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Short Commentary

Regulatory T Lymphocytes in Chronic Kidney Disease and Renal transplantation

Michalis Christodoulou[1]; Georgios Lioulios[1]; Erasmia Sampani[1]; Asimina Fylaktou[2]; Maria Stangou[1]*

[1]Department of Nephrology, Aristotle University of Thessaloniki, Hippokration Hospital, 56442 Thessaloniki, Greece.

[2]National Peripheral Histocompatibility Center, Department of Immunology, Hippokration Hospital, 56442 Thessaloniki, Greece.

***Corresponding Author: Maria Stangou**

Department of Nephrology, Aristotle University of Thessaloniki, Hippokration Hospital, 56442 Thessaloniki, Greece.

Email: mstangou@auth.gr

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Introduction

Two parts that are mainly involved in the Immune System are the innate and the adaptive immunity [1]. Although its role is crucial for survival, protecting from pathogens and destroying viral and cancer cells, it is also important for maintenance of self-tolerance [2,3]. Regulatory T cells (Tregs) are a subset of well differentiated T helper cells (CD4CD25 T lymphocytes) which are initially produced by the thymus, as functionally mature cells, also known as Natural T regs [4]. Their role is to provide self- tolerance and prevent potentially hazardous T cell clones from expanding and causing autoimmune disease [5,6]. The vital role of Tregs is evidenced by the in vivo development of various autoimmune diseases, such as autoimmune thyroiditis and type I Diabetes Mellitus, as a result of CD25+CD4+ T cell depletion [6,7]. Tregs are characterized by the presence of forkhead box p3 (Foxp3) transcription factor and unlike other T lymphocyte subpopulations, they are characterized by the unique feature of being fully functional even before encountering specific antigens. Survival and function of Tregs critically depends on IL-2 [5,8]. Lack of IL-2 or IL-2R is known to cause multiorgan inflammatory disease early in childhood. Foxp3 Tregs are also generated from naïve T lymphocytes, during antigenic response to non-self or neoantigens in the presence of transforming growth factor (TGF) and IL-2. The derived lymphocytes consist the induced Tregs (iTregs) [5,9].

Regulatory T cell in chronic kidney disease at pre-dialysis stage

Chronic kidney disease (CKD) is characterized by immune dysregulation that involves both the innate and adaptive immunity. Recent evidence suggests a significant reduction in CKD patients even at pre-dialysis stage, compared to healthy controls [10-12]. Accumulation of uremic toxins, malnutrition, oxidative stress, acid-base disorders and subclinical inflammation seem to contribute to the alteration of the immune response. These changes are unique for CKD, and although they resemble immune alterations seen at the aging population, they are still different in many aspects. The immune changes observed in CKD patients concerning adaptive immunity include impaired T cell activation, reduced total lymphocyte count, helper T cell count, Tregs and effector T lymphocytes, reduced ratio of Th1/Th2 response, and a shift towards to advanced differentiated subsets, such as memory and senescent T cells [11,13,14].

Regulatory T cells in end stage renal disease (ESRD)

Progression to ESRD as well as induction to dialysis treatment seem to further impact those immunological profile alterations [11,13]. As renal function declines and patients progress to ESRD, the circulating microenvironment further deteriorates, with more acid-base and electrolyte disorders, exacerbation of frailty, malnutrition and chronic inflammation, conditions

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which even further exacerbate immune disturbances. Initiation of dialysis carries a very interesting role, and choice of dialysis method, that is Hemodialysis (HD) or Continues Ambulatory Peritoneal Dialysis (CAPD) is crucial for Tregs.

Hemodialysis vs CAPD

Regulatory T cells are further reduced in patients undergoing HD, and in a recent prospective study, we proved that a substantial reduction happens very early following initiation of the method. In the same study, there was no such detrimental effect in patients who started on CAPD. Even more, we proved a significant negative correlation between time of hemodialysis and peripheral Regulatory T cells [12-14].

The role of regulatory T cell in renal transplantation

In recent studies, we have found that Tregs are restored shortly after a successful renal transplantation, however, this finding was more prominent in patients without anti-HLA antibodies [15]. This is a very significant finding, considering the recent reports regarding the role of Tregs in renal transplant outcome.

The role of Tregs and their specific activities have been extensively studied in pathogenesis and progression of autoimmune diseases, however, over the last few years, their significant participation in renal transplantation has been proved and attracted investigators interest. Salama et all were the first to demonstrate the existence of antigen specific Tregs capable of suppressing alloresponses to donor HLA peptides in human kidney transplant recipients [16,17].

Recent evidence supports their role in transplant tolerance and chronic allograft rejection. In animal models of transplantation, Tregs are present in allografts and seem to migrate to the allograft tissue. Recent studies show that Tregs, induced in vitro, or expanded ex vivo, promote allograft tolerance [18,19].

On the other hand, migration of Tregs into the graft, as part of an inflammatory response, suggests a role for Tregs in immune-mediated allograft injury. Clinical and prognostic significance of FoxP3+ cell infiltrates in renal allograft recipients with acute rejection are contradictory. FoxP3 expression has been both regarded as a beneficial or unpropitious prognostic factor, considering the early outcome of renal transplantation. There has been an ongoing investigation in order to answer the question whether FoxP3 graft infiltrations could predict graft survival. Evidence from animal models have tried to explain the role of FoxP3 in suppression of alloimmune responses. Unfortunately, results are conflicting and do not lead to safe conclusions [17-20].

Furthermore, Treg cells seem to be lower in patients with chronic allograft rejection comparing to those patients with stable renal function. Treg cells are found to be reduced immediately after renal transplantation and there is evidence that their absolute number gradually increases over time.

Conclusion

Regulatory T cells are largely affected in CKD starting from pre-dialysis stages, and deteriorating thereafter. Hemodialysis seems to have a worse effect on their population, compared to CAPD, however, successful renal transplantation is the method of choice and has the potential to reinstate regulatory T cells, apparently through restoring renal function together with the chronic inflammatory conditions.

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