# Immunoglobulin G Antibodies Activate Lysosome/Phagosome Targeting

by Dr. Axel Nohturfft

Around the turn of the 20th century an epic controversy was fought on the question of how the body defends itself against infections. In one camp were the "cellularists," led by zoologist Elie Metchnikoff, who believed the principal instruments of the immune system to be white blood cells that engulf and digest invading microorganisms. Their opponents, called "humoralists," disagreed and argued instead that the chief weapons of the immune system were soluble molecules called antibodies.

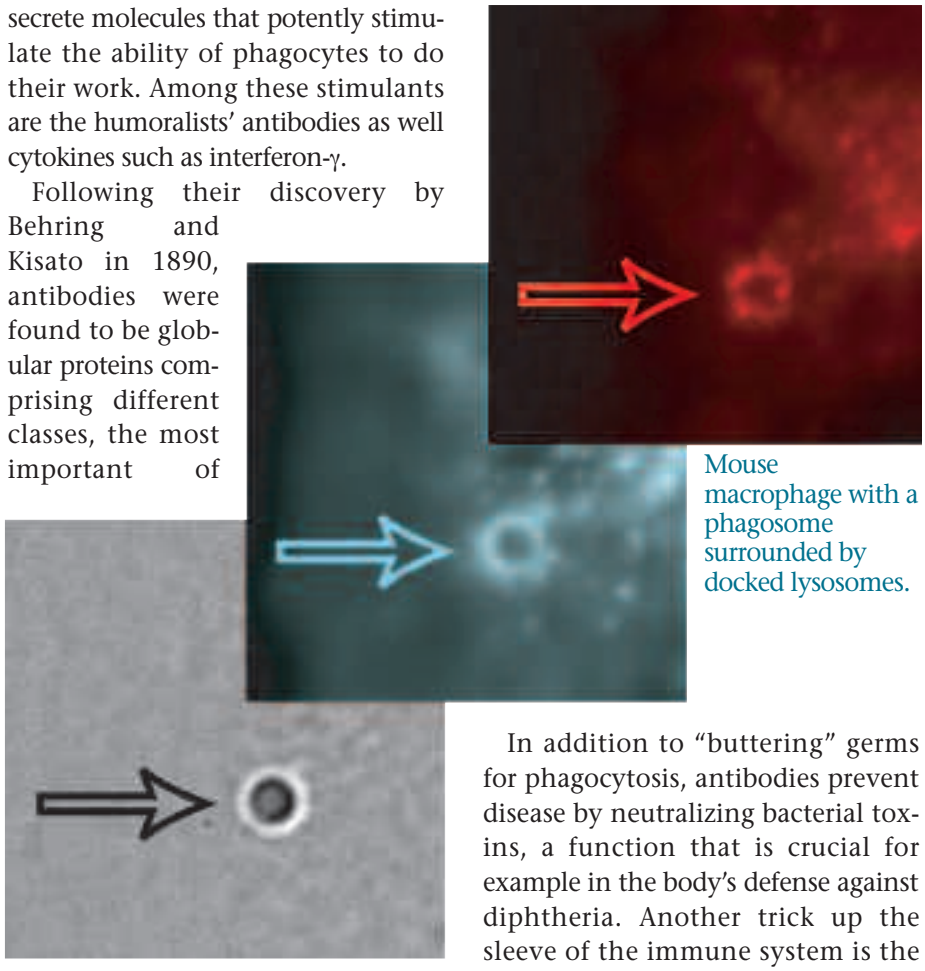
As it turned out, the truth lies in the middle, a possibility that was first proposed by Wright and Douglas in 1903 and popularized by George Bernard Shaw in the preface to his play "The Doctor's Dilemma":

*"…Sir Almroth Wright, following up on Metchnikoff's most suggestive biological romances, discovered that the white corpuscles or phagocytes…do their work only when we butter the disease germs appetizingly for them with a natural sauce which Sir Almroth named opsonin …"*

Amoeba-like phagocytes such as neutrophils, macrophages, and dendritic cells are our first line of defense against microbes that enter the body. Phagocytes can swallow microbes whole and store them in membrane-bound phagosomes where the prey is slowly digested. Digestion requires the fusion of phagosomes with lysosomes, which deliver hydrolytic enzymes as well as proteins involved in acidification, microbe killing, and presentation of antigens to T lymphocytes.

If an infection persists other cells of the immune system will mount a second line of defense and begin to secrete molecules that potently stimulate the ability of phagocytes to do their work. Among these stimulants are the humoralists' antibodies as well cytokines such as interferon-γ.

Following their discovery by Behring and Kisato in 1890, antibodies were found to be globular proteins comprising different classes, the most important of which is referred to as immunoglobulin G, or IgG. The immune system produces billions of different IgG antibodies, each of which can avidly bind to another foreign molecule.



Mouse macrophage with a phagosome surrounded by docked lysosomes.

IgG molecules have two domains. One domain binds foreign antigens, while the other is recognized by specific receptors on the surface of phagocytes. IgG thus enhances the recognition of microbes by phagocytes and potently accelerates their engulfment. Following Sir Almroth Wright's suggestion, IgG and other phagocytosis-stimulating "sauces" such as complement are still referred to as opsonins.

In addition to "buttering" germs for phagocytosis, antibodies prevent disease by neutralizing bacterial toxins, a function that is crucial for example in the body's defense against diphtheria. Another trick up the sleeve of the immune system is the ability of phagocytes to produce their own toxins, reactive oxygen species and nitric oxide, to kill microbial intruders, a process strongly enhanced when microbes are covered with antibodies.

In a paper appearing in the November 28, 2006, issue of the *Proceedings of the National Academy of Sciences* we are now describing yet another aspect of IgG's ability to promote the destruction of foreign particles. When IgG binds to receptors on phagocytes, a signal is transmitted to the cytoplasm that activates the merger of phagosomes with lysosomes. We speculate that

IgG-induced activation of the lysosome/phagosome targeting pathway is particularly important in the defense against microbial intracellular pathogens. Many of these pathogens survive in phagocytes by blocking lysosome/phagosome fusion; examples of public health importance include microbes responsible for tuberculosis, toxoplasmosis, salmonellosis, and chlamydia.

We found that the IgG-induced boost of lysosome/phagosome targeting required the activity of protein kinase C (PKC), an enzyme that had already been shown to mediate other IgG-enhanced processes, such as particle engulfment and generation of microbicidal oxygen species. PKC thus emerges as a central coordinator of IgG-induced stimulation of phagocyte function.

Similar to processes in other parts of the cell, lysosome/phagosome targeting proceeds in three sequential steps referred to as tethering, docking, and fusion. The cytosolic face of phagosomes is topologically equivalent to the plasma membrane where fusion is often regulated in response to extracellular signals. In most cases of regulated exocytosis, influx of calcium ions leads to rapid fusion of already docked vesicles. According to *in vitro* data, the effect of IgG on lysosome/phagosome targeting is different in that the antibodies appear to specifically stimulate the tethering step. Microscopy studies are currently under way to test this conclusion *in vivo*.

Few examples of extracellular signals affecting membrane tethering are known. However, according to a recent paper by Gonzalez and McGraw in the October 2006 issue of *Molecular Biology of the Cell*, insulin promotes the movement of glucose transporters to the surface of adipocytes in part by activating the tethering of transporter-carrying vesicles to the plasma membrane. Whether activation of membrane tethering is a rare phenomenon or a more widespread device remains to be seen.

*Dr. Axel Nohturfft*

ASBMB member Axel Nohturfft is an associate professor in the Department of Molecular and Cellular Biology at Harvard University. After finishing his undergraduate degree at the Free University of Berlin in 1993, Nohturfft moved to Canada, where he spent the early 1990s doing research at the University of Victoria in British Columbia. From there, he immigrated to the United States for a Ph.D. in Biochemistry, which he completed at the University of Texas Southwestern Medical Center in Dallas in 1998. He remained at the University of Texas as a postdoctoral fellow until he accepted a position as assistant professor in the Department of Molecular and Cellular Biology at Harvard University in 2001.

Nohturfft has published more than 20 times and is the recipient of multiple honors and awards, including a 2004 Merck-Wiley Award and a 2002 Searle Scholarship. His professional memberships include the Faculty of 1000. His research focuses on lipid distribution within cells and the mechanisms behind membrane biogenesis, as well as phagocytosis as a real life function of the immune system.

## Letters Continued ...

*Continued from page 2*

ving the biotechnology industry that is a vital part of our economy.

As to the first item—near term benefits to public health—I can think of some concrete examples (for example, yesterday I heard at a seminar that the FDA is working on incorporating research results on genetically based contraindications into labeling of specific drugs), but it might be helpful to have a publicly accessible list of tangible benefits that have derived from NIH- and NSF-funded research. Maybe such a list already exists. Could the ASBMB help in some way with this?

Randy Morse
Chief, Laboratory
of Developmental Genetics
Wadsworth Center, Albany, NY

1. D. Sarewitz, Journal of Health Politics, Policy, and Law, Volume 25, No. 5, October 2000, 988-991.