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Special Feature Editorial

Multifaceted roles of antibody Fc effector functions: from protection to pathology

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Antibodies are evolutionarily conserved immune proteins that have been protecting vertebrate creatures for millennia. Traditionally, the main focus of antibody research has been upon the recognition of antigens through the **Fab** (Fragment antigen binding) region, in order to inhibit pathogens or block receptors. However, in recent years, there has been a growing appreciation for the critical value of the **Fc** (Fragment crystallizable) or the constant region of antibodies. Fc antibody functions act as an invaluable bridge between the adaptive and innate immune system, where the antibody provides the specificity of the adaptive immune system (via the Fab) while engaging the rapid response of the innate immune system (via the Fc). Despite the Fc region being designated as "constant," it is a surprisingly mutable region, regulated by genetics including allotypes, isotypes, subclasses and post translational modifications such as glycosylation, each of which can result in structural changes that determine Fc functional capacity[1].

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This collection of Special Feature reviews covers the multifaceted functions of Fc antibodies for the (i) control and protection against a range of infectious diseases including viral, parasitic and bacterial pathogens, (ii) enhancement of monoclonal antibody therapeutic interventions but (iii) also highlights the pathogenic consequences of dysregulated Fc effector functions.

The first review by Vandervan *et al.*[2] summarizes the diverse array of antiviral Fc effector functions, with a focus upon influenza infection, illustrating how Fc effector functions can work in synergy with antibody neutralisation for protection, and discusses how a universal vaccine could be elicited by Fc-mediated functions to conserved target antigens.

Similarly, Aitken *et al.*[3] discuss the large variety of antibody functions that have been described against parasites, especially malaria, which has a complex life cycle and vastly more antigenic targets, with different effector functions potentially contributing to control at different life cycle stages.

IgA has traditionally been studied as a mucosal antibody. Davis *et al.*[4] provide a different perspective, examining serum IgA, which surprisingly can play dual roles in activation and inhibition of Fc effector functions, discussing this balance in the control of bacterial and viral pathogens, as well as its emerging potential for use in antibody therapeutics.

Beyond infectious diseases, several cancer immunotherapies currently utilize antibody Fc effector functions to improve the effectiveness of anti-tumour clearance. Chenoweth *et al.*[5] explore the mechanisms behind how antibody Fc regions can be modulated to enhance the most effective antibody functions, which are amongst some of the most critical questions for the development of next generation vaccines and antibody monoclonal therapeutics.

While the benefits of antibodies are undeniable, it is also important to acknowledge that antibodies can contribute to dysregulation of immunity and disease pathology, including autoimmunity and even enhancement of infection or promotion of tumorigenic microenvironments as highlighted by Goldberg *et al.*[6]

Collectively, these Special Feature reviews describe the complexity behind the modulation of protective Fc effector functions, examines how different antibody functions may be relevant dependant on the pathogen or target, cautions against the induction of antibody mediated immunopathology, while also highlighting the many unknowns and exciting avenues of research that are yet to come.

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