROS), hypertension, hyperglycaemia, proteinuria, and hypoxia, have been implicated in driving renal fibrosis.

A number of molecular pathways that mediate renal fibrosis have been revealed, which include TGF- β /Smad3, Wnt/ β -catenin, and p38 MAPK (previously reviewed elsewhere (Meng et al. 2015; Edeling et al. 2016)). Various types of immune cells are recruited into the kidney in the process of renal fibrosis; these includes macrophages, T cells, dendritic cells, and mast cells (Meng et al. 2014). During the past few decades, the role of these infiltrating cells in renal fibrosis were extensively studied and a series of novel therapies were

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tested in animal models. However, experimental results has not been successfully translated to clinical application.

Since its discovery 50 years ago (Gitlin and Nussenzweig 2015), B cells are largely regarded as active in antibody dependent immune responses. However, recent studies are starting to indicate antibody-independent roles that B cells may play in autoimmune diseases (Shen and Fillatreau 2015). Indeed, B cell deficient mice were resistant to silica-induced lung fibrosis (Arras et al. 2006), carbon tetrachloride-induced liver fibrosis (Thapa et al. 2015), and unilateral ureteral obstruction (UUO) -induced renal interstitial fibrosis (Han et al. 2016). In idiopathic pulmonary fibrosis, peripheral B cells were shown to be more antigen-differentiated and are with more plasmablast proportions, and CD20+ B cell aggregates are more prominent in diseased lungs than in healthy ones (Xue et al. 2013; Nuovo et al. 2012). Notably, CXCL13, a chemokine previously shown to mediate B-cell recruitment, is also elevated three-fold in idiopathic pulmonary fibrosis lungs (Vuga et al. 2014). In carbon tetrachloride induced liver fibrosis, the profibrogenic activity of B cells were shown to be promoted by hepatic stellate cells (HSCs) through MyD88-dependent signaling (Thapa et al. 2015), indicating B cells as important responders of the intrahepatic immunity.

Accumulating evidence indicates that B cells may play an important role in renal fibrosis as well. This is mainly evidenced by B cell depletion studies in experimental renal fibrosis models. A study in unilateral ureteral obstruction (UUO) mice showed that renal recruitment of B lymphocytes exacerbates tubulointerstitial fibrosis by promoting monocyte mobilisation and infiltration through CC chemokine ligand-2 (CCL2), which is derived mostly from B cells in the setting of UUO model. The B cell-induced fibrosis is attenuated by administration of anti-CD20 monoclonal antibody one hour before the surgery (Han et al. 2016). In chronic allograft disease model, where interstitial fibrosis and tubular atrophy were the major pathological presentation, B220+ B cells were observed to progressively accumulate in perivascular areas in allograft kidney; also, in vitro cultured allograft B cells were shown to produce various cytokines, among which the most abundant cytokines were CXCL1 (GRO- α), CCL5 (RANTES), IL-6 and CCL2 (MCP-1) (Tse et al. 2015). In this model, administration of anti CD20 antibody also significantly reduced renal fibrosis.

Constitutive existence of B cells in healthy and diseased kidneys

Data of the constitutive composition of B lymphocytes within normal human kidney tissue is scarce. This is probably due to the difficulty of obtainment of renal tissues from healthy population. B cell infiltrates were observed in the kidney during various kidney diseases, including IgA nephropathy, interstitial nephritis, lupus nephritis, ANCA-associated nephritis, and

chronic allograft disease. In rejected renal allograft, CD20+ B cell infiltration has long been identified. Studies focused on peripheral B subsets in patients planning on renal transplantation indicated that a decrease in peripheral transitional B cells before transplantation, is associated with increased risk of acute allograft rejection (San Segundo et al. 2015; Shabir et al. 2015; Svachova et al. 2016). In rejected kidney allografts with detectable B cell infiltrates, somatic hypermutations (SHMs) are more frequent in the graft than in the blood (Ferdman et al. 2014). In antibody-mediated rejection, infiltrate rich in CD138+ plasma cell predominated in the rejected allograft (Carpio et al. 2014).

Cytokines produced by B cells in renal fibrosis

B cells are involved in autoimmune diseases through several pathways that include antibody production, immune complex, antigen presentation, co-stimulation on other immune cells, and cytokines secretion (Martin and Chan 2006). For example, intragraft IL-10 gene expression is up-regulated in renal biopsies with early interstitial fibrosis, tubular atrophy and subclinical rejection (Hueso et al. 2010). Also, IL-10 producing regulatory B cells (B10) are shown to exacerbate lung fibrosis by inhibiting Th1 response and modulating the Th balance in an silica-induced lung fibrosis model (Liu et al. 2016). However, in a human study, TNF- α secreting B cells, but not IL-10, IL-6 or IL-4 secreting B cells, contribute to myocardial fibrosis in dilated cardiomyopathy and its frequency positively correlated procollagen type III in the patients tested (Hueso et al. 2010). Chemokine (C-C motif) ligand 7 (CCL7) that can be produced by B cells may also play a part in renal fibrosis. In unilateral ureteral obstruction mice, CCL7-KO mice displayed attenuated tubulointerstitial fibrosis in earlier stages (0–8 days) and increased tubulointerstitial fibrosis in later stages (10–14 days), suggesting a possible dual effect of CCL7 in renal interstitial fibrosis (Gonzalez et al. 2013). In acute myocardial infarction mice model, mature B cells produce CCL7 and induce Ly6C(hi) monocyte mobilisation and recruitment to the heart, leading to enhanced tissue injury and deterioration of myocardial function (Zouggari et al. 2013). CCL7 is also found to immunolocalise to the fibrotic zone of *Schistosoma japonicum* induced granuloma in mice liver (Burke et al. 2010), further indicating a possible relation between CCL7 and fibrosis.

However, manipulation of a single cytokine does not seem to achieve protective effects against fibrosis. For example, blocking of transform growth factor- β (TGF- β) pathway by deleting the TGF- β type II receptor in matrix producing interstitial cells does not protect against renal fibrosis induced by UUO or aristolochic acid (Neelisetty et al. 2015). Similarly, mice overexpressing antifibrotic cytokine IL-9 but genetically lacks mature B cells are susceptible to pulmonary fibrosis induced by silica particles, whereas transfer of B cells

significantly reduces collagen deposition and ameliorates fibrosis (Arras et al. 2006), indicating IL-9 alone is not sufficient to protect against fibrosis.

B-cell interaction with macrophages and T cells in renal fibrosis

Certain types of early renal injury result in the recruitment of circulating neutrophils and monocytes that develop into polarized macrophages. Emerging evidence indicates that macrophages are important players in the process of renal fibrosis. Macrophages induce renal fibrosis through the recruitment, proliferation, and activation of fibroblasts. In some cases, macrophages may directly transit into myofibroblasts through a process termed macrophage-myofibroblast transition (MMT) (Nikolic-Paterson et al. 2014). In mice UUO model, interstitial B cell infiltrates are shown to exacerbate renal fibrosis via increasing macrophage mobilisation and infiltration (Han et al. 2016). In lipopolysaccharides (LPS) or silica particle induced pulmonary fibrosis, secretion of protective antifibrotic cytokine prostaglandin (PGE2) by macrophages is dependent on its interaction with B cells (Arras et al. 2006). Also, as mentioned in the last section, in experimental acute myocardial infarction, mature B cells induce Ly6C(hi) monocyte mobilisation and recruitment to the heart, possibly via the B cell secretion of CCL7 (Zouggari et al. 2013).

One of the most important functions of B cells is through regulating T cell response. In multiple sclerosis, B cell depletion by rituximab resulted in diminished proinflammatory (Th1 and Th17) responses of CD4⁺ and CD8⁺ T cells, and soluble products from activated B cells of untreated patients reconstituted the diminished T-cell response (Bar-Or et al. 2010). In systemic lupus erythematosus patients, B cell depletion induced with rituximab inhibited T cell differentiation and activation by downregulating CD40, CD80 and CD40L expression (Iwata et al. 2011). However, a randomized, double blind placebo-controlled study in renal transplantation patients showed that at 12 months after transplant and a single dose of rituximab which was administrated during the transplant surgery, the repopulated peripheral B cells consisted of transitional B cells, without affecting T-cell phenotype and function (Kamburova et al. 2014). In antibody-mediated rejection, B lymphocytes significantly contribute to indirect donor-specific T-cell reactivity in vitro in patients with antibody-mediated rejection (AMR) (Shiu et al. 2015).

B cells within the ectopic lymphoid follicle in renal fibrosis

Lymphoid neogenesis is a process during which scattered lymphocytic infiltrates evolve into aggregates. Under certain

circumstances, the cellular aggregates may develop into a highly organised structure resembling secondary lymphoid tissue, i.e. the tertiary lymphoid organ (TLO) or tertiary lymphoid tissue (TLT), whose microarchitecture is characterised by distinct T-cell areas containing dendritic cells and high endothelial venules (HEVs) and distinct B-cell follicles with germinal centers (GCs) (Aloisi and Pujol-Borrell 2006). TLOs could develop in various inflamed tissues with a frequency that varies greatly depending on the disease. TLOs has been discovered in kidney diseases including IgA nephropathy (Pei et al. 2014), renal allograft rejection (Jonker et al. 2015), and chronic leptospiral nephritis (Pezzolato et al. 2012).

It has been speculated that these lymphoid aggregates undergo progressive organisation over time and may relate to the therapy resistance in inflammatory processes. In renal transplant rejection, B-cell clusters have been shown to associate with steroid resistance and poorer transplant survival (Hippen et al. 2005; Tsai et al. 2006). However, there is also study with contradicting results (Jonker et al. 2015). Similar lymphoid aggregates were observed in IgA nephropathy patients, and is shown to be correlated with worse clinical outcome (Pei et al. 2014).

The mechanism by which infiltrating B cells organise the ectopic follicle and germinal center is speculated to resemble the lymphogenesis process in secondary lymphoid organs (the development of TLOs is comprehensively reviewed elsewhere (Jones and Jones 2016)). There are evidence suggesting the existence of local PDGFR β + perivascular precursor cells which can develop into functional follicular dendritic cells (Krautler et al. 2012), which then recruit B cells via CXCL13/CXCR5 pathway. However, how does the organised ectopic lymphoid organ function, and how they correlate with inflammation and fibrosis are not clear.

B-cell interaction with fibroblasts in renal fibrosis

Fibroblasts are activated and overproduce collagen in fibrosis, through a process that is not fully understood. Study targeting pulmonary capillary vascular niche where macrophages, pulmonary capillary endothelial cells and perivascular fibroblasts interact was shown to promote lung alveolar repair and ameliorates fibrosis (Cao et al. 2016). Recent studies implicated a novel and surprising role of the B cell in regulating fibroblasts in fibrosis. In scleroderma, fibroblasts exhibit a two-fold increase in collagen production when co-cultured with B cells compared with culture alone. This stimulating effect is comparable to that of TGF- β , and is further enhanced by B-cell activating factor (BAFF) (Francois et al. 2013). Indeed, microarrays from scleroderma skin disclosed upregulated genes in fibroblasts, endothelial cells and B cells compared with normal skin (Whitfield et al. 2003).

Recent studies have revealed that B cells may be regulated not only by traditional immune cells e.g. follicular dendritic

cells, but also by renal cells such as proximal tubular epithelial cells (PTECs). In vitro PTECs are capable of inducing a decreased level of CD27 in B cells, and decreased number of B cells secreting both IgG and IgM and overall levels of antibody production. Blocking studies with anti-PD-L1 led to partial restoration in antibody production (Sampangi et al. 2015).

B cells in the activation of myofibroblast phenotype

Myofibroblasts are considered to be a dominating contributor in the progress of renal fibrosis (Falke et al. 2015). The number of myofibroblasts significantly increase during fibrosis (Falke et al. 2015). Myofibroblasts express alpha smooth muscle actin (α -SMA) and α -SMA immunostaining is widely used as a marker for identification of myofibroblasts, though there are also evidence that other cells that do not express α -SMA can also be considered as myofibroblasts (Falke et al. 2015). Myofibroblasts are a main producer of extracellular matrix (ECM), crosslinking enzymes and inhibitors of matrix degrading metalloproteinases. The extracellular matrix produced by myofibroblasts include collagen, fibronectin, elastin, tenascin, fibrillin, proteoglycan, and transforming growth factor β -binding protein (Mack and Yanagita 2015). These molecules are involved in fibrosis formation. Accumulating evidence has demonstrated a diverse origins of myofibroblasts in kidney fibrosis. Those origins include resident fibroblasts, pericytes, circulating bone marrow-derived cells, or transition from either epithelial or endothelial cells (Mack and Yanagita 2015; Falke et al. 2015). However, how the myofibroblast phenotype is being activated in the setting of diseased kidney is still under debate (Falke et al. 2015). In IgG4-related disease patients, B-cell depletion by Rituximab has been shown to attenuates serological biomarkers of fibrosis and myofibroblast activation (Arai et al. 2015), indicating a possible link between B cell and myofibroblast phenotype. But the exact mechanisms still require further research.

B-cell targeting therapy in the treatment of renal fibrosis

One of the B-cell targeting therapies is through B cell depletion, usually with a B- cell targeting monoclonal antibody. In experimental renal fibrosis, B cell depletion by anti-CD20 monoclonal antibody has achieved some exciting results (Han et al. 2016). In a mice UUO model, the B cell-induced fibrosis is attenuated by administration of anti-CD20 monoclonal antibody one hour before the ureteral obstruction surgery (Han et al. 2016). Blockage of B cell survival signaling is another B cell targeting therapeutic strategy. B cell receptor

(BCR) and B cell activating factor receptor (BAFF-R) signaling are essential for the survival of mature B cells (Mackay and Browning 2002). In bleomycin induced lung fibrosis, genetic ablation of BAFF or BAFF neutralization by a soluble receptor attenuated pulmonary fibrosis and IL-1 β level (Francois et al. 2015). Also, earlier study showed that BAFF antagonist, BAFF-R-Ig, inhibited the development of skin fibrosis in systemic sclerosis mice model, through the augmentation of antifibrogenic cytokines including IFN-gamma (Matsushita et al. 2007).

Spleen tyrosine kinase (Syk), which is expressed by all leukocytes except mature T cells, plays a central role in the activation of BCR (Hobeika et al. 2015; Ryan et al. 2016). In progressive glomerulonephritis, glomerular and interstitial cells exhibiting Syk activation correlated with renal function and systemic inflammation (Ryan et al. 2016). Mice with conditional Syk gene deletion in myeloid cells showed significantly reduced crescent formation, inflammation and fibrosis compared with control mice when exposed to nephrotoxic serum nephritis (Ryan et al. 2016). Recent study shows that, administration of a Syk inhibitor BAY 61–3606 attenuated extracellular matrix protein deposition and expression of α -SMA, type I collagen, and fibronectin in a dose-dependent manner in UUO mice (Chen et al. 2016). In induced scleroderma mice model, treatment with Syk inhibitor fostamatinib reduced bleomycin-induced fibrosis and inflammation in the skin and lung (Pamuk et al. 2015). Sorafenib, a tyrosin kinase inhibitor, that is first applied to treat liver cancer, is recently shown to attenuate renal fibrosis in UUO mice (Ma et al. 2016).

Renal fibrosis is a complex process that involves multiple molecular signaling and multiple cellular components. In renal interstitial fibrosis with marked inflammation, B cells appear to be one of the important players. Clinical success of B cell depletion or inhibition therapies has encouraged a resurgence in investigating the mechanisms by which B lineage cells participate in the induction and maintenance of autoimmune diseases and fibrosis. Future research regarding B cells and their interaction with other cell types and how this interaction drives fibrosis may provide new therapy targets for the inhibition of renal fibrosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

- Aloisi F, Pujol-Borrell R (2006) Lymphoid neogenesis in chronic inflammatory diseases. *Nat Rev Immunol* 6(3):205–217
- Arai H et al (2015) Tubulointerstitial fibrosis in patients with IgG4-related kidney disease: pathological findings on repeat renal biopsy. *Rheumatol Int* 35(6):1093–1101
- Arras M et al (2006) B lymphocytes are critical for lung fibrosis control and prostaglandin E2 regulation in IL-9 transgenic mice. *Am J Respir Cell Mol Biol* 34(5):573–580
- Bar-Or A et al (2010) Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? *Ann Neurol* 67(4):452–461
- Burke ML et al (2010) Temporal expression of chemokines dictates the hepatic inflammatory infiltrate in a murine model of schistosomiasis. *PLoS Negl Trop Dis* 4(2):e598
- Cao Z et al (2016) Targeting of the pulmonary capillary vascular niche promotes lung alveolar repair and ameliorates fibrosis. *Nat Med* 22(2):154–162
- Carpio VN et al (2014) Expression patterns of B cells in acute kidney transplant rejection. *Exp Clin Transplant* 12(5):405–414
- Chen KH et al (2016) Inhibition of spleen tyrosine kinase (syk) suppresses renal fibrosis through anti-inflammatory effects and down regulation of the MAPK-p38 pathway. *Int J Biochem Cell Biol* 74:135–144
- Edeling M et al (2016) Developmental signalling pathways in renal fibrosis: the roles of notch, Wnt and hedgehog. *Nat Rev Nephrol* 12(7):426–439
- Falke LL et al (2015) Diverse origins of the myofibroblast-implications for kidney fibrosis. *Nat Rev Nephrol* 11(4):233–244
- Farris AB et al (2011) Morphometric and visual evaluation of fibrosis in renal biopsies. *J Am Soc Nephrol* 22(1):176–186
- Ferdman J et al (2014) Expansion and somatic hypermutation of B-cell clones in rejected human kidney grafts. *Transplantation* 98(7):766–772
- Fioretto P et al (2006) Remodeling of renal interstitial and tubular lesions in pancreas transplant recipients. *Kidney Int* 69(5):907–912
- Francois A et al (2013) B lymphocytes and B-cell activating factor promote collagen and profibrotic markers expression by dermal fibroblasts in systemic sclerosis. *Arthritis Res Ther* 15(5):R168
- Francois A et al (2015) B cell activating factor is central to bleomycin- and IL-17-mediated experimental pulmonary fibrosis. *J Autoimmun* 56:1–11
- Gitlin AD, Nussenzweig MC (2015) Immunology: fifty years of B lymphocytes. *Nature* 517(7533):139–141
- Gonzalez J et al (2013) Dual effect of chemokine CCL7/MCP-3 in the development of renal tubulointerstitial fibrosis. *Biochem Biophys Res Commun* 438(2):257–263
- Han H et al. (2016) Renal recruitment of B lymphocytes exacerbates tubulointerstitial fibrosis by promoting monocyte mobilisation and infiltration after unilateral ureteral obstruction. *J Pathol*
- Hippen BE et al (2005) Association of CD20+ infiltrates with poorer clinical outcomes in acute cellular rejection of renal allografts. *Am J Transplant* 5(9):2248–2252
- Hobeika E et al (2015) CD19 and BAFF-R can signal to promote B-cell survival in the absence of syk. *EMBO J* 34(7):925–939
- Hueso M et al (2010) Intra-graft expression of the IL-10 gene is up-regulated in renal protocol biopsies with early interstitial fibrosis, tubular atrophy, and subclinical rejection. *Am J Pathol* 176(4):1696–1704
- Iwata S et al (2011) Phenotypic changes of lymphocytes in patients with systemic lupus erythematosus who are in long-term remission after B cell depletion therapy with rituximab. *J Rheumatol* 38(4):633–641
- Jones GW, Jones SA (2016) Ectopic lymphoid follicles: inducible centres for generating antigen-specific immune responses within tissues. *Immunology* 147(2):141–151
- Jonker M et al (2015) Lymphoid-like structures with distinct B cell areas in kidney allografts are not predictive for graft rejection. A non-human primate study. *Inflammation* 38(6):2191–2202
- Kamburova EG et al (2014) Longitudinal analysis of T and B cell phenotype and function in renal transplant recipients with or without rituximab induction therapy. *PLoS One* 9(11):e112658
- Krautler NJ et al (2012) Follicular dendritic cells emerge from ubiquitous perivascular precursors. *Cell* 150(1):194–206
- Liu F et al (2016) Role of IL-10-producing regulatory B cells in modulating T-helper cell immune responses during silica-induced lung inflammation and fibrosis. *Sci Rep* 6:28911
- Ma W et al (2016) Sorafenib inhibits renal fibrosis induced by unilateral ureteral obstruction via inhibition of macrophage infiltration. *Cell Physiol Biochem* 39(5):1837–1849
- Mack M, Yanagita M (2015) Origin of myofibroblasts and cellular events triggering fibrosis. *Kidney Int* 87(2):297–307
- Mackay F, Browning JL (2002) BAFF: a fundamental survival factor for B cells. *Nat Rev Immunol* 2(7):465–475
- Martin F, Chan AC (2006) B cell immunobiology in disease: evolving concepts from the clinic. *Annu Rev Immunol* 24:467–496
- Matsushita T et al (2007) BAFF antagonist attenuates the development of skin fibrosis in tight-skin mice. *J Invest Dermatol* 127(12):2772–2780
- Meng XM, Nikolic-Paterson DJ, Lan HY (2014) Inflammatory processes in renal fibrosis. *Nat Rev Nephrol* 10(9):493–503
- Meng XM et al (2015) TGF- β /Smad signaling in renal fibrosis. *Front Physiol* 6:82
- Neelisetty S et al (2015) Renal fibrosis is not reduced by blocking transforming growth factor- β signaling in matrix-producing interstitial cells. *Kidney Int* 88(3):503–514
- Nikolic-Paterson DJ, Wang S, Lan HY (2014) Macrophages promote renal fibrosis through direct and indirect mechanisms. *Kidney Int* 4(1):34–38
- Nuovo GJ et al (2012) The distribution of immunomodulatory cells in the lungs of patients with idiopathic pulmonary fibrosis. *Mod Pathol* 25(3):416–433
- Pamuk ON et al (2015) Spleen tyrosine kinase (syk) inhibitor fostamatinib limits tissue damage and fibrosis in a bleomycin-induced scleroderma mouse model. *Clin Exp Rheumatol* 33(4 Suppl 91):S15–S22
- Pei G et al (2014) Renal interstitial infiltration and tertiary lymphoid organ neogenesis in IgA nephropathy. *Clin J Am Soc Nephrol* 9(2):255–264
- Pezzolato M et al (2012) Development of tertiary lymphoid structures in the kidneys of pigs with chronic leptospirosis. *Vet Immunol Immunopathol* 145(1–2):546–550
- Racusen LC, Solez K, Colvin R (2002) Fibrosis and atrophy in the renal allograft: interim report and new directions. *Am J Transplant* 2(3):203–206
- Ryan J et al (2016) Myeloid cell-mediated renal injury in rapidly progressive glomerulonephritis depends upon spleen tyrosine kinase. *J Pathol* 238(1):10–20
- Sampangi S et al (2015) Human proximal tubule epithelial cells modulate autologous B-cell function. *Nephrol Dial Transplant* 30(10):1674–1683
- San Segundo D et al (2015) Frequencies of circulating B-cell subpopulations before kidney transplantation identify patients at risk of acute rejection. *Transplant Proc* 47(1):54–56
- Shabir S et al (2015) Transitional B lymphocytes are associated with protection from kidney allograft rejection: a prospective study. *Am J Transplant* 15(5):1384–1391
- Shen P, Fillatreau S (2015) Antibody-independent functions of B cells: a focus on cytokines. *Nat Rev Immunol* 15(7):441–451
- Shiu KY et al (2015) B-lymphocytes support and regulate indirect T-cell alloreactivity in individual patients with chronic antibody-mediated rejection. *Kidney Int* 88(3):560–568

- Svachova V et al (2016) Dynamic changes of B-cell compartments in kidney transplantation: lack of transitional B cells is associated with allograft rejection. *Transpl Int* 29(5):540–548
- Thapa M et al (2015) Liver fibrosis occurs through dysregulation of MyD88-dependent innate B-cell activity. *Hepatology* 61(6):2067–2079
- Tsai EW et al (2006) CD20+ lymphocytes in renal allografts are associated with poor graft survival in pediatric patients. *Transplantation* 82(12):1769–1773
- Tse GH et al (2015) Intrarenal B cell cytokines promote transplant fibrosis and tubular atrophy. *Am J Transplant* 15(12):3067–3080
- Vuga LJ et al (2014) C-X-C motif chemokine 13 (CXCL13) is a prognostic biomarker of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 189(8):966–974
- Whitfield ML et al (2003) Systemic and cell type-specific gene expression patterns in scleroderma skin. *Proc Natl Acad Sci U S A* 100(21):12319–12324
- Xue J et al (2013) Plasma B lymphocyte stimulator and B cell differentiation in idiopathic pulmonary fibrosis patients. *J Immunol* 191(5):2089–2095
- Zouggari Y et al (2013) B lymphocytes trigger monocyte mobilization and impair heart function after acute myocardial infarction. *Nat Med* 19(10):1273–1280