PERSPECTIVES: IMMUNOLOGY

Catalytic Antibody Bridges Innate and Adaptive Immunity

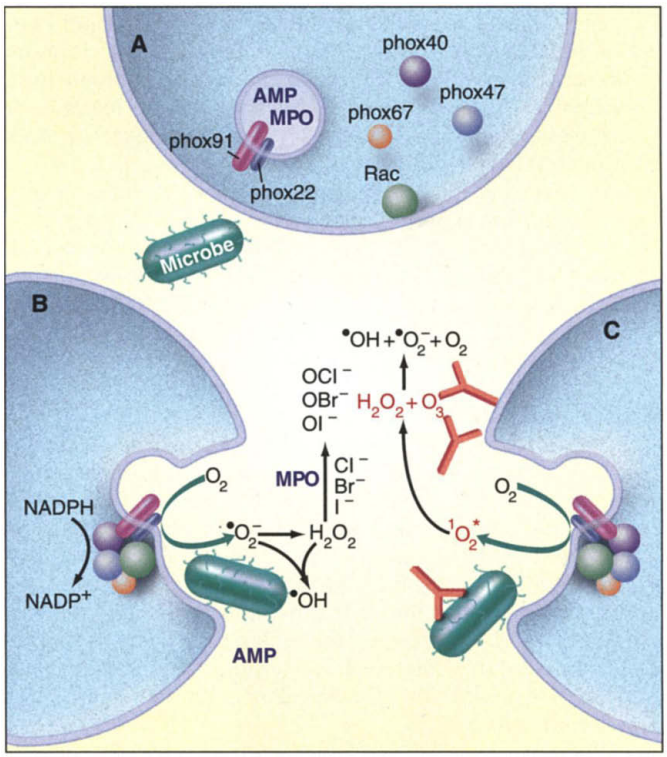
Carl Nathan

Adaptive immunity relies on a huge range of variable antigen receptors expressed on the surface of T and B lymphocytes that detect infected host cells and microbial pathogens. T cells generally cannot kill pathogens directly but instead instruct infected host cells to shut down protein synthesis or commit suicide. B cells respond to antigens by secreting their own antigen receptors as antibodies. Antibodies prevent pathogens from invading host cells and neutralize their toxins. However, when it comes to outright destruction, antibodies call on the innate immune system for help. Antibody, when combined into complexes with antigen, can activate the complement enzyme cascade that disrupts microbial membranes. In addition, antibody forms a bridge between the pathogen and the immunoglobulin receptors (FcRs) of phagocytic cells of the innate immune system (neutrophils and macrophages), triggering ingestion of the pathogen. Destruction of microbes within phagocytes ensues by at least three cooperative processes: production of reactive intermediates of oxygen (ROI) and nitrogen (RNI) (*1*), and exposure to preformed polypeptide antibiotics (*2*). Thus, despite its small invariant set of antigen receptors, the innate immune system deploys most of the chemical processes that directly kill pathogens.

On page 2195 of this issue, Wentworth *et al.* (*3*) breach a conceptual wall separating the innate and adaptive immune system with their discovery of a new way in which antibody contributes to the innate immune system's arsenal. They demonstrate that antibody can kill bacteria by catalytically converting relatively nontoxic ROI supplied by phagocytes into a more toxic form. In effect, antibody acts as a supercharger, taking electronically excited molecular dioxygen (singlet O_2 or $^1O_2$*) that is released by phagocytic cells or generated during inflammation and reacting it with water to generate a mixture of hydrogen peroxide (H_2O_2) and a compound similar to ozone (O_3). O_3 is a powerful oxidant. Moreover, H_2O_2 reacts with O_3 to generate hydroxyl radical ($^{\cdot}OH$), also a potent oxidant. Most cells have enzymes to detoxify superoxide ($^{\cdot}O_2^-$) and H_2O_2. In contrast, no enzymes are known to catabolize O_3 or $^{\cdot}OH$. In reaching these conclusions, Wentworth and his team raise provocative questions about inflammation and autoimmunity and invite a reevaluation of the ways in which phagocytes kill microbes with ROI.

Wentworth, Lerner, and colleagues have already established that antibody molecules can catalyze the production of H_2O_2 from $^1O_2$* (*4*). To produce $^1O_2$*, this group irradiated antibody solutions with ultraviolet light in the presence of a photosensitizer. In their new study, Wentworth *et al.* (*1*) reveal a biological counterpart to the ultraviolet light/photosensitization experiments and add a new player to the story. First, they strengthen earlier controversial findings that activated phagocytes produce $^1O_2$*. Second, they use ingenious heavy-isotope chemistry to demonstrate three biological sources of O_3—antibody that comes into contact with $^1O_2$*, activated phagocytes, and inflamed tissues. These sources may be interrelated; in fact, the investigators postulate that cell-bound antibody molecules are responsible for converting phagocyte-derived $^1O_2$* into H_2O_2 and O_3 (see the figure).

The implications of these findings range as widely as the settings in which antibodies may encounter $^1O_2$*. The consequences may be cytotoxic or may even contribute to signal transduction depending on the amounts of the $^1O_2$* products. For example, if B cells encounter $^1O_2$* released by activated phagocytes, their antigen receptors (antibodies) could catalyze the generation of H_2O_2 + O_3. These products or the $^{\cdot}OH$ radical that is generated from them might damage B cells



ROI production by the neutrophil. **(A)** The resting neutrophil has several classes of specialized lysosomal granules containing myeloperoxidase (MPO) together with about a dozen types of antimicrobial polypeptides (AMP). The membrane of the granules bears two chains of the phagocyte oxidase (phox) complex, phox91 and phox22. The cytosol contains three more components: phox47, phox67, and phox40; a sixth component, the GTPase Rac, lies at the plasma membrane. **(B)** When the neutrophil is activated—for example, upon encounter with a microbial pathogen—its granules fuse with the cell membrane, discharging MPO and AMP into the forming phagosome or extracellular space. The six components of phox unite at the plasma membrane and transfer electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH) in the cytosol to O_2 in the extracytosolic space, forming superoxide ($^{\cdot}O_2^-$). $^{\cdot}O_2^-$ dismutates to hydrogen peroxide (H_2O_2), which interacts with $^{\cdot}O_2^-$ to form hydroxyl radical ($^{\cdot}OH$). MPO catalyzes the H_2O_2-dependent oxidation of ambient halides to hypohalites. **(C)** Wentworth *et al.* (*3*) propose additional reactions catalyzed by antibody (Y-shape). Antibody is either free in the extracellular fluid, or attached nonspecifically to the neutrophil, or attached specifically to the microbial pathogen. Phox produces singlet oxygen ($^1O_2$*), perhaps indirectly by way of MPO. Antibody catalyzes the conversion of $^1O_2$* to H_2O_2 and the reactive species ozone (O_3). H_2O_2 + O_3 can react to produce the $^{\cdot}OH$ radical. (Not all reactants and products are shown, and stoichiometry is not indicated.)

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or even cause oncogenic mutations. Immunoglobulin E (IgE) is a class of antibody that binds to cells antigen-nonspecifically via specialized receptors (FcεRs) on mast cells, basophils, eosinophils, and monocytes. Cross-linking of IgE triggers production of ROI, which help to mediate the release of the inflammatory mediators histamine and eicosanoids (*5*). Perhaps IgE contributes further to mast cell activation by catalyzing formation of more potent oxidants. Furthermore, cells can bear antibody molecules when antibody is directed against an antigen on the cell surface, as in some forms of autoimmunity and immunotherapy. For example, patients with rheumatoid arthritis or an inflammatory bowel disorder called Crohn's disease may benefit from injection of antibodies against the cytokine tumor necrosis factor (TNF); those with rheumatoid arthritis may also benefit from injection of soluble TNF receptors. It is assumed that both reagents work by neutralizing TNF. However, TNF-specific antibody may also bind to activated macrophages, mast cells, and T cells that express TNF on their surface (*6*). Antibodies against leukocyte surface molecules can trigger production of ROI. Then, cell-bound antibody might convert these ROI into toxic forms, injuring the cells to which the antibody is attached and ameliorating inflammatory disease.

Immune complex disorders are also settings in which antibody is brought into proximity with $^1O_2$*. For example, antigen-antibody complexes can accumulate in the glomeruli of the kidney and fix complement, attracting and activating phagocytes. In rheumatoid arthritis, affected joints contain rheumatoid factor, an antigen-antibody complex in which the antigen is itself antibody. The rheumatoid joint also holds large numbers of neutrophils that respond to TNF by releasing copious ROI (*7*). Rheumatoid factor may catalyze the conversion of these ROI to forms that inactivate protease inhibitors and damage the joint.

Finally, nonphagocytic cells produce ROI as second messengers in mitogenic and other signaling reactions. These reactions are mediated in part by a family of enzymes (NOXs) that includes the phagocyte oxidase (phox) responsible for ROI production by the innate immune system (*8*). Autoantibodies, therapeutic antibodies, and immune complexes may thus encounter $^1O_2$* produced by diverse cell types.

Like most discoveries, the Wentworth *et al.* (*3*) work leaves critical questions open for future investigation. The receptors for antibody (FcRs) expressed by neutrophils are not thought to retain antibody in the absence of antigen. Thus, the display of nonspecific antibody on the neutrophil surface suggested by the Wentworth *et al.* study requires explanation. The extent to which cell-bound antibody contributes to O_3 production by phagocytes or to their antibacterial activity has not yet been tested. The quantitative dependence of microbial killing on H_2O_2 + O_3 has not been defined or compared with the amounts of those products produced by antibody or by phagocytes with and without phagocyte-bound, bacteria-bound, or soluble antibody. It is not clear whether production of O_3 leads to more ·OH radical than phagocytes might form by other routes, such as the reaction of H_2O_2 with $·O_2^-$ (see the figure) or with ferrous or cuprous ions.

ENZYMATIC GENERATION OF PHYSIOLOGICALLY IMPORTANT GASES IN MAMMALS

Gas	Enzyme	Functions
$·O_2^-$	Phox, other NOXs	Killing; signaling (*8*)
·NO	NOX synthases	Killing; signaling (*1*)
CO	Heme oxygenase	Signaling (*12*)
O_3	Antibody	Killing (*3*); signaling?

The study by Wentworth *et al.* opens a new chapter in the book on the phagocyte oxidase, phox. The importance of phox in host defense is clear, because people genetically deficient in this enzyme are highly susceptible to infection (*9*). An even wider role for phox is revealed when a partially compensating enzyme, nitric oxide synthase–2, is also absent (*10*). Some have argued that phox acts indirectly to activate antibacterial proteases (*11*). That conclusion was based on the inefficiency of relatively stable phox products as antibacterial agents when tested in isolation. The Wentworth *et al.* findings remind us that it can be misleading to analyze the antibacterial efficacy of single, relatively stable phox products. Instead, the more evanescent products are the most powerful killers and arise from interactions among ROI. Now, the interacting products include a newcomer, O_3, that kills by itself and offers a facile route to ·OH production. Perhaps we will come to regard the antibody molecule as the seventh component of the phox complex (see the figure), as well as the fourth mammalian enzyme shown to produce a functionally important gas (see the table).

References and Notes

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PERSPECTIVES: ULTRACOLD MATTER

The Quest for Superfluidity in Fermi Gases

Lev Pitaevskii and Sandro Stringari

Over the past decade, studies of ultracold atomic gas clouds have yielded unprecedented insights into the quantum statistical properties of matter. Most studies have focused on boson gases. On page 2179 of this issue, O'Hara *et al.* (*1*) report an ultracold Fermi gas that may provide a test bed for new theories of Fermi systems, from high-temperature superconductors to neutron stars.

The elementary constituents of matter can be divided into fermions and bosons. Fermions are particles whose intrinsic angular momentum (or spin) is an odd multiple of $\hbar/2$, where $\hbar$ is the Planck constant divided by 2π. In contrast, the angular momentum of bosons is an even multiple of $\hbar/2$. The dramatically different thermodynamic properties of fermions and bosons at low temperature are a direct result of quantum statistical effects.

The fundamental constituents of atoms (electrons, neutrons, and protons) are

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