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EDITORIAL

Costimulatory blockade: A novel approach to the treatment of glomerular disease?

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Abstract

Costimulatory pathways (Cluster of differentiation 28, tumor necrosis factor-related, adhesion and T Cell Ig- and mucin-domain molecules) regulating the interactions between receptors on the T cells and their ligands expressed on several cell types, have a key role in controlling many immunological and non immunological processes. Indeed, accumulating evidence indicate that these molecules are involved in the pathogenesis of numerous conditions, such as allograft rejection, atherosclerosis, rheumatoid arthritis, psoriasis and renal diseases, including glomerulonephritis. Primary or secondary (*i.e.*, associated with infections, drugs or systemic diseases, such as systemic lupus erythematosus, diabetes, *etc*.) glomerulonephritis represent a group of heterogeneous diseases with different pathogenic mechanisms. Since costimulatory molecules, in particular CD80 and CD40, have been found to be expressed on podocytes in the course of different experimental and clinical glomerulonephritis, costimulation has been thought as a new therapeutic target for patients with glomerular diseases. However, although experimental data suggested that the blockade of costimulatory pathways is effective and safe in the prevention and treatment of glomerular diseases, clinical trials reported contrasting results. So, at this moment, there is not a strong evidence for the general use of costimulatory blockade as an alternative treatment strategy in patients with primary or secondary glomerulonephritis. Here, we critically discuss the current data and the main issues regarding the development of this innovative therapeutic approach.

Key words: Costimulation; Glomerulonephritis; Cluster of differentiation 80; Cytotoxic T-lymphocyte-associated antigen-4; Lupus nephritis; Abatacept; Proteinuria; Podocytes

Core tip: Glomerulonephritis refer to a group of renal disorders, primary or secondary to infections, drugs or systemic diseases, characterized by inflammation within the glomerulus. Among glomerular diseases there is a great clinical, histological and prognostic heterogeneity

and several different pathogenetic mechanisms have been implied. Current standard treatments include steroids and cytotoxic agents, which present important side effects and an unsatisfactory remission rate. Therefore, experimental and clinical research is addressed to the development of alternative therapies. Here, we critically discuss new therapeutic opportunities provided by the use of agents acting on the modulation of costimulatory pathways.

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COSTIMULATORY PATHWAYS

Costimulatory pathways regulating the interactions between receptors on the T cells and their ligands expressed on several cell types (including immunocompetent cells, fibroblasts, endothelial cells, *etc.*) play a crucial role in the modulation of immunological and non-immunological processes[1].

In particular, costimulation is essential for the full activation of naïve T cells after antigen-specific recognition, and without costimulation the T cell-antigen interaction results in anergy[2].

Different costimulatory families [Cluster of differentiation 28 (CD28), tumor necrosis factor (TNF)-related, adhesion and T Cell Ig- and mucin-domain (TIMs) molecules], characterized by structural and functional analogies, have been described. These molecules can interact with each other either up- or down-regulating T cell activation[3] (Table 1).

Among the identified costimulatory molecules, the best characterized are the CD28:B7 and the TNF-related families. The CD28:B7 family includes the following receptor-ligand pairs: CD28/CTLA4:CD80/CD86, induced costimulatory molecules (ICOS:ICOSL) and the programmed death-1 pathway (PD-1:PD-L1/PD-L2)[4]. CD28 is a disulfide-bound molecule that belongs to the immunoglobulin superfamily and is constitutively expressed on T cells[5].

Its interaction with CD80 (B7.1) and CD86 (B7.2), expressed on the surface of antigen-presenting cells (APCs), leads to the full activation of T cells[6]. Conversely cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), a structural homologous of CD28 with a higher avidity for CD80 and CD86, acts as a negative regulator of T cells[7].

TNF superfamily comprises: CD40:CD40L, OX40:OX40L, CD30:CD30L, CD27:CD70, CD137:CD137L, *etc*. CD40 is mainly expressed on B-cells, but also on monocytes, dendritic cells, endothelial cells, smooth muscle cells and fibroblasts[8]. The engagement of CD40 with its ligand, CD40L (CD154), leads to B cell expansion and differentiation and it is decisive in the regulation of APCs and dendritic cells functions[9]. It is important to underline that costimulatory molecules, expressed by a broad variety of cells, seem to be involved in the pathogenesis of numerous conditions, such as atherosclerosis, rheumatoid arthritis, psoriasis and renal diseases, including allograft rejection and glomerulonephritis[10-14].

The insights regarding the contribution the costimulatory molecules in these conditions has not only allowed elucidating important regulatory mechanisms, but has also provided novel targets for therapeutic interventions[15].

Table 1 Immunomodulatory effects of costimulation pathways

Family	Ligand	Receptor	Effects on immune cells
CD28	CD80 (B7.1)/	CD28	+
	CD86 (B7.2)	CTLA-4	-
	ICOSL	ICOS	+
	PDL1	PD-1	-
TNF-related	CD40	CD40L (CD154)	+
	OX-40	OX-40L	+
Adhesion molecules	ICAM-1	LFA-1	+
TIM	TIM4/9	TIM1/3	+/-

Costimulatory pathways may influence immune response through stimulatory (+) or inhibitory (-) signals. Ligands may be present on antigen-presenting cells, including B-lymphocytes and dendritic cells, but also on muscle, endothelial, fibroblast, platelets and epithelial-derived cells. Receptors are mainly expressed on T-cells[48]. CTLA-4: Cytotoxic T-lymphocyte-associated antigen-4; ICOS: Induced costimulatory molecule; PD-1: Theprogrammeddeath-1; LFA-1: Lymphocyte function-associated antigen 1; ICAM-1: Intracellular adhesion molecule 1; TIM: T cell Ig and mucin.

COSTIMULATION AND GLOMERULONEPHRITIS

Glomerulonephritis refer to a group of renal disorders, primary or secondary to infections (human immunodeficiency virus, hepatitis C virus, *etc.*), drugs and systemic diseases (for example, systemic lupus erithematosus-SLE, cancer and diabetes), characterized by inflammation within the glomerulus[16].

Among glomerular diseases there is a great clinical, histological and prognostic heterogeneity and several different pathogenic mechanisms are implied, including podocyte damage, immunoglobulin deposition and immune cell infiltration[17]. During the last years growing evidence suggest a role for costimulatory molecules also in this specific setting.

In particular, CD80 expression has been detected in podocytes, which integrity is essential to maintain a regular glomerular function[18].

Indeed, in experimental models of genetic, drug-induced, immune-mediated and bacterial toxin-induced kidney diseases, CD80 overexpression on podocytes might be harmful for glomerular permeability, disturbing the slit diaphragm and down-regulating podocytes-β1

integrin activation, finally leading to the development of proteinuria and loss of renal function[19,20]. The crucial role of CD28:CD80 pathway in the pathogenesis of glomerular diseases is also confirmed by the evidence that CD80 knockout mice present an attenuated form of proliferative glomerulonephritis, associated with a significant reduction of renal tissue lesions[21].

Moreover, the use of monoclonal antibodies targeting CD28 or CTLA-4 was effective in treating and preventing different forms of experimental nephritis, including lupus-like nephritis[22]. Interestingly, similar results were also found in human glomerulonephritis. In particular, a significant increase in CD80 podocyte expression and urinary excretion has been reported in patients with minimal change disease (MCD) in relapse compared to those in remission or with focal segmental glomerulosclerosis (FSGS)[23,24]. Similarly, patients with proliferative lupus nephritis present a strong podocyte surface expression of CD80[20].

Beyond CD28:CD80 pathway, also costimulatory molecules of TNF-related family, *i.e.,* CD40:CD154, have been found expressed in renal tissue in the course of both experimental and human glomerular diseases. CD40 was isolated in murine models of proteinuric disease, such as membranous glomerulonephritis, lupus nephritis and necrotizing nephritis[25]. Moreover, glomerular and tubular CD40 expression was up-regulated in human lupus nephritis and in other inflammatory renal diseases, being associated with the presence of CD40L+ mononuclear cells[26]. Furthermore, the inhibition of CD40 pathway through the administration of a CD40-Ig fusion protein or anti-CD40L antibodies prevented the development of proteinuric kidney diseases in mice[27,28].

COSTIMULATORY BLOCKADE AS A NOVEL TREATMENT FOR GLOMERULONEPHRITIS

As a consequence of the role of costimulation in the pathogenesis of several pathological conditions, costimulatory blockade has been thought as a new rational therapeutic approach[29]. Therefore different strategies, mainly based on the design of specific monoclonal antibodies (mAbs) interfering with these critical pathways, have been tested. However, the clinical development of the majority of these new strategies is currently suspended for safety concerns.

This is, for example, the case of anti-CD40L mAb, which although effective in the prevention of glomerular diseases and renal allograft rejection in murine and primate experimental models, significantly increased the occurrence of thromboembolic events[27,30-32]. More severe complications occurred during the development of anti-CD28 mAbs. Indeed, six healthy volunteers enrolled in a phase I clinical trial and treated with a humanized superagonistic anti-CD28 mAb, developed a life-threatening systemic inflammation due to massive cytokine release, determining the complete abandon of this approach[33]. A more promising strategy- the only one that has found clinical applications so far- seems to be the development of CTLA-4 immunoglobulin fusion proteins. These proteins are composed by an extracellular portion of human CTLA4 plus a Fc part of human IgG1, which, binding CD80 and C86 with high avidity, prevent CD28 ligation, acting as potent inhibitors of CD28:CD80/CD86 pathways[34,35]. Abatacept, which has been approved by FDA for the treatment of rheumatoid arthritis in 2005, and its derivate, Belatacept, belong to this category of drugs.

Belatacept has been extensively studied mainly in the experimental and clinical setting of renal transplantation.

Belatacept was evaluated in 2 open-label, randomized, multicenter, controlled phase 3 studies: the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and BENEFIT-EXT ("extended criteria").

These studies showed that Belatacept was non-inferior to Cyclosporine in terms of patient and graft survival, being associated to a better graft function and a reduced incidence of chronic nephropathy[36,37]. Hence, although the administration of belatacept was not exempt from adverse effects, in 2011 it was approved by Food and Drug Administration (FDA) as the first costimulatory blocker for use in renal transplantation[38].

Regarding the specific setting of primary and secondary glomerulonephritis, instead, only Abatacept has been used in clinical studies with discordant results.

Two recent randomized trials investigated the safety and efficacy of Abatacept in addition to standard treatments in patients with lupus nephritis.

A twelve months blind multicentre trial, performed by Furie *et al*[39], enrolled 298 patients with active lupus nephritis and proteinuria, randomized to receive corticosteroids and Mycophenolate mofetil in association with Abatacept (30 mg/kg loading for 3 mo, followed by 10 mg/kg), Abatacept (10 mg/kg) or placebo. The authors found that the treatment with Abatacept was associated with a reduction of antiDNA antibody, C3 and C4 levels and proteinuria. However, there were not significant differences in the time to reach a complete response and in the proportion of subjects with confirmed complete response after 52 wk of follow-up among the three groups.

Similar results have been reported by Askanase *et al*[40] who evaluated the efficacy of Abatacept *vs* placebo added to a standard treatment regimen with Cyclophosphamide followed by Azathioprine in 134 patients with active lupus nephritis. They also found no significant differences between the groups in terms of number of patients reaching and/or maintaining complete or partial response.

So, even if previous studies reporting the strong expression of podocyte CD80 in human proliferative lupus nephritis appeared promising, the results of these clinical trials have unexpectedly called into question the

utility of Abatacept in patients with SLE.

Abatacept has been also studied in patients with primary glomerulonephritis.

In a recent paper, Yu *et al*[41] tested Abatacept in 5 patients with FSGS (4 with recurrent FSGS after kidney transplantation and 1 with primary FSGS) who presented positive CD80 (B7.1) immunostaining of podocytes in kidney-biopsy specimens.

After treatment with Abatacept all these patients presented a partial or complete remission, expressed as a significant reduction of serum creatinine and/or proteinuria. Interestingly, the authors provided also a rationale for the beneficial effects of Abatacept, demonstrating that the drug *in vitro* blocks podocyte migration and stabilizes β1-integrin activation in podocytes[41].

Although exciting, these results have been criticized for several important methodological issues[42,43]. First of all, it should be considered that the 4 patients with recurrent FSGS underwent intensive plasmapheresis, aimed to remove putative circulating permeability factors. Thus, it is not possible to recognize if the disease remission was due to this treatment independently of the use of Abatacept. Moreover, subsequent reports arose doubt about the immunostaining techniques used to detect CD80 in renal tissue, highlighting the lack of any negative controls. In particular, Larsen *et al*[44] tested the presence of CD80 in 60 renal biopsy specimens from patients with different proteinuric glomerular diseases with two immunostaining methods (immunoperoxidase and immunofluorescence). The authors found that for both staining techniques and in all cases, CD80 was undetectable within podocytes. The presence of so contrasting results among experimental and clinical trials raises doubt about the potential role of Abatacept in patients with proteinuric glomerulonephritis[45].

To be thorough, it has to point out that the efficacy of Abatacept in the treatment of MCD has been recently reported in a single case[46].

Considering the overall above reported data, we might infer that, although the podocyte CD80 pathway seems to have an important role in some proteinuric glomerular diseases, clinical results suggest that current therapeutic strategies do not warrant a satisfactory control of glomerulonephritis.

CONCLUSION

The critical analysis of the currently available data suggests some conclusions: (1) costimulatory pathways might be implied in the pathogenesis of glomerulonephritis, especially the forms associated with proteinuria and nephrotic syndrome; (2) the development of drugs targeted to block costimulation is of great potential utility, also considering that the current available therapeutic options are limited[47]; (3) clinical trials have shown insufficient or, at least, contrasting effects of this kind of approach in the achievement of therapeutic targets and disease remission.

So, it appears clear that further molecular, cellular and clinical studies, including the design and evaluation of new drugs and exploration of new pathways, should be performed before considering costimulatory blockade as a valid alternative treatment in the general population of patients with glomerulonephritis.

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