

Summary

Momir Macanovic and Peter Lachmann

The complement system in renal diseases

This chapter gives an overview of the role of complement in the pathogenesis of renal disease, particularly the many forms of glomerulonephritis and explores the paradox that while some renal diseases are associated with chronic complement activation others are associated with complement deficiency.

Summary

Wuding Zhou and Steven H. Sacks

Complement in renal transplantation

Renal transplantation is an intricate procedure which, we now realize, awakens the innate arm of the immune system, as well as stimulating the adaptive immune system. Activation of the complement cascade occurs at an early stage after surgery, and is marked by the deposition of complement fragments in the graft and increased local synthesis of essential components such as C3. Studies in knockout and transgenic animals have generated strong evidence for a role of complement in several transplant pathologies. These include ischemia/reperfusion injury, hyperacute rejection, maturation of the anti-donor humoral response and acute cell-mediated rejection. Therapeutic evaluation of recombinant inhibitors has indicated the potential for future clinical development to prevent some of these injuries. An important challenge is the issue of local synthesis, where key components secreted into the renal interstitial space may be instrumental in tissue pathology, but may be out of reach of systemically administered inhibitors. In addition to the new therapeutic targets posed by complement, products such as C4d appear to serve as diagnostic markers for previously unrecognized humoral rejection. This has started a new line of enquiry concerning the role of alloantibodies in chronic rejection.

Key Words: Complement system, complement effector products, C3, C4d, C5b-9, complement regulatory protein, renal transplantation, ischemia/reperfusion injury, hyperacute rejection, acute rejection, xenotransplantation, allografts, gene expression, local synthesis.

Summary

S.P. Berger, T.W.L. Groeneveld, A. Roos and M.R. Daha

C1q and the glomerulonephritides: therapeutic approaches for the treatment of complement-mediated kidney diseases

C1q is the recognition molecule of the classical pathway. Classical pathway activation is thought to be an important contributor to renal damage in various forms of glomerulonephritis. Both the beneficial as well as detrimental roles of C1q in renal inflammation are described.

Antibodies to C1q are associated with renal involvement in SLE nephritis. The recent evidence demonstrating an important role of these antibodies in the pathophysiology of lupus nephritis is presented. Finally approaches towards C1q-targeted therapy and possible risks of classical pathway inhibition are briefly discussed.

Key Words: Anti-C1q antibodies, C1q, classical pathway, complement inhibition, glomerulonephritis, lupus nephritis, SLE.

Summary

Joshua Thurman and Mike Holers

Complement deficient mice as model systems for kidney diseases

This chapter focuses on the various strains of mice with deficiencies of one or more complement proteins. The strains with gene-targeted deletions of complement proteins as well as those with naturally occurring deficiency of proteins in the complement system are reviewed. These include mice deficient in proteins of all three activation pathways, the various complement inhibitors, or complement receptors. Numerous studies have utilized complement deficient mice in models of renal disease in order to examine the role of complement in these diseases. These studies are discussed in regard to how they have elucidated the role of the complement system in disease. In some disease models, such as models of lupus nephritis, the role of complement has turned out to be more complex than initially thought. The study and comparison of several different strains of complement deficient mice in these models has revealed both pro- and anti-inflammatory functions of the complement system, and has provided a rationale for the therapeutic use of complement inhibition in several renal diseases.

Summary

Marina Noris and Giuseppe Remuzzi

Non-Shiga toxin-associated hemolytic uremic syndrome

Hemolytic uremic syndrome (HUS) is a disease of non-immune hemolytic anemia, thrombocytopenia and renal failure due to platelet thrombi in the microcirculation of the kidney. The characteristic lesion consists of vessel wall thickening, with swelling and detachment of the endothelial cells and accumulation of fluffy material in the subendothelium. In children the disease is most commonly triggered by Shiga-like toxin (Stx)-producing *E. coli* and manifests with diarrhea, often bloody. Acute renal failure occurs in 60-70% of cases; however, renal function recovers in most of them. By contrast, non-Stx-associated-HUS (non-Stx-HUS) has a much poorer prognosis and is often relapsing; end-stage renal failure or death is the final outcome in the majority of cases. In selected cases there is a clustering of affected individuals within families, which is suggestive of an underlying genetic predisposition to the disease. Reduced serum levels of the third component of complement have been reported in patients with non-Stx-HUS and genetic studies have documented abnormalities of the complement regulatory proteins, Factor H, membrane cofactor protein and Factor I.

This chapter is focused on the pathology and treatment of non-Stx-HUS. The possible impact of emerging information on complement regulatory abnormalities to patients' management and treatment is also discussed.

Key Words: Alternative pathway of complement, complement C3, endothelial cells, factor I, factor H, hemolytic uremic syndrome, kidney, membrane cofactor protein, pathology, shiga-like toxin, thrombotic microangiopathy.

Summary

Christine Skerka and Mihály Józsi

Role of complement and factor H in haemolytic uremic syndrome

Defective complement control is a cause for atypical hemolytic uremic syndrome (aHUS). A number of recent studies have identified mutations of several complement regulatory genes in aHUS patients. Mutations have been identified in the genes encoding the fluid-phase

complement regulator Factor H, the serine protease Factor I and the surface-bound regulator membrane cofactor protein (MCP/CD46). All three proteins control the activity of the central alternative pathway amplification convertase C3bBb. A total of 65 mutations have been identified in the Factor H gene, 4 in the Factor I gene and 4 mutations in the gene coding for MCP. In addition, autoantibodies that bind and inactivate the function of the immune regulator Factor H have been reported.

The functional analyses of the mutant proteins have defined a protective role of Factor H, Factor I and MCP for the integrity of host endothelial cells. These analyses are also indicative for the disease mechanism of aHUS, as defective alternative pathway complement regulation causes generation of aggressive complement-activation products that relate to endothelial cell damage.

The majority of the identified Factor H gene mutations are clustered in the C terminus of the protein, which includes the cell surface recognition region. This clustering of mutations in the C terminus indicates a central role of the cell surface recognition domain for pathophysiology of aHUS. Mutations of additional complement regulatory genes, whose products control the activity of the central amplification convertase C3bBb, are associated with aHUS. These scenarios indicate that defective local inhibition of complement, occurring most likely upon an inflammatory reaction, results in endothelial cell damage. Here we discuss how mutated, defective or inactivated complement regulatory proteins relate to the disease aHUS and focus on complement Factor H.

Key Words: Acute renal failure, autoantibody, alternative complement pathway, Factor I, membrane cofactor protein (MCP).

Summary

Timothy H.J. Goodship, Veronique Fremeaux-Bacchi, John P. Atkinson

Genetic testing in atypical HUS and the role of membrane cofactor protein (MCP;CD46) and Factor I

Key Words: Complement, genotyping, Factor H, Factor I, HUS, MCP, transplantation.

Summary

Maren Salzmann, Michael Hoffmann, Gisa Schlueh, Peter Riegler, Markus Cybulla, Hartmut PH Neumann

Towards a new classification of haemolytic uremic syndrome

Hemolytic uremic syndrome (HUS) and thrombotic-thrombocytopenic purpura (TTP) are currently diagnosed and classified clinically. Here we summarize the relevant literature and propose a genetic classification. At least 15% of HUS and possibly a similar figure of TTP patients are carriers of germline mutations predisposing to these disorders. For HUS currently well recognized are these genes FH1 and CD46 (also named MCP), whereas the susceptibility gene for TTP is ADAMTS13. All reported mutations are listed here.

Key Words: ADAMTS13, CD46, factor H, haemolytic uremic syndrome, thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP), von Willebrand factor, vWF-cleaving protease, membrane cofactor protein (MCP).

Summary

Reinhard Würzner and Lothar B. Zimmerhackl

Therapeutic strategies for atypical and recurrent haemolytic uremic syndromes (HUS)

Atypical and recurrent HUS have a poor prognosis with regards to renal outcome. Complement activation is an important culprit in the development of the disease. Lack of soluble and membrane bound complement inhibitors is the main cause. Substitution of complement inhibitors is only possible by plasma. Recommended procedures include plasma infusion and exchange. With this empirical approach deterioration of renal function can be reduced.

However, renal transplantation is a major challenge. Most of these patients tend to demonstrate recurrence.

New therapeutic strategies (C5 inhibitors) are needed to improve outcome of these patients.

Key Words: Factor H, plasmapheresis, plasma therapy, renal insufficiency, transplantation.

Christoph Licht and Bernd Hoppe

Complement defects in children which result in kidney diseases: diagnosis and therapy

(No summary & key words available)

Peter F. Zipfel, Richard J.H. Smith and Stefan Heinen

The role of complement in membranoproliferative glomerulonephritis

(No summary & key words available)

Pearl L. Lewis

The experience of a patient advocacy group

(No summary & key words available)



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