APL-2 Prevents Both C3 and C5 Convertase Formation and Activity: A Potential Therapeutic for Renal Diseases

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Introduction

C3 glomerulonephritis (C3G) is a group of rare inflammatory renal diseases classified into 2 major subgroups: C3 glomerulonephritis (C3G) and dense deposit disease (DDD). While most children develop renal disease in up to 50% of affected patients within 5-10 years of diagnosis, C3G can be associated with a more chronic, progressive alternative pathway of the complement system. This is caused by the presence of autoantibodies, C3 and C5 nephritic factors (NeFs), which bind and stabilize the inactivating convertase complexes responsible for C3 and C5 cleavage, thus preventing the ultimate formation of the lytic C5b-9 complex.

Here, we explore the role of APL-2, an antibody fragment that selectively binds to human C3, as a potential therapeutic for C3G and C3D.

Methods

Overview of the Complement Cascade and Prevention of Alternative Pathway

Objective

To test the effect of APL-2 in vitro on the generation of C3 convertase. To test whether APL-2 interferes with the formation of C3 convertase, we studied the activity of the alternative pathway in the presence and absence of APL-2.

Results

Impact of APL-2 on C3 and C5 Convertase Activity

APL-2 significantly inhibits C3 and C5 convertase activity, which is associated with a decrease in the formation of C5b-9 and subsequent activation of complement.

Discussion

The results demonstrate the potential of APL-2 as a therapeutic agent for C3G and C3D, offering a new approach to targeting the alternative pathway in these diseases.

Conclusions

APL-2 significantly inhibits the cleavage of C3 and C5 by their respective convertases, stabilizing the alternative pathway and preventing the formation of C5b-9. This suggests a potential therapeutic role for APL-2 in the management of C3G and C3D.

References

