TEXT SUPPLEMENT (Ch 5): Complement

Evolution of antibodies and complement. One of Michael Behe's claims is that antibody function is irreducibly complex and could not have evolved piecemeal. Antibodies are soluble proteins that are part of the immune system of vertebrates. The antibodies attach to disease-causing bacteria and reduce their harmfulness in a number of different ways described further in Chapter 15. Antibodies vary significantly in shape and each is effective against a particular type of bacteria. Fortunately, the number of possible antibody shapes is very large (in the hundreds of billions) because the genes that code for antibodies have the unusual ability to rearrange themselves by cutting out different portions of their DNA each time, thus multiplying greatly the number of possible protein sequences (and thus antibody shapes) produced. How, asks Behe, could this system ever have evolved by natural selection?

Behe claimed that antibody function is irreducibly complex. However, immunologists have shown that many parts of this system function independently of the rest, and so could have evolved piecemeal. In fact, the comparative study of immunology shows that many species survive quite well with only parts of the complete system, and that antibody function did indeed evolve step by step. For example, DNA recombination and splicing gives us the ability to produce many different kinds of antibodies that can combine with different bacterial molecules, and this splicing is accomplished by an enzyme that appears in backboned animals (vertebrates). Thus, a very large change in capability was acquired by the emergence of one enzyme. Animals other than vertebrates have proteins very similar to basic antibody molecules, and these proteins are useful for other reasons, for example, as molecules that hold cells together. Thus, if we allow for changes in function, molecules that hold on to other cells within the body could well have evolved into antibodies that hold on to bacteria and incapacitate them. Natural selection certainly favors such changes.

In addition to their ability to bind to many different bacterial molecules, antibodies come in different types that show clear evolutionary patterns. Cartilaginous fishes, including sharks, have only the immunoglobin M (IgM) type; reptiles and amphibians have IgM and another variant called IgG. Bird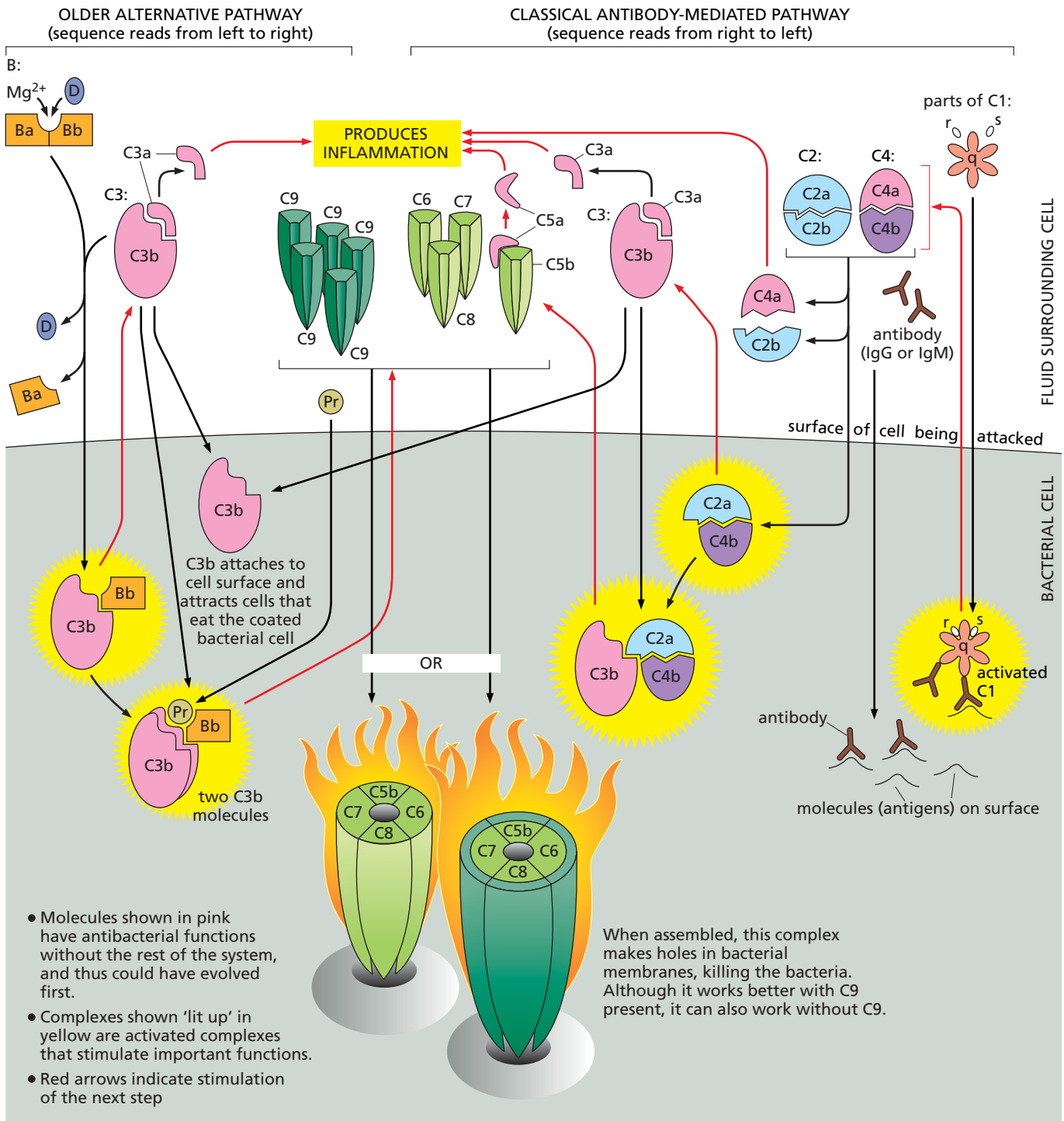s have IgM, IgG, and a third type called IgA. Finally, mammals have IgE in addition to the three earlier types. Each type is a variant on the molecular theme, not a completely new type of molecule. In other words, each was the result of a gene duplication and mutation in the DNA, and each remained in the population because each offered an additional immune capability not afforded by the others. Scientists use comparative genomics (Chapter 4) to trace the molecular evolution of antibody molecules in many species.

Any protein that could immobilize any invading bacteria would be an asset to the organism and would be favored by natural selection, meaning that individuals having such a protein would more often live (and pass on to future generations the ability to make such a protein), while individuals not having such a protein would more often be killed and so would not pass on their genes. The system would not need to be perfect at first, or even very good—just a small benefit that worked against only a few types of bacteria would be favored by natural selection. Once such a system was in place, any improvement in its effectiveness would be favored by natural selection. First of all, natural selection would favor any increase in the number of different bacterial substances recognized. Second, natural selection would also favor a more effective attack on, or immobilization of, the bacteria once they are recognized, and any gradual improvement in the system would be passed on to future generations. As is the case of evolved systems, this one is far from perfect—there are many bacteria and other pathogens that are not recognized (they do not provoke an immune response), and the system sometimes attacks the body's own cells (in so-called autoimmune diseases). A system designed by an omnipotent and intelligent designer could certainly work better than this, with more efficiency and fewer errors.

One of the many ways in which antibodies work is to activate a series of proteins called 'complement.' Through a 'cascade' of biochemical reactions, one protein in the series activates another until a complex is assembled that punctures a hole in bacterial cell membranes, then inserts itself into the membrane, forming a tube through which water can flow into the bacteria until it bursts and dies. The activation of this hole-punching mechanism is shown in the figure opposite.

Behe claims that this system is 'irreducibly complex' because the entire series of proteins must be present before the system can work, no part being able to function without the rest. On the contrary, many species are known in which only parts of this entire system are present. For example, one pathway of complement activation (the alternative pathway in the figure opposite) does not require antibodies, and this pathway exists in such non-vertebrate animals as arthropods (including insects, spiders, and crabs). Now, any change that enhanced the ability of complement to kill the bacteria or render it ineffective would surely be favored by natural selection because any individual that had such an ability would be more likely to survive and pass on its ability to future generations. Thus, the evolution of antibodies among vertebrates was favored as an additional way of activating the complement proteins, and a new pathway was added to the existing pathway. Antibodies also enabled vertebrates to distinguish among different bacterial types, and to respond more rapidly and more potently against bacteria that a particular organism had encountered before.

Also arguing against intelligent design is the fact that there are several redundant systems within the complement cascade. The earlier a protein is in the cascade, the more other functions it has. Therefore, even if the rest of the cascade were not present, the portion still has an immune function. For example, the activated C1 protein can also coat bacteria and make them more able to be 'eaten' and killed by cells of the immune system called phagocytic cells. Such cells exist even in starfishes (phylum Echinodermata), but they become more efficient with the evolution of complement proteins. In humans, genetic deletions of each of the complement poteins are known, and the effects of deletion range from almost no effect (for protein C9) to a large increase in the probability of infectious disease (for protein C3). Thus, the cascade could evolve piecemeal, with each useful mutation leading to the addition of a new molecule that increased the fitness of the organisms possessing it. Any new protein that further inactivated or debilitated invading bacteria would befavored by selection, as would any protein that increased the body's production of an antibacterial protein by any means.

OLDER ALTERNATIVE PATHWAY
(sequence reads from left to right)

CLASSICAL ANTIBODY-MEDIATED PATHWAY
(sequence reads from right to left)

B:

Mg²⁺ — (D)

Ba Bb

C3a

C3:

C3b

(D)

Ba

PRODUCES INFLAMMATION

C9 C9 C9

C6 C7

C5a

C5b

C8

C9

C9

(Pr)

C3a

C3:

C3b

C3a

C2:

C2a

C2b

C4:

C4a

C4b

parts of C1:

r   s
q

C4a

C2b

antibody
(IgG or IgM)

FLUID SURROUNDING CELL

surface of cell being attacked

BACTERIAL CELL

C3b

C3b attaches to
cell surface and
attracts cells that
eat the coated
bacterial cell

Bb

C3b

(Pr) Bb

C3b

two C3b
molecules

OR

C5b
C7   C6
C8

C5b
C7   C6
C8

C2a

C4b

C2a

C3b   C4b

r   s
q

activated
C1

antibody

molecules (antigens) on surface

• Molecules shown in pink
  have antibacterial functions
  without the rest of the system,
  and thus could have evolved
  first.
• Complexes shown 'lit up' in
  yellow are activated complexes
  that stimulate important functions.
• Red arrows indicate stimulation
  of the next step

When assembled, this complex
makes holes in bacterial
membranes, killing the bacteria.
Although it works better with C9
present, it can also work without C9.

The mechanisms by which the various 'complement' proteins protect against bacteria. Although the entire system is complex, many parts are functional by themselves and could therefore have evolved one at a time.