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Control of Neisseria gonorrhoeae by complement effector functions and potentiation of antimicrobials by the membrane attack complex.

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Background

Two prominent immune effectors against Neisseria gonorrhoeae (Gc) are neutrophils and the complement cascade. Complement enhances bacterial killing by activating phagocytes and promoting complement-mediated opsonophagocytosis. Additionally, complement generates the pore-forming membrane attack complex (MAC) which inserts into the outer membrane of Gram-negative bacteria. However, the exact mechanisms by which the MAC kills Gc are not fully elucidated. In the quest for a gonococcal vaccine, it is important to understand how complement effector functions contribute to the protective efficacy of

immunization-elicited antibodies.

Aim/Methods

Strain FA1090, H041, and MS11 Gc were incubated with human serum, with or without addition of antimicrobials with specific mechanisms/sites of action. Serum bactericidal activity was measured by CFU enumeration, and bacterial membrane integrity by permeability to fluorescent compounds. A whole blood model was used to test complement-mediated killing and the contribution of antigonococcal antibodies, including those elicited by the serogroup B meningococcal vaccine 4CMenB. Complement effector functions were interrogated using the C5 inhibitor OMCI, use of complement component-depleted serum, and heat-inactivated serum.

Results

MAC deposition at sublethal concentrations potentiated the antimicrobial activity of the canonically Gram-positive specific antibiotics vancomycin and nisin which act at the peptidoglycan and inner membrane, respectively, and the periplasm-acting immunologic enzyme, lysozyme. Sublethal MAC deposition decreased the resistance of multidrug-resistant H041 to ceftriaxone and azithromycin. The MAC increased Gc permeability to outer and inner membrane targeting fluorescent compounds. Complement-dependent killing of Gc was enhanced in whole blood when polyclonal rabbit anti-Gc antibodies were added. However, IgG isolated from individuals immunized with the meningococcal 4CMenB vaccine did not increase killing of Gc in whole blood.

Conclusions

The MAC enables antimicrobial access to the periplasm, inner membrane, and cytoplasm by permeabilizing the outer and inner membranes. Consequently, the MAC enhances antigonococcal activity of antimicrobials, including against multidrug-resistant Gc. Antibodies can increase complement-mediated antigonococcal activity in whole blood, although 4CMenB-purified IgG did not do so. Ongoing studies are dissecting which complement effector functions contribute to control of Gc.