nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Editorial

Kidney, hypertension and complement activation. In search of new therapeutic targets☆

Riñón, hipertensión y activación del complemento. En búsqueda de nuevas dianas terapéuticas

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The complement system plays a fundamental role for innate immunity. Its main function, from an evolutionary point of view, is to provide an essential line of defense against bacteria, fungi and viruses. Obviously it has more functions (facilitate the elimination of apoptotic cells and immune complexes, interact with leukocytes and platelets, anti-inflammatory effects, embryogenesis). The complement proteins are inactive and they are activated in response to various stimuli, through three different routes: the classical pathway, the alternative pathway and the mannose-binding lectin pathway. A key feature of this system is that it is rapidly activated in pathogens and damaged cells, but is not activated on the surfaces of the host. Several regulatory proteins (especially the alternative pathway) on cell surfaces protect us from this complement activation. The ability of the complement system to discriminate between the different biological surfaces is accomplished by a fine balance between activating and regulatory proteins. Thus it is easily explained that an alteration of these regulatory proteins is the pathogenic basis of several well-known diseases that affect the kidney, such as atypical HUS, glomerulonephritis C3 and dense deposits disease. The role of complement in these diseases is clearly defined,[1] and their therapeutic targets are also identified.

For many years, nephrologists have observed deposits of complement proteins, especially C3, in renal biopsies of very diverse pathologies. We have not paid much attention to this histological evidence, probably because we did not fully understand what it meant. In recent years, I have had an explosion of knowledge and the publication of studies that are identifying some of these signals mediated by complement. Below, we present new advances in the knowledge of some of these entities.

Membranous nephropathy. Animal models have indicated that complement activation plays a central role in the pathogenesis of this disease.[2,3] Clinical studies[4] and experimental models[5] showed that urinary levels of the membrane attack complex C5b-9 are related to disease activity. The absence of C1q and the presence of C3 and C4d[6] in most cases suggest

DOI of original article:
https://doi.org/10.1016/j.nefro.2018.10.002.
☆ Please cite this article as: Rodríguez de Córdoba S, Espinosa Hernández M. Riñón, hipertensión y activación del complemento. En búsqueda de nuevas dianas terapéuticas. Nefrologia. 2019;39:111–114.
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that the alternative pathway and/or the lectin pathway are the main pathways of complement activation.[7] This is compatible with the finding of IgG4[8] (and not IgG1) deposits which is the only subclass of IgG that does not activate the classical pathway. It is interesting to note that few years ago there was a study designed to evaluate the effect of eculizumab treatment on the evolution of proteinuria in patients with membranous nephropathy; there were no significant differences as compared to the control group but these results were not published. However, it should be mentioned that these patients were treated with doses lower than those currently used and for a short period of time, only 16 weeks.

Nowadays, there is no doubt that the central treatment of membranous nephropathy should be aimed at reducing the levels of antibodies against the receptor of phospholipase A2, and this is achieved with various well known immunosuppressive strategies. However, the role of complement inhibitors has not been explored sufficiently, and it is possible that they have some beneficial effect in certain patients.

Vasculitis associated to ANCA and rapidly progressing Gn. Experimental models[9] of ANCA associated vasculitis have shown the potential pathogenic role of complement activation through the alternative pathway. This is also suggested by sufficient clinical and histological evidence.[10,11] A study by our group showed that the deposit of C3 in the renal biopsy is an independent factor associated to a worse long-term prognosis.[12] Research is being conducted to modulate complement activation in these diseases. Avacopan, a selective inhibitor of C5aR, has been tested in patients with ANCA positive vasculitis.[13] The conclusion is that avacopan has the same efficacy as high doses of corticosteroids but without its side effects.

IgA nephropathy (IgAN). There is a large body of evidence suggesting that activation of the alternative pathway and lectins is implicated in the pathogenesis of this disease. Genomic association studies showed that the homozygous protein deletion related to factor-Hα1 and γ 3 (CFHR1, CFHR3) was a protective factor against the development of the disease.[14] In this line, two different groups[15,16] have shown that an increase in the ratio FHR1-5/FH is involved in the progression of IgAN. Interestingly, one of these studies[16] suggests that the development of renal failure by itself may contribute to this dysregulation of the complement by increasing the levels of FHR1. The alternative pathway of complement seems to be clearly involved in the pathogenesis of IgAN. Furthermore the deposition of C4d, which results from the activation of the lectin pathway, is associated with a worse long-term prognosis.[17] There are cases with IgAN that have responded to treatment with eculizumab.[18,19] Avacopan has also been used in a few patients with IgAN, showing a beneficial effect on proteinuria.[20] Right now there are clinical trials underway (NCT03608033) to explore the role that inhibitors of the lectin pathway. This is promising, and it is possible that in the near future this disease will treated by acting on these targets.

Hypertension. Recently, it has been proposed that complement activation may play an important role in the pathogenesis of hypertension, and although there are still more questions than answers, the research work provides remarkable data.

The literature shows many clinical cases describing the association of malignant hypertension with microangiopathic hemolytic anemia/aHUS.[21] Classically, this hemolytic anemia has been explained by hemodynamic abnormalities associated to severe hypertension. Some reviews have shown that 25% of patients with malignant hypertension present data of thrombotic microangiopathy.[22] Recent data from the group of Glomerular Diseases of the Spanish Nephrology Society (GLOSEN)[23] estimate that 32% of patients with aHUS have malignant hypertension. With these clinical observations it may be hypothesized that malignant hypertension is another manifestation of MAT/aHUS which involves an alteration in the regulation of complement. Some studies have shown that these patients with malignant hypertension have the same genetic mutations observed patients with aHUS.[24] Other studies using different methodology have not found such mutations.[25]

The association between complement disregulation and non-malignant hypertension is not that clear and the evidence is mainly from experimental work.[26] It is speculated that the activation of complement generates C5a that exerts its functions through its receptor C5aR expressed on the surface of several types of cells, including endothelial cells.[27,28] In an experimental model of rats treated with angiotensin II, C5aR blockade resulted in a significant reduction of inflammation, perivascular fibrosis and cardiac hypertrophy.[29] Interestingly, C5aR blockade did not change the blood pressure, despite the fact that all these manifestations associated with hypertension did. In this same line additional surprising data is being reported; Békássy et al.[30] show that, in vitro, plasma renin is able to activate complement in a manner identical to the activation by C3 convertase. Renin would excise C3 forming its C3a and C3b products, triggering the activation of the alternative pathway. In addition, this activation is inhibited in vitro by the renin inhibitor, aliskiren. This interesting work, shows, in 3 patients with disease due to dense deposits, clinical evidence suggesting a beneficial effect of renin inhibition on the complement profile at the systemic (increase in serum C3 levels) and renal level (decrease in proteinuria and reduction of the intensity of C3 deposits) These patients were treated for 4–7 years with aliskiren. Taken together, all this information suggests that the inhibition of renin could have a beneficial effect in a significant number of pathologies with activation of the complement.

Although debatable, it is possible that the use of angiotensin-converting enzyme inhibitors or angiotensin-blockers are not the most indicated strategy in patients with significant C3 deposits.

The possible activation of complement by renin may have to do with the increasingly relevant role of the activation of C5 and C3 by proteolytic enzymes, independent of the classical C3 and C5 convertases. These mechanisms of complement activation, that could be considered atypical, were first described

in an experimental model in which it was shown that thrombin (in the absence of C3) was able to activate C5 and form C5a31.[31] These evidences of extrinsic or indirect activation have also been observed in lung tumor cells tumors that were able to generate C5a in the absence of serum.[32]

It is clear that the view that the complement system is only a complex network of proteins whose sole mission is to protect us from pathogens is simply wrong. Also, it may not be entirely true that the complement is the main pathogenic mediator in all these renal diseases or related with hypertension. What is clear is that there are enough reasons to explore these hypotheses and clarify the specific role that complement alterations in each disease; and, it is particularly important to know if its inhibition or regulation (for example with renin inhibitors) may have a role in the clinical management.

Conflict of interests

SRC and ME have received Alexion fees for training talks, but this has had no influence on the writing of the paper.

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