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By binding to receptors on immune cells, antibodies mediate immune responses ranging from neutralizing pathogens to suppressing inflammation. The Ravetch lab investigates the complex biology of these antibody-Fc receptor interactions, and their roles in normal immune function and disease. These studies are providing novel approaches to treating infectious and inflammatory diseases, as well as cancer.

Pairs of activating and inhibitory molecules, known as Fc receptors, are found on the surface of nearly all immune cells. The Ravetch lab's studies of Fc receptors have led to the discovery that, by binding to these receptors, antibodies coordinate the immune system's effector responses. The lab continues to investigate the roles and mechanisms of Fc-mediated interactions, and applies its findings to improve treatments for disease.

By disrupting activating receptors, lab members found they could ablate antibody-dependent inflammatory reactions, such as those characteristic of lupus. Subsequent studies established Fc receptors' pre-eminence in the pro-inflammatory activity of both protective and pathogenic immunoglobulin G (IgG) in vivo. Even the classical neutralizing antibodies for bacterial toxins and viruses require Fc receptor engagement, and ongoing studies are examining its role in the response to the Ebola virus. The lab also studies antibodies made by people who have been infected with SARS-CoV-2 to determine which Fc variants are best capable of eliminating virus.

Likewise, the lab's work has shown that therapeutic anti-tumor antibodies, including rituximab, Herceptin, and others, achieve their effects through Fc receptor-dependent pathways. Fc receptor-mediated effector activity is now accepted as the dominant mechanism for anti-cancer antibodies in humans.

The lab has sought to enhance effector activity by engineering antibodies' Fc domains, and a number of the modified antibodies developed by the group have been approved or are awaiting approval for clinical use against cancer. Lab members continue to dissect Fc interactions with the goal of enhancing antibodies' ability to both kill tumors and activate a memory response to them.

Interactions with inhibitory Fc receptors, meanwhile, enable antibodies to mediate tolerance to harmless antigens. Experiments in animal models and human populations have shown that when this mechanism breaks down, autoimmunity ensues. This condition can be reversed, however, by restoring the inhibitory Fc receptor pathway. The lab has defined and is characterizing a family of Fc receptors, Type II FcRs, involved in immune suppression.

These inhibitory and activating mechanisms alone do not fully explain how antibodies mediate the full range of effector responses. The discovery that modifications to antibodies can alter Fc interactions has provided the final piece to the puzzle. When investigating the anti-inflammatory activity of high doses of IgG, the lab discovered that a fraction of it contained a specific modification: the addition of a sialic acid to an Fc domain glycan. Sialylation switches the binding specificity from the canonical activating Fc receptors to Type II FcRs.

The lab has since begun investigating the role of Fc domain modifications in responses to infection and vaccination, including those for flu, dengue, and malaria. Fc sialylation is correlated with the production of higher affinity antibodies after the flu vaccine, and is being studied as a mechanism for a "universal" flu vaccine. Meanwhile, Fc afucosylation appears to contribute to severe secondary dengue infections. The lab is currently dissecting its role in antibody-dependent enhancement in dengue and developing strategies to mitigate it.

EDUCATION

B.S., 1973
Yale University

Ph.D., 1978
The Rockefeller University

M.D., 1979
Cornell University Medical College

POSTDOC

National Institute of Child Health and Human Development, National Institutes of Health, 1979–1982

POSITIONS

Assistant Professor, 1982–1986
Associate Professor, 1986–1990
Professor, 1990–1996
Cornell University Medical College

Assistant Member, 1982–1986
Associate Member, 1986–1990
Member, 1990–1996
Memorial Sloan-Kettering Cancer Center

Professor, 1996–
Director, Cooperative Center for Human Immunology, 2014–
The Rockefeller University

AWARDS

Burroughs Wellcome Fund Award, 1986

Lee C. Howley Sr. Prize for Arthritis Research, 2004

Meritorious Career Award, American Association of Immunologists–Huang Foundation, 2005

Coley Award, Cancer Research Institute, 2007

Canada Gairdner International Award, 2012

Sanofi–Institut Pasteur Award, 2012

Wolf Prize in Medicine, 2015

National Cancer Institute Outstanding Investigator Award, 2015

Ross Prize, 2017

Robert Koch Award, 2018

National Cancer Institute Outstanding Investigator Award, 2022

HONORARY SOCIETIES

National Academy of Sciences

National Academy of Medicine

American Academy of Arts and Sciences

Fellow, American Association for the Advancement of Science

SELECTED PUBLICATIONS

Kao, K.S. et al. Synthetic nanobodies as tools to distinguish IgG Fc glycoforms. *Proc. Natl. Acad. Sci. U.S.A.* 119, e2212658119 (2022).

Yamin, R. et al. Fc-engineered antibody therapeutics with improved anti-SARS-CoV-2 efficacy. *Nature* 599, 465470 (2021).

Bournazos, S. et al. Antibody fucosylation predicts disease severity in secondary dengue infection. *Science* 372, 1102–1105 (2021).

Garris, C.S. et al. Dendritic cell targeting with Fc-enhanced CD40 antibody agonists induces durable antitumor immunity in humanized mouse models of bladder cancer. *Sci. Transl. Med.* 13, eabd1346 (2021).

Bournazos, S. et al. Fc-optimized antibodies elicit CD8 immunity to viral respiratory infection. *Nature* 588, 485–490 (2020).