Potential role of Akt signaling in chronic kidney disease

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ABSTRACT

Renal fibrosis, particularly tubulointerstitial fibrosis, is the common final outcome of almost all chronic kidney diseases. However, the mechanisms involved in the development of renal fibrosis are poorly understood. The Akt (also known as protein kinase B, PKB) family is serine/threonine protein kinases that play critical roles in regulating growth, proliferation, survival, metabolism and other cellular activities. Cytokines, high-glucose medium, transforming growth factor-β1 or advanced glycation end-products activate Akt in different renal cells. Increased Akt activation has been found in experimental tubulointerstitial fibrosis. In addition, Akt activation is also an important node in diverse signaling cascades involved in kidney damage. These data give evidence for a role for Akt in renal fibrosis, but no reviews are available on the role of Akt in the process. Thus, our aim is to review the role of Akt activation and signaling in renal fibrosis.

Keywords: chronic kidney diseases, mesangial cells, podocytes, renal fibroblasts, tubular epithelial cells

INTRODUCTION

Chronic kidney disease (CKD) currently affects 13% of the adult population in the USA and is considered to be an irreversible process eventually progressing to end-stage kidney failure [1, 2], a devastating condition that requires the patients to be dependent on life-long treatments with dialysis or kidney transplantation [3–5]. Numerous epidemiological studies suggest that the population of patients with end-stage renal disease is increasing at a rate of 7% every year [5, 6]. As a result, CKD has become a major public health problem, which imposes enormous socioeconomic burdens on the affected individuals, families and societies.

Renal fibrosis is considered to be the final common manifestation of a wide variety of CKDs, characterized by cell proliferation and progressive deposition of the extracellular matrix (ECM) in the glomeruli (glomerulosclerosis) and/or the interstitial space (tubulointerstitial fibrosis), resulting in a progressive decline of renal function [7]. The intracellular signaling pathways involved in fibrogenesis remain incompletely understood. The relevance of transforming growth factor-β1 (TGF-β1) in the origin and maintenance of glomerulosclerosis and tubulointerstitial fibrosis has been shown in the last years [8–10]. These effects of TGF-β1 are a consequence of its effects on cell proliferation [11, 12] and renal ECM synthesis and degradation [8, 13, 14]. TGF-β1 engages Type II and Type I (ALK5) receptors at the plasma membrane, triggering phosphorylation of Smad2/3, which then form dimmers with Smad4 that accumulate in the nucleus, driving transcriptional events that mediate the TGF-β1 response [15]. TGF-β1 also activates non-Smad-dependent signaling events that may contribute to fibrosis. The role for Akt has been described downstream from TGF-β1 in various cell types including mammary epithelial cells and keratinocytes [16]. Once active, Akt controls fundamental cellular processes such as the cell cycle and cell survival [17, 18].

Proteins of the Akt (also known as protein kinase B, PKB) family are serine/threonine kinases, are activated by growth factors, such as the insulin-like growth factor-1 receptor (IGF-IR) and the epidermal growth factor (EGF) family of receptor or TGF-β1. Akt acts as a major signal node in signal transduction cascades that control a wide number of biological actions including proliferation and apoptosis in physiological conditions and constitutes an important transducer downstream of activated PI3K (phosphoinositide 3-kinase) [19]. Cell proliferation and apoptosis also play relevant roles in the genesis and
progression of renal fibrosis. The roles of Akt signaling in glucose homeostasis, tumor development, cardiovascular disease and neurological disease, have been recently reviewed [20, 21]. However, no reviews are available on the role of Akt in CKD. Thus, the purpose of this manuscript is to review the most recent data on the role of Akt activation in fibrotic nephropathies. This has direct clinical implications, as in the past years an impressive arsenal of drugs devoted to interference with PI3K/Akt pathways and its effectors have been developed for use in the treatment of tumor progression. It is possible that at least some of these drugs can also be used to prevent renal fibrosis and renal failure progression.

**AKT PROTEINS**

Akt/PKB is a serine/threonine kinase which is important in various signaling cascades and acts a major signal transducer downstream of activated phosphoinositide 3-kinase (PI3K). In mammalian cells, there are three closely related and highly conserved isoforms of Akt, termed Akt1, -2 and -3. Akt1 and Akt2 are ubiquitously expressed, whereas Akt3 has been reported to have a more limited tissue distribution (such as in the brain) [22]. They also exhibit different functions; for example, Akt1 plays an important role in cardiac development and pathology, Akt2 is associated with tumors with a much higher frequency than with Akt1 and also plays a major role in diabetes, Akt3 is associated with a host of neurological conditions [23, 24]. Owing to their ability to control cell growth, proliferation as well as other aspects of cell biology including glucose metabolism, differentiation and survival, Akt protein must play an important role in renal fibrosis progression.

**Mechanisms of Akt activation**

Akt is normally maintained in an inactivated state that is activated by phosphorylation at two sites (Thr308 and Ser473) through a 3-phosphoinositide-dependent kinase-1 (PI3K)-dependent process. Specifically, growth factor signals and other stimuli that active PI3K promotes the accumulation of D3 phosphorylated phosphoinositides at the plasma membrane. These 3-phosphoinositides form binding sites for PH domain-containing proteins, such as Akt and PDK1 (3-phosphoinositide-dependent protein kinase 1), thereby recruiting them to the membrane, where they undergo phosphorylation by PDK1 at Thr308 and by mammalian target of rapamycin complex-2 (mTORC2) at Ser473 [19, 25, 26] (see Figure 1). Upon Akt phosphorylation and activation, Akt dissociates from the membrane and translocates to the cytosol, where it activates downstream signaling pathways through phosphorylation of a plethora of Akt substrates. Akt signaling is terminated by dephosphorylation of Thr308 by PP2 (protein phosphatase 2) and dephosphorylation of Ser473 by PHLPP1 (PH domain leucine-rich repeat phosphatase 1), respectively [26, 27]. Membrane-bound phosphatase and tensin homology, a constitutively active 3’-phosphatase frequently mutated in cancer [28], can also negatively regulate PI3K-dependent activation of Akt by hydrolyzing PI (3, 4, 5) P3 to PI (4, 5) P2.

**Akt effectors**

Activated Akt regulates many cellular processes, such as proliferation, survival, growth, metabolism and angiogenesis. This is mediated through serine and/or threonine phosphorylation of downstream substrates. These substrates and their functions are shown in Figure 2 [18, 24].
ROLE OF AKT IN THE PROGRESSIVE LOSS OF RENAL FUNCTION

Renal fibrosis, the common end point of progressive kidney disease, is a complex process involving not only derangements in both the synthesis and degradation of ECM, but also macrophage/lymphocyte infiltration, mesangial cells and podocyte apoptosis and survival, accumulation of activated fibroblasts, epithelial-mesenchymal transition (EMT) and increased deposition of ECM [29, 30] (Figure 3). Accordingly, an ideal therapy should have the potential to target multiple events along the pathogenic pathway to inhibit both glomerular and tubular interstitial fibrosis. Growing evidence supports a potential role for active Akt in the process of renal fibrosis and kidney dysfunction in view of its targeted effects on multiple pathogenic pathways. It is reported that LY294002 reduced proliferation and ECM synthesis in fibroblasts obtained from rat kidney tissue after unilateral ureteral obstruction (UUO) [31]. Further evidence of the involvement of the PI3K-Akt signaling pathway in renal damage have been given by a recent study [32], reporting that early pharmacological down-regulation of the PI3K-Akt signaling pathway in renal damage have been given by a recent study [32], reporting that early pharmacological down-regulation of the PI3K-Akt signaling pathway reduces not only the fibrotic interstitial cells, but also the potential number of tubular cells that have been described as responsible for excessive interstitial matrix production at later stages of UUO [31]. Further evidence of the involvement of the PI3K-Akt signaling pathway in renal damage have been given by a recent study [32], reporting that early pharmacological down-regulation of the PI3K-Akt signaling pathway reduces not only the fibrotic interstitial cells, but also the potential number of tubular cells that have been described as responsible for excessive interstitial matrix production at later stages of UUO. All these data suggest that activated Akt plays an essential role in regulating renal cells proliferation, as well as fibroblast activation and matrix production in CKD. Pharmacological inhibition of PI3K-Akt signaling pathways could be a potential target to reduce ECM deposition in the interstitium of damaged kidneys and, therefore, contributes to preventing the development of progressive nephropathy.

ECM synthesis and proliferation and activation of interstitial fibroblasts, glomerular mesangial cells and tubular epithelial cells play essential roles in the development of renal fibrosis [33–35].

Effects on fibroblast

Historically, resident fibroblasts were assumed to be the key origin of the matrix-producing myofibroblasts by phenotypic activation after renal injury [36]. Although this concept has lately been challenged, it remains largely authenticated [37, 38]. Fibroblast activation leads to cell proliferation and an increase in ECM deposition, thus, renal fibroblast activation is involved in the pathophysiology of interstitial fibrosis. Different cytokines (such as TGF-β1) and growth factors [such as EGF and platelet-derived growth factor (PDGF)] involved in proliferation also activate intracellular signaling pathways that converge on Akt proteins [39]. It is reported that PI3K/Akt activation is involved in increases in TGF-β1-induced collagen mRNA synthesis in the lung [40], in PDGF-induced collagen synthesis in cultured fibroblasts [41] and in EGF-induced survival in human and mouse osteoblastic cells [42]. Furthermore, PI3K inhibition decreased fibronectin and collagen Type 1 expression in fibroblasts [43]. So, Akt activation may be related to the increases in ECM synthesis after renal injury. TGF-β1, as a profibrotic cytokine, has a major role in the origin and maintenance of fibrosis [44–47] as a consequence of the regulatory role of TGF-β1 in cell proliferation. It has recently been reported that TGF-β1 induced fibroblast proliferation modulated by Akt activation. Further evidence support
this view, for example, PI3K activation induces proliferation in renal fibroblasts [31], in NIH3T3 fibroblast treated with Wnt3a protein [48] and in lung fibroblast stimulated with ionizing radiation [49]. Ly294002 (the inhibitor of PI3K) inhibits fibroblast proliferation. Fibroblast migration is also a key process in the development of renal fibrosis [50, 51]. Fuentes-Calvo and Crespo [52] showed that Akt inhibition reduced migration of fibroblast from wild-type mice, suggesting the mediation of the PI3K/Akt pathway in fibroblast migration. In particular, Akt has been described as a fibroblast proliferation promoter [53, 54]. Recently, the role of GSK-3β in wound healing has been analyzed [55]. GSK-3β is a downstream member of the PI3K pathway that is degraded after Akt-mediated phosphorylation. Interestingly, GSK-3β knockdown results in increased in vivo-activated fibroblast accumulation in the wound area and enhanced proliferation and migration in vitro [56]. Together with the above findings, this highlights the relevance of the PI3K/Akt pathway as an important mediator during renal fibrogenesis and its importance in the regulation of fibroblast activation, proliferation and migration and ECM deposition after renal injury. The involvement of Akt activation in activated fibroblast accumulation may contribute to a better understanding of the pathophysiological processes of wound healing that give rise to fibrogenesis. Therefore, the Akt signaling may be a therapeutic target for the treatment of fibrotic wounds.

Effects of podocytes and mesangial cells

Accumulation of ECM in CKD is also preceded by renal hypertrophy, especially glomerular mesangial hypertrophy. Mesangial cells among the three cell types in the glomerulus act as the predominant site for the synthesis of ECM proteins, which contribute to glomerular hypertrophy and the renal fibrosis found in CKD [57]. Various growth factors and cytokines produced by the infiltrating cells during the disease process and by the local kidney cells participate in the fibrotic process [58]. TGF-β1, as fibrogenic and inflammatory cytokine, causes augmented deposition of ECM proteins including collagen, laminin and fibronectin at the glomerular level [59]. Increased glomerular expression of TGF-β1 has been reported in both experimental and human kidney disease [60, 61]. Mice with increased plasma TGF-β1 levels displayed enhanced renal fibrosis [62]. On the other hand, blockage of TGF-β1 prevented renal, especially glomerular, hypertrophy and fibrosis in mice with diabetes [63, 64]. Importantly, TGF-β1 activates PI3K/Akt signaling in glomerular mesangial cells [16, 65]. Moreover, TGF-β1 regulated PI3K/Akt to increase cellular hypertrophy, including mesangial cell hypertrophy [66–68]. In addition, more recent studies have shown that PI3K-activated Akt controls TGF-β1-stimulated hypertrophy and expression of plasminogen activator inhibitor-1, which contributes to the abundance of several matrix proteins in kidney disease [66, 69]. In mesangial cells, TGF-β1-mediated expression of fibrillar proteins such as fibronectin and collagen is regulated by PI3K/Akt signal transduction [65, 68, 70]. Connective tissue growth factor (CTGF) plays a specific role in the fibrogenic pathways in kidney cells, facilitates TGF-β1 signaling and promotes renal fibrosis [71]. Moreover, CTGF produced by mesangial cells is involved in renal ECM accumulation leading to diabetic fibrosis and nephropathy [59, 71].
advanced glycation end-products augment fibronectin and collagen IV production in rat mesangial cells [72]. The renal mesangial cell proliferation rate is known to be increased under pathological conditions. High glucose (HG), protein glycation products, angiotensin II, endothelin-1 and PDGF and EGF can induce mesangial cells proliferation [73–75]. It is reported that mesangial cell proliferation, in response to PDGF and EGF, was coupled to activation of Akt, a downstream target of P13K. Interestingly, inhibition of P13K with LY294002 mimicked the effects of LXA4 with respect to PDGF and EGF, was coupled to activation of Akt, a down-regulated Akt signaling in ALD-induced podocytes with ALD (aldosterone) decreases the phosphorylation of GSK3β, a downstream target of Akt, which suggests a role for down-regulated Akt signaling in ALD-induced podocyte apoptosis [98]. Interestingly, it has recently been reported that Akt2, as one isoform of Akt, is essential to maintaining podocyte viability and function during CKD [99]. In this study, in an analysis of human kidney biopsies from patients with different types of CKD, the authors found that Akt2 was mainly expressed in podocytes. By combining an experimental mouse model of nephron reduction with genetic deletion of Akt2, they showed that Akt2 has a pivotal role in podocyte adaptation under increased workload caused by nephron reduction. Disruption of this adaptive pathway leads to glomerular lesions and albuminuria in both humans and mice. Therefore, these findings delineate Akt2 as a prognostic marker, as well as a therapeutic target for the maintenance of glomerular functions to prolong renal survival during CKD.

**Effects on tubular cells**

Accumulating evidence has demonstrated that renal tubular epithelial cells are one of the major sources of myofibroblasts [100]. It is reported that more than one-third of the matrix-producing fibroblasts are derived from tubular epithelial cells through EMT [101]. However, the degree to which EMT contributes to kidney fibrosis remains a matter of intense debate because recent cell lineage-tracking experiments do not support that EMT occurs in diseased kidneys in vivo [102, 103]. Anyway, it is agreed that renal tubular epithelial cells can undergo EMT in vitro. EMT of tubular epithelial cells is an important mechanism involved in tubulointerstitial fibrosis [101]. EMT is characterized by loss of epithelial cell characteristics and gain of ECM-producing myofibroblast characteristics. Tubular EMT can be induced by multiple stimuli such as TGF-β1 [104], advanced-glycation end-products [105] and angiotensin II [106]. Akt proteins function as intracellular switches in signal transduction cascades that play a central role in the regulation of cell proliferation and differentiation. Previous study demonstrated that Akt activation is involved in...
TGF-β1-induced renal EMT in vitro and in vivo [107], in HG-induced EMT [108] and in albumin-induced EMT [109]. Moreover, it has been found to mediate certain pathological effects of the molecules involved in renal fibrosis. For example, kindlin-2 regulates renal tubular cell plasticity by activation of Akt signaling [110]. And it is reported that up-regulated DJ-1 (an oncogene product, is identified as a protein with various functions in cellular transformation, oxidative stress response and transcriptional) promotes renal tubular EMT by activating Akt [111]. These studies suggest that Akt activation is also a necessary step in the induction of EMT. However, which isoform of Akt plays a crucial role in this process is not yet clearly known. Recently, we detected that TGF-β1 treatment enhanced Akt2 expression but not Akt1, in HK-2 cells, knock-out of Akt2 suppressed TGF-β1 induced EMT (Aiping Lan, unpublished). This indicates that Akt2 may be involved in EMT induced by TGF-β1. It is known that an EMT process might cause tubular transport dysfunction. Akt is well known to regulate the cellular transport of glucose [112–114], amino acids [115, 116], Ca2+ [117], H+ [118], Na+ [119] and K+ [120]. So far, little is known about the role of Akt in the regulation of renal tubular transport. Interestingly, Lee et al. [108] reported that an HG-induced EMT process causes Na+-glucose cotransporter (SGLT) dysfunction, the major carrier accomplishing renal tubular reabsorption of glucose. However, inhibition of PI3K/Akt with Ly294002 or Akt inhibitor restored HG-induced reduction in SGLT protein expression. These observations suggested that inhibition of EMT-related signaling pathways such as PI3K, Akt are important in the recovery of HG-induced reductions in glucose uptake. Moreover, Kempe et al. [121] reveals a role of Akt2 in the regulation of renal tubular glucose transport; the glucose-depolarization was significantly smaller and the renal excretion of glucose was significantly larger in Akt2 knockout mice than in their wildtype littermates indicating that Akt2 stimulates renal tubular glucose transport and thus participates in the regulation of SGLT1.

In addition, the role of Akt in renal tubulointerstitial fibrosis was also confirmed in animal models of CKD induced by UUO. Studies have shown a marked increase in renal Akt activation in a model of tubulointerstitial fibrosis induced by UUO in C57BL/6J mice [122]. In ligated kidneys, P-Akt and Akt staining intensity was notably up-regulated in HK-2 cells, knock-out of Akt2 suppressed TGF-β1 induced EMT (Aiping Lan, unpublished). This indicates that Akt2 may be involved in EMT induced by TGF-β1. It is known that an EMT process might cause tubular transport dysfunction. Akt is well known to regulate the cellular transport of glucose [112–114], amino acids [115, 116], Ca2+ [117], H+ [118], Na+ [119] and K+ [120]. So far, little is known about the role of Akt in the regulation of renal tubular transport. Interestingly, Lee et al. [108] reported that an HG-induced EMT process causes Na+-glucose cotransporter (SGLT) dysfunction, the major carrier accomplishing renal tubular reabsorption of glucose. However, inhibition of PI3K/Akt with Ly294002 or Akt inhibitor restored HG-induced reduction in SGLT protein expression. These observations suggested that inhibition of EMT-related signaling pathways such as PI3K, Akt are important in the recovery of HG-induced reductions in glucose uptake. Moreover, Kempe et al. [121] reveals a role of Akt2 in the regulation of renal tubular glucose transport; the glucose-depolarization was significantly smaller and the renal excretion of glucose was significantly larger in Akt2 knockout mice than in their wildtype littermates indicating that Akt2 stimulates renal tubular glucose transport and thus participates in the regulation of SGLT1.

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In addition, the role of Akt in renal tubulointerstitial fibrosis was also confirmed in animal models of CKD induced by UUO. Studies have shown a marked increase in renal Akt activation in a model of tubulointerstitial fibrosis induced by UUO in C57BL/6J mice [122]. In ligated kidneys, P-Akt and Akt staining intensity was notably up-regulated compared with non-ligated kidneys. Akt activation is related to cell proliferation and ECM deposition in the ligated kidneys. Treatment with the PI3K inhibitor Ly294002 led to decreased levels of fibroblast-myofibroblast markers in the interstitium and reduced the number of proliferating cells and the amount of interstitial ECM deposition. These data suggest a role for the renal Akt signaling pathway in early obstruction-induced EMT and ECM deposition. Based on previous studies, we also found that UUO-induced renal fibrosis was significantly suppressed in Akt2 knockout mice (Ak2−/−) compared with their wild-type littermates (Akt2+/+) (Aiping Lan, unpublished), indicating that Akt, in particular, Akt2 plays a major role in fibrosis following UUO.

It has been reported that autophagy was increased in the obstructed renal tubules after UUO [123]. For the regulation of autophagy, multiple signaling pathways are involved. The classic Akt-mTOR signaling pathway is considered one of the key regulatory mechanisms of autophagy [124]. Activated Akt-mTOR signaling pathway suppresses autophagy at initiation of the vesicular double membrane formation. A previous study reported that mTOR signaling is activated in the contralateral kidney after unilateral nephrectomy and activation of mTOR signaling plays a role in modulating RNA and protein synthesis in compensatory renal hypertrophy [125]. Importantly, a recent study [126] revealed that autophagy is induced earlier than tubular apoptosis or tubulointerstitial fibrosis and autophagy plays a protective role for tubular cell apoptosis and tubulointerstitial fibrosis in the obstructed kidney after UUO.

In the contralateral kidney, the Akt-mTOR signaling pathway is involved in the induction of autophagy. These findings would suggest a novel strategy for the development of potential novel therapy for renal injury of the obstructed kidney after UUO.

Repeated tubular ischemia plays a major role in chronic renal fibrosis [127]. The PI3K/Akt pathway has been reported to be activated by ischemia/reperfusion in various organs, including the kidney [128–131], and after mechanical injury in renal proximal tubular cells [132]. Kwon et al. [133] observed that Akt is activated by hypoxia/reoxygenation (H/R) in renal epithelial cells; their results suggest that H/R induces activation of the PI3K/Akt survival signaling pathway. These signals were associated with proliferation of epithelial cells during the early stage of reperfusion after hypoxia. Proliferation of dedifferentiated intrinsic renal tubular cells has been recognized to be the major cellular event that contributes to renal repair after acute kidney injury. Phosphorylation of Akt was increased after ischemia/reperfusion in the mouse kidney and reduced by wortmannin administration. Renal cell proliferation, which increased after ischemia/reperfusion injury in the mouse, was inhibited by wortmannin, suggesting that activation of the PI3K/Akt signaling pathway maintains cell viability after ischemia, thus playing an important role in the regulation of renal repair after ischemia/reperfusion injury [134]. Treatment with crythropoietin partially prevents renal damage by preventing epithelial cell apoptosis. The anti-apoptotic effects of crythropoietin were dependent on JAK2 signaling and the phosphorylation of Akt by PI3K [135].

CONCLUSION AND PERSPECTIVES

In conclusion, activation of Akt and/or mTOR participates in renal fibrogenesis, pharmacological inhibitors of the PI3K-Akt signaling pathway, which have been extensively studied as potential drugs in cancer therapy, could be a potential target to reduce ECM deposition in the interstitium of damaged kidneys or may even revert the progression of fibrosis and the consequent end-stage renal failure. However, the fact that Akt signaling is involved in so many different biological processes suggests that several side effects will be observed. Indeed, there are an increasing number of reports that Akt inhibitors induce hyperinsulinemia and hyperglycemia upon administration in mice [136, 137] and humans [138]. mTOR inhibition early after renal mass reduction caused further reduction in renal
function [139] and delayed recovery from renal ischemia reperfusion injury in mice [140] and rats [141, 142] and aggravated protein overload nephropathy [143]. Based on the above side effects, caution will be required when using Akt and/or mTOR inhibitors in humans with CKD. Furthermore, in mammalian cells, the Akt family includes three isoforms of Akt, Akt1, -2 and -3. Although the three Akt isoforms are structurally homologous and share similar mechanisms of activation, they also exhibit distinct features and functions in tumor progression. However, the functions of the isoforms in glomerulosclerosis and/or in tubulointerstitial fibrosis remain to be resolved. The above problems urge us to further study the potential role of isoforms of Akt in CKD and well-designed studies are needed to confirm this.

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CONFLICT OF INTEREST STATEMENT

None declared.

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Systemic lupus erythematosus (SLE) is characterized by autoantibodies that mediate tissue injury. However, the pathogenesis of SLE remains poorly understood and available therapeutic approaches are not fully satisfactory. Belimumab, a monoclonal antibody that neutralizes B-cell activating factor (BAFF), was the first drug approved to treat SLE in more than 50 years. However, it is not labelled for use in severe lupus nephritis. Recently, a novel high-throughput multiplex protein microarray platform to profile circulating immunoglobulin G (IgG) autoantibodies in SLE patients identified IgG autoantibodies against several cytokines and growth factors at higher titres in SLE patients than in controls. The presence of autoantibodies to BAFF was validated in a subset of SLE patients by enzyme-linked immunosorbent assay. Low levels of anti-BAFF autoantibodies were also present in healthy controls. The association of anti-BAFF reactivity to clinical features and response to therapy was not addressed. However, preliminary data suggested an association to an interferon-α-responsive mRNA signature, itself associated with severity. Functional studies disclosed a neutralizing activity of autoantibodies against BAFF. These findings raise new questions regarding the role of BAFF in SLE and the functional and therapeutic significance of anti-BAFF and anti-cytokine autoantibodies.

**Keywords:** autoimmunity, b cells, lupus, TNF superfamily

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In the movie ‘That Obscure Object of Desire’ an aging Frenchman falls in love with a young Spanish woman who repeatedly frustrates his overtures [1]. This female character had only one suitor, unlike the two suitors targeting tumour necrosis factor ligand superfamily member 13b (TNFSF13B), also known as B-cell activating factor (BAFF), B-lymphocyte stimulator (BLyS) and CD257. In systemic lupus erythematosus (SLE) patients, both physicians and the patient’s own immune system may target BAFF with neutralizing antibodies. The European Medicines Agency (EMA) authorized in 2011 the use of the monoclonal antibody belimumab (Benlysta) to treat SLE [2]. The therapeutic benefit of belimumab is consistent with both