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GUEST COMMENTARY

Antibody-Mediated Immunity against Intracellular Pathogens: Two-Dimensional Thinking Comes Full Circle

Arturo Casadevall*

Departments of Medicine and Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York 10461

The view that antibody-mediated immunity against many prokaryotic and eukaryotic intracellular pathogens is not important was popular until recently (6). The concept of a division of labor whereby antibody-mediated immunity protected against extracellular pathogens and cell-mediated immunity protected against intracellular pathogens may have had its intellectual origins in the great debate between the advocates of humoral and cellular immunity at the turn of the 20th century. The humoralists, championed by Paul Ehrlich, viewed immunity as being conferred by soluble substances in the blood and the generation of an effective antibody response, with phagocytic cells functioning primarily to clean up microbial debris (42). The cellularists, championed by Elie Metchnikoff, viewed immunity as being conferred by macrophages and other phagocytic cells, with the role of humoral factors being to provide opsonins (42). This debate was fueled by the success and difficulties associated with demonstrating antibody-mediated protection against certain pathogens in passive immunization studies. Administration of immune serum protected against toxin-mediated diseases such as tetanus and diphtheria and a certain subset of bacterial pathogens exemplified by the organisms now known as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. However, passive immunization provided little or no protection against other microbes such as *Mycobacterium tuberculosis* (reviewed in reference 19).

By the 1960s, classical studies with facultative intracellular pathogens such as *Listeria monocytogenes* had shown that effective control of infection depended on cellular immunity, as manifested by granuloma formation and participation of T lymphocytes (28). The microbes for which passive antibody was not protective and cell-mediated immunity appeared to be paramount for host defense were often facultative intracellular pathogens. This association gave credence to the concept of an immunological division of labor whereby humoral and cellular immunity provided effective control for extracellular and intracellular pathogens, respectively (3, 8, 28). Furthermore, this division of labor was conceptually consistent with a large body of experimental observations that indicated an inverse and mutually antagonistic relationship between humoral and cellular immunity (35). In recent years, the view that antibody-mediated immunity protects against extracellular pathogens and cell-mediated immunity protects against intracellular pathogens has been modified and extended by the Th1/Th2 paradigm, which posits a division of labor at the level of T-cell differentiation. According to this view, Th1-polarized responses result in granulomatous inflammation that effectively controls intracellular pathogens, whereas Th2-polarized responses result in the production of antibodies that control extracellular pathogens and parasites.

The fact that a microbe inside a cell is separated from serum antibody has contributed to the belief that serum antibody cannot be effective against an intracellular pathogen. However, the two-dimensional separation and categorization of microbes as either intracellular and extracellular pathogens was never absolute, since tissue examination often revealed that pathogens classified as intracellular could be found in the extracellular space and vice versa. Furthermore, at some point in the infectious cycle, most intracellular pathogens reside in the extracellular space, where they are vulnerable to antibody action, and Fc receptor cross-linking can have profound effects in the intracellular milieu through signal transduction.

In this issue of *Infection and Immunity*, we have an example of how the investigation of mechanisms by which passive antibody protects against the obligate intracellular pathogen *Ehrlichia chaffensis* led to the discovery of an extracellular phase that may include replication (27). Hence, the wheel has turned full circle, since an investigation to explain how antibody protects against an obligate intracellular pathogen has revealed that it may not always reside in the intracellular space and thus could become accessible to serum antibody.

DECONSTRUCTING A PARADIGM

The notion of an immunological duality whereby immunity to intracellular pathogens is conferred by cell-mediated mechanisms and immunity to extracellular pathogens is conferred by antibody-mediated mechanisms was a reigning paradigm in the closing decades of the 20th century and still has wide credence. However, this view is problematic because it is not universally applicable to all pathogens and because the induction of antibody mediated-immunity is sufficient to prevent infection with some intracellular pathogens. For example, the major childhood viral diseases and smallpox were drastically reduced in incidence or eradicated by vaccines that elicited antibody-mediated immunity despite the fact that all viruses are obligate intracellular pathogens. For some intracellular bacterial pathogens, such as *Salmonella enterica* serovar Typhimurium, it was

* Mailing address: Dept. of Medicine, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461. Phone: (718) 430-4259. Fax: (718) 430-4259. E-mail: casadeva@aecom.yu.edu.

TABLE 1. Prokaryotic and eukaryotic intracellular pathogens for which antibody has been shown to modify the course of infection to the benefit of the host[a]

Pathogen	Reference(s)
Bartonella grahamii	24
Brucella spp.	2, 15
Chlamydia trachomatis	34, 36
Cryptococcus neoformans	9, 17, 32, 40
Erhlichia chaffeensis	23, 26, 27, 47
Francisella tularensis	18
Histoplasma capsulatum	Nosanchuk et al., abstract
Legionella pneumophila	4, 14
Leishmania mexicana	1
Listeria monocytogenes	11
Mycobacterium tuberculosis	37, 45
Salmonella enterica Serovar Typhimurium	13
Shigella flexneri	38
Toxoplasma gondii	22, 41

[a] The references cited are not a complete list of citations supporting a role for antibody-mediated immunity.

clear that antibody responses were protective in certain hosts (13). The concept of an immunological division of labor based on whether or not a microbe assumed intracellular residence defied the common-sense view that the most effective immune response was one that combined both humoral and cellular components.

Perhaps the most important advance in suggesting a resolution to the cellular versus humoral controversy was the application of hybridoma technology to investigate the potential of antibody-mediated immunity against certain pathogens for which immune serum did not manifest efficacy. In contrast to immune serum, which varied greatly in the composition, isotype, and specificity of microbe-binding antibodies, monoclonal antibodies provided a homogenous preparation or defined reagents with which to investigate the variables that contributed to antibody-mediated protection. Studies with monoclonal antibodies have now demonstrated passive protection for several microbes where experiments with immune serum had provided negative or inconsistent results, including *Candida albicans* (20), *Cryptococcus neoformans* (9, 17, 32, 40), *Listeria monocytogenes* (11), *Leishmania mexicana* (1), *Mycobacterium tuberculosis* (45), and *Histoplasma capsulatum* (J. D. Nosanchuk, A. Casadevall, and G. Deepe, Abstr. Annu. Meet. Am. Soc. Microbiol., 2001, abstr. F-143). For these pathogens, the identification of protective monoclonal antibodies established the precedent that antibody could be effective and dispelled the notion that humoral immunity was ineffective due to an inherent limitation in the activity of this arm of the immune system. The list of intracellular pathogens for which antibody has been shown to modify the course of infection to the benefit of the host is extensive (Table 1).

INTERPRETATION OF NEGATIVE RESULTS

A central argument for the concept that antibody lacked efficacy against certain intracellular microbes was the observation that transfer of immune serum was not protective in animal models of infection. In fact, Mackaness proposed six criteria for establishing the importance of cellular immunity, of which the first one stated that "there should be no evidence that protection can be conferred by passive transfer of antibody alone" (29). However, the absence of demonstrable protection in passive antibody experiments does not mean that antibody has no role in protection, since this conclusion cannot be made from a negative experimental result. In recent years, studies with monoclonal antibodies to *Cryptococcus neoformans* and other pathogens have provided several insights as to why passive antibody experiments can produce negative results even when protective antibodies exist and protective antibody responses are possible.

A dramatic example of the limitations of passive antibody transfer experiments is provided by the observation that transfer of either too little or too much antibody can result in no protection. In 1987, Dromer et al. generated a protective immunoglobulin G1 (IgG1) monoclonal antibody to *Cryptococcus neoformans* and demonstrated that a certain amount of immunoglobulin was necessary to observe protection in a murine model of cryptococcosis (9). This observation suggested that the inability to protect with immune serum may have been a consequence of inadequate amounts of protective antibody. Similarly, it was noted that a monoclonal antibody to listeriolysin O was protective against *Listeria monocytogenes* if administered in large doses but that antibodies with that specificity were not common in immune serum (11). More recently, my group has shown prozone-like effects with protective IgM and IgG, such that the administration of large amounts of immunoglobulin can result in reduced or abolished protective effects (43, 44). Consequently, too much or too little antibody can yield a negative result in a passive protection experiment despite the fact that antibody can be protective against the relevant pathogen.

Apart from antibody amount, immunoglobulin-related variables such as antibody specificity (31), isotype (49), and idiotype (39) can have profound effects on antibody protective efficacy. However, host-related variables can also determine the outcome of passive protection experiments. For example, the protective efficacy of passive antibody to *Salmonella enterica* serovar Typhimurium is dependent on the mouse strain used (13). For some pathogens, the efficacy of passive antibody is dependent on the presence of intact cellular immunity (48). Adding to the uncertainty associated with negative results in passive transfer experiments is the observation that antibody efficacy can depend on the microbial strain used despite the presence of the target antigen (33).

Clearly, negative results in passive protection experiments do not exclude the existence of protective antibodies. Conversely, the discovery that it is possible to make protective monoclonal antibodies against several intracellular pathogens does not necessarily imply that antibody immunity plays a major role in natural resistance, since the antibodies that mediate protection may be absent or rare in the immune response to natural infection. Experimental variables that can lead to a negative result in passive protection experiments are listed in Table 2.

LESSON FROM *ERHLICHIA CHAFFEENSIS*

The obligate intracellular bacterium *Ehrlichia chaffensis* is the causative agent of human monocytic ehrlichiosis. Accord-

TABLE 2. Outcome of antibody protection experiments is dependent on multiple independent variables

Variable	Parameter	Problem/example
Antibody	Amount	
	Too little	Insufficient amounts of antibody in immune serum can translate into lack of protective efficacy; studies show that a defined amount of antibody is necessary for protection against *C. neoformans* (9) and *L.nocytogenes* (11)
	Too much	Administration of large amount of specific antibody can produce a prozone-like effect whereby more antibody is less protective than less antibody; this phenomenon has been described for polyclonal antibody preparations for *S. pneumoniae* and *C. neoformans* (43, 44). For *C. neoformans*, the mechanism may reflect interference with host killing mechanisms and/or alterations in cytokine response
	Affinity/avidity	Higher-affinity antibodies can be more effective against certain pathogens; however, the relationship between affinity and protective efficacy is poorly understood for most pathogens; for *E. chaffensis*, higher affinity correlated with protective efficacy (26); for *S. pneumonia* avidity is an important parameter of antibody efficacy (46).
	Specificity	Reactivity with targeted antigen is a necessary but insufficient criterion for a protective antibody; two IgM antibodies with specificity for capsular glucuronoxylomannan differ in fine specificity with one being protective and the other nonprotective (31)
	Isotype	Effector function of antibodies can depend on isotype; the efficacy of passive antibody for *C. neoformans* and *E. chaffensis* is highly dependent on antibody isotype (26, 49)
	Idiotype	Protective human antibodies to encapsulated pathogens employ certain variable region genes (reviewed in reference 39)
	Preparation	Immune serum is a polyclonal preparation that includes antibodies to multiple specificities and isotypes; consequently, polyclonal sera may contain blocking antibodies (21) and antibodies to other specificities that can affect the of infection; monoclonal antibodies represent one specificity and one isotype
Host	Genetic background	Passive antibody efficacy depends on mouse strain for *L. pneumophila* (13) and *C. neoformans* (10)
	Immune competency	For some pathogens, passive antibody efficacy requires a competent cell-mediated immune system (48)
Model	Timing	Demonstrating the efficacy of passive antibody is easier if antibody is given before or shortly after experimental infection (7)
	Route of infection	Efficacy of passive antibody can vary depending on the route of infection (5)
	Efficacy	Usual parameters of antibody efficacy are survival and reduction in organ burden, but these do not necessarily respond in parallel; for *C. neoformans* (16) and *M. tuberculosis* (45), administration of antibody prolongs survival without reducing organ colony counts
Microbe	Genetic background	Some strains are more susceptible to antibody than others; an antibody to *C. neoformans* demonstrated highly variable efficacy against genetically different strains despite reactivity with the polysaccharide capsule (33)
	Inoculum	Magnitude of the infecting inoculum is a critical variable in antibody protection studies (7, 44)

ing to the immunological division of labor discussed above, host protection against *E. chaffensis* would have been expected to be conferred exclusively by cell-mediated immune mechanisms. However, there was evidence that specific antibody could mediate protection against *Erhlichia* spp. (23), possibly by blocking cellular entry or promoting the expression of proinflammatory cytokines (25, 30). Studies by Winslow and colleagues subsequently established that specific antibody could protect against *E. chaffensis* in both normal and SCID mice (47). That result was surprising because it might have been anticipated that cell-mediated immunity would play a major role in promoting antibody efficacy against an intracellular pathogen, as was shown for *Cryptococcus neoformans* (48).

The efficacy of passive antibody against *E. chaffensis* in SCID mice suggests that antibody-mediated protection was independent of T cells and implied that other mechanisms must be operative. In pursuit of that question, Li and Winslow now describe an extracellular phase for *E. chaffensis* during which the bacteria are potentially susceptible to serum antibody (27). Although it has not been proven that antibody-mediated protection against *E. chaffensis* occurs in the extracellular phase, this observation suggests a mechanism that is fundamentally different from that reported for *Listeria monocytogenes* (12), where antibody is active intracellularly. Ironically, the finding that *E. chaffensis* has an extracellular phase that is presumably susceptible to serum antibody is consistent with the older view that antibodies are active only against extracellular microbes. Nonetheless, antibody may be effective against *E. chaffensis* when a threshold portion of the microbial pool is extracellular and accessible to antibody. This discovery suggests that other obligate intracellular pathogens may also have extracellular phases during which they are susceptible to humoral immunity. This elegant study illustrates the connectivity of scientific thought in that pursuing an explanation for an observation that defied one paradigm led to findings that undermined another and, in so doing, provided new insights into microbial pathogenesis and immunology.

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