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The Damage of Glomerulonephritis and Kidney Transplantation Shares Common Pathogenetic Pathways

Maurizio Salvadori*

Professor of Nephrology, Director of Transplant Department, Careggi University Hospital, Florence, Italy

***Corresponding author:** Maurizio Salvadori, Professor of Nephrology, Director of Transplant Department, Careggi University Hospital, Florence, Viale Pieraccini 18 50139, Italy, Tel: 0039 055 597151; **E-mail:** maurizio.salvadori1@gmail.com

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Editorial

In the past, glomerular diseases and renal transplantation have always been considered as independent fields of nephrology. This concept has been supported by the prevalent rate of antibody production and immune complexes formation in glomerulonephritis versus the direct action of immune cell in renal transplantation [1]. Recent findings have shown that the pathogenetic mechanisms operating in both conditions share common pathways that offer identical new therapeutic approaches identical for both conditions. In this review, after having described which these common pathogenetic pathways are, we will review in details which are to date the principal biologic medicines adopted in both conditions.

Keywords: Glomerulonephritis; Renal transplantation; Innate immune system; B cell network; T cell network; Systemic inflammation

Common Pathogenetic Pathways

a) Innate immune system

The innate immunity acts through the recognition of pathogen associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) by macrophages, dendritic cells (DCs), leukocytes [2,3]. Innate immunity acts on antigen processing, so representing a link to adaptive immunity, favoring the antigen presentation, the T and B cell responses and the specific adaptive immune response [4]. The activation of the innate immunity has been documented in several glomerulonephritis (GN) among which IgA-GN [5-7], crescentic GN, anti-neutrophil cytoplasmic autoantibody-GN [ANCA-GN [8,9]] and lupus GN [10,11].

The complement is another essential component of the innate immune system. Complement involvement has been clearly identified in several renal diseases as lupus GN, membranoproliferative GN (MPGN) and C3 glomerulonephritis (C3GN), and hemolytic uremic syndrome (HUS) [12,13]. Its role has recently been recognized in autoimmune GN and ANCA vasculitis [14,15].

Recent studies have documented a pivotal role of the innate immunity also in renal transplantation where it causes two step damage. Early after transplantation the innate immunity contributes, principally via the complement activation, to the ischemia-reperfusion injury (IRI) [16,17]. Later on, IRI represents a link with the adaptive immunity and may cause cell mediated rejection (CMR), antibody mediated rejection (ABMR) and progressive graft injury [18-20].

b) B cells and antibody network

Circulating antibodies are deeply involved in the development of GN as well as in the renal transplantation damage. Circulating antibodies are involved in the pathogenesis of membranous nephropathy (MN) where they are directed against neutral endopeptidase [21], as well as against other podocyte enzymes as M-type phospholipase-2-receptor [22], aldosereductase and manganese superoxide dismutase [23-25]. Circulating nephrotoxic auto antibodies have also been recognized in ANCA vasculitis [26], in hepatitis C-related cryoglobulinemia [27], in lupus GN [28], and in the anti glomerular basement GN [29].

In renal transplantation a relevant proportion of rejection episodes is mediated by circulating antibodies that, after binding to the antigens of the graft donor cells, cause the ABMR. In addition, the activation of the complement cascade recruits macrophages and neutrophils and cause additional graft injury [30]. Moreover, recent data document the antibody involvement also in antibody mediated chronic rejection where the "bad" activity of antibodies may also be involved in previously considered "chronic" lesions (i.e. transplant glomerulopathy) [31,32].

c) T cells network

Several lines of evidence support a role for T cells in the pathogenesis of several GN. T cells are clearly involved in the pathogenesis of ANCA vasculitis [33,34]. In ANCA GN CD4 and CD8 T cells are present within the disease lesions in relationship with antigen presenting cells (APCs) and B cells [35].

Similarly, abnormalities in T cells and in T cell activation have been reported in lupus GN [36,37], in anti GBM GN [38] and in IgA GN [39]. Clearly T cells are deeply involved in renal transplantation and the regulation of all reactive T cells ultimately determines whether the graft is rejected or accepted [40].

d) Systemic inflammation

An inflammatory "milieu" and its related cytokines are involved in the pathogenesis of several GN.

Up-regulation of pro-inflammatory cytokines and the efficacy of blocking agents have been documented in focal segmental glomerular sclerosis (FSGS) [41]. Similarly, cytokine network up-regulation has been documented in ANCA GN [42,43] and in lupus GN. In the latter disease newer cytokines have been identified in the pathogenesis [44]. Finally, macrophage up-regulation is also involved in the pathogenesis of the inflammation and its block is under investigation in a safety study for IgA-GN [45].

In renal transplantation the cytokine up-regulation and the increased network of inflammatory factors contributes to cause renal damage [46,47]. A study from Wu et al. [47] allowed identifying the role of several inflammatory proteins in the disease progress. Trials with anti-inflammatory agents are ongoing, but to date their usefulness seems to be related only to the islet transplantation.

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