Trends in Molecular Medicine

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Review

Modulating Antibody Functionality in Infectious Disease and Vaccination

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Induction of pathogen-specific binding antibodies has long been considered a signature of protective immunity following vaccination and infection. The humoral immune response is a complex network of antibodies that target different specificities and drive different functions, collectively acting to limit and clear infection either directly, via pathogen neutralization, or indirectly, via pathogen clearance by the innate immune system. Emerging data suggest that not all antibody responses are equal, and qualitative features of antibodies may be key to defining protective immune profiles. Here, we review the most recent advances in our understanding of protective functional antibody responses in natural infection, vaccination, and monoclonal antibody therapeutics. Moreover, we highlight opportunities to augment or modulate antibody-mediated protection through enhancement of antibody functionality.

Constantly Functional: The Other End of the Antibody

Humoral immune responses evolve following infection and serve as readout for vaccine responsiveness in all clinically approved vaccines to date. However, the mechanisms by which vaccine-induced antibodies act to provide protection is varied, where direct pathogen neutralization accounts for protective immunity in only a small fraction of clinically approved vaccines [1]. Thus, while vaccine design efforts often aim to induce **'neutralizing' antibodies** (see Glossary), increasing evidence suggests that the development of non-neutralizing antibody responses may contribute to vaccine-mediated protection from infection/disease.

Beyond their role in neutralization, mediated by the antibody antigen-binding arms (**Fabs**), antibodies also drive a remarkably wide array of additional antipathogen and immune-regulatory functions via their constant regions (Fc). The **Fc domain** of the antibody directs the **effector functions** of antibodies via Fc-binding proteins, including **complement** proteins, lectin-like proteins, and **Fc-receptors** found on all innate immune cells. Effector functions include: first, **phagocytosis** of antibody-coated pathogens and/or infected cells by monocytes, macrophages, neutrophils, and dendritic cells; and second, direct killing of infected cells by cytotoxic **natural killer (NK) cells** and complement-mediated lysis. Given that Fc-receptors are differentially expressed on innate immune cells (Figure 1 and Box 1), antibody binding to specific Fc-receptors enables the elicitation of distinct effector functions. In addition, antibodies initiate the complement cascade through both classical and lectin pathways, contributing to the direct destruction of target cells and their enhanced phagocytic clearance via complement receptors found on macrophage/monocytes, neutrophils, and dendritic cells. Thus, the production of qualitatively unique antibody profiles that selectively bind particular classes of Fc-binding receptor may enable the selective induction of particular antibody effector functions and protective mechanisms of action.

Trends

An antibody Fc domain interacts with innate immune cells, mediating a range of functions, including effector mechanisms, to limit and clear infection.

Fc-mediated antibody functionality is increasingly being recognized as a critical aspect of humoral immunity against infectious diseases.

Antibody functionality is modulated during disease and vaccination through both subclass selection and glycosylation of the antibody Fc domain.

Broadly neutralizing monoclonal antibodies against HIV-1 and influenza viruses require Fc-mediated functionality to confer immune protection.

Comprehensive profiling of the humoral response beyond titer and neutralization can identify underlying protective signatures of antibody-mediated protection.

Different vaccines, adjuvants, regimens, and vectors induce distinct antibody functional profiles, and future vaccines may be designed to direct antibody functionality.

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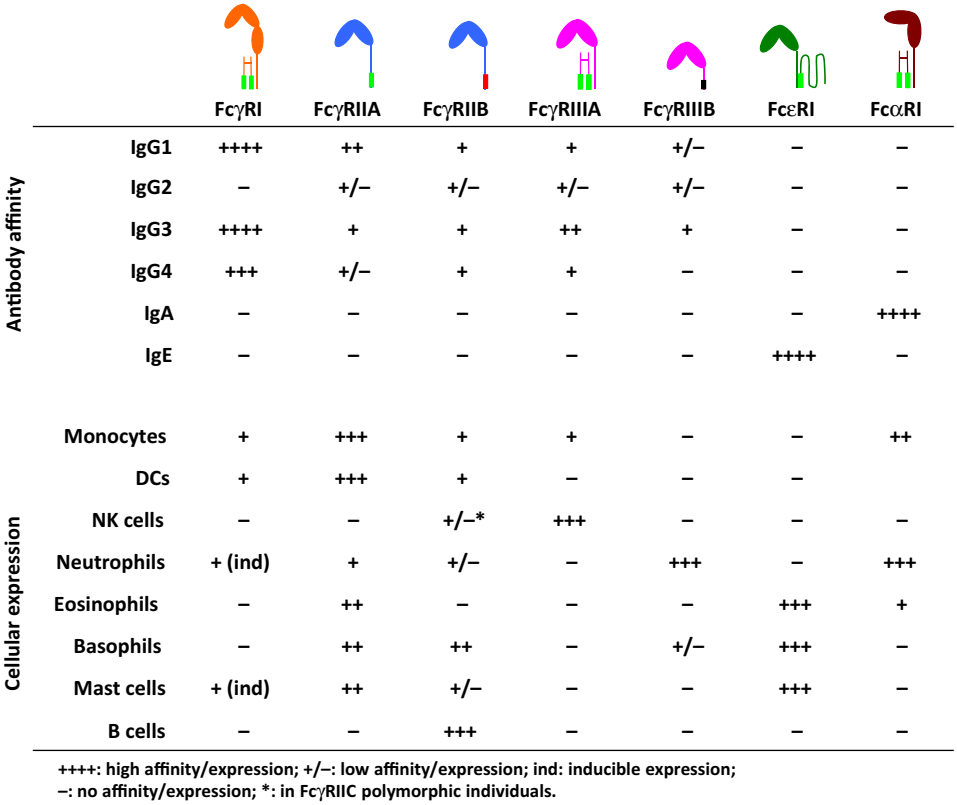

		FcγRI	FcγRIIA	FcγRIIB	FcγRIIIA	FcγRIIIB	FcεRI	FcαRI
Antibody affinity	IgG1	++++	++	+	+	+/–	–	–
	IgG2	–	+/–	+/–	+/–	+/–	–	–
	IgG3	++++	+	+	++	+	–	–
	IgG4	+++	+/–	+	+	–	–	–
	IgA	–	–	–	–	–	–	++++
	IgE	–	–	–	–	–	++++	–
Cellular expression	Monocytes	+	+++	+	+	–	–	++
	DCs	+	+++	+	–	–	–	
	NK cells	–	–	+/–*	+++	–	–	–
	Neutrophils	+ (ind)	+	+/–	–	+++	–	+++
	Eosinophils	–	++	–	–	–	+++	+
	Basophils	–	++	++	–	+/–	+++	–
	Mast cells	+ (ind)	++	+/–	–	–	+++	–
	B cells	–	–	+++	–	–	–	–

++++: high affinity/expression; +/–: low affinity/expression; ind: inducible expression;
–: no affinity/expression; *: in FcγRIIC polymorphic individuals.

Trends in Molecular Medicine

Figure 1. Antibody Affinity for FcRs and FcR Expression on Immune Cells. Antibody isotypes and subclasses have different affinities for various FcRs. The FcγR family of receptors binds IgG, FcεRI binds IgE, and FcαR binds IgA. Within IgG, IgG1 and IgG3 bind to all FcγRs with higher affinity compared with IgG2 and IgG4, and IgG2 does not bind FcγRI. Cellular expression of the different FcRs also varies on innate immune cells. Monocytes and macrophage express the high-affinity FcγRI, high levels of the FcγRIIA, low levels of FcγRIIB, and low levels of FcγRIIIA. Dendritic cells (DCs) express FcγRI, FcγRIIA, and FcγRIIB, as well as the type II Fc receptor DC-SIGN. NK cells predominantly express activating FcγRIIIA, although polymorphisms in the *FCGR2C* gene allow for FcγRIIC expression on NK cells a subset of individuals. Neutrophils express high levels of the GPI-linked FcγRIIIB, low levels of FcγRIIA, and can induce expression of the high-affinity FcγRI. Eosinophils, basophils, and mast cells predominantly express the FcεR to bind IgE, but also express FcγRIIA and FcγRIIB, and mast cells can induce FcγRI. B cells express only one FcγR, the inhibitory FcγRIIb, which provides negative feedback to the B cell, and plays a key role in immune tolerance.

Given that every circulating antibody has both a Fab and an Fc domain, every antibody must harbor an intrinsic ability to interact with the innate immune system. Moreover, since antibody functionality can be tuned up or down, an antibody must be considered as a whole, rather than just its Fab or Fc domains. This concept has been most recently demonstrated by studies

Box 1. The Human FcRs

Humans possess five major types of Fc-receptor, differentiated by the antibody isotype they bind: FcγR, FcαR, FcεR, FcδR, and FcμR binding IgG, IgA, IgE, IgD, and IgM, respectively. In addition, C-type lectin receptors, such as DC-SIGN and CD23, represent another class of Fc-receptors, termed type II Fc-receptors, shown to bind IgG and to mediate anti-inflammatory as well as immune-regulatory functions in both mouse and human systems [76,89–91]. Human FcγRs can be further divided into inhibitory (FcγRIIB/CD32b) and activating receptors (FcγRI/CD64, FcγRIIA/CD32a, FcγRIIC/CD32c, FcγRIIIA/CD16a, and FcγRIIIB/CD16b), and different innate immune cells express varying combinations and levels of FcγRs (see Figure 1 in main text). With the exception of the high-affinity FcγRI, FcγRs are generally low in affinity for IgG, relying more heavily on avidity for activation. However, allelic polymorphisms found within the activating FcγRs, FcγRIIA (H131/R131) and FcγRIIIA (V158/F158), have been shown to confer higher and lower binding affinity for IgG, respectively [92–94]. Thus, individuals with the higher affinity polymorphisms generally exhibit higher levels of antibody function, which may play a role in protection or pathology, depending on the disease setting [95].

Glossary

Adjuvant: a substance that augments an immune response against an antigen and enhances vaccine efficacy.
Affinity: the strength of interaction between a single antibody and a single antigen.
Antibody-dependent cellular cytotoxicity (ADCC): directed killing of an opsonized target cell by an innate immune cell, such as an NK cell, macrophage, or neutrophil.
Antibody glycan: a carbohydrate post-translational modification that is added to the antibody heavy chain at position N297 during antibody synthesis in B cells. Antibodies are exclusively glycosylated with a biantennary glycan structure.
Arthus reaction: a type III hypersensitivity reaction that is characterized by vasculitis and primarily caused by activation of the complement cascade by immune complexes.
Avidity: the strength of interaction between several antibodies and antigen(s).
B cell: a lymphocyte that develops in the bone marrow and the only cell that secretes antibodies.
B cell priming: the process that promotes B cell differentiation and maturation through stimulation of B cells by activated $CD4^+$ T helper (T_H) cells.
Complement cascade: an extracellular innate immune program that can directly lyse pathogens and infected cells, augment phagocytosis, enhance antigen presentation, and modulate inflammation.
Effector functions: mechanisms of pathogen clearance mediated by innate immune cells, including phagocytosis, complement-mediated killing, and direct killing through release of cytotoxic granules.
Epitope spreading: expansion of the adaptive immune response from the immunodominant epitope of an antigen to subdominant epitopes, allowing for an increase in the diversity of epitopes recognized by both T cells and antibodies.
Fab domain: the part of the antibody that binds specifically to antigens. There are two Fab arms per IgG antibody.
Fragment crystallizable (Fc) domain: the 'constant' domain of the antibody that interacts with innate immune cells, B cells, and