The Damage–Response Framework as a Tool for the Physician-Scientist to Understand the Pathogenesis of Infectious Diseases

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The Damage–Response Framework (DRF) is a powerful tool to inform research in infectious diseases. It can integrate clinical observation with microbiology and immunology to incorporate the role of the host response into the outcome of microbial pathogenesis. Although the role that microbial factors may play in the pathogenesis of infectious diseases is well recognized, the DRF brings the indispensable role of the host response to the fore. For example, inflammation may induce microbial control, but it can also produce host damage. On the other hand, insufficient inflammation may fail to induce sufficient microbial control. Each scenario may lead to the diagnosis of an infectious disease. Given the central role that the host response plays in the pathogenesis of infectious diseases, new strategies for treatment need to consider the nature of the host response as well as microbial factors.

Keywords. damage–response framework; host; microbe; inflammation; infectious diseases; microbial pathogenesis.

The Damage–Response Framework (DRF) is an integrated theory that views microbial pathogenesis as an outcome of host–microbe interaction [1]. Formulated in 1999, the DRF first served as an educational tool for the inaugural microbial pathogenesis course at Albert Einstein College of Medicine, for which we were course leaders. Although we were invited to teach the course because we were scientists, it was our experiences as infectious diseases physicians that convinced us of the need for an integrated theory of microbial pathogenesis. At that time (the 1990s), the human immunodeficiency virus (HIV)/AIDS pandemic raged in New York City. Many of our patients were terminally ill with cryptococcosis, toxoplasmosis, and pneumocystis pneumonia, diseases never before seen in such a large number of patients. Equally as vexing was a marked increase in cases of disease with Candida albicans and Staphylococcus epidermidis, microbes only rarely considered pathogens during our infectious diseases training. Available concepts of microbial pathogenesis and virulence simply could not explain how such microbes could cause disease in some patients, but not others, or how so many rare infectious diseases could suddenly emerge. In an attempt to define pathogenic microbes based on the hosts in whom they caused disease, the terms “opportunistic” and “primary” pathogen were used. For example, Candida albicans was opportunistic in patients with AIDS and a primary pathogen in normal women with vaginitis. However, this was futile and imprecise because the same microbe required different terms for different hosts and the terms did not account for host variables that affect susceptibility [1, 2]. Thus, the microbial pathogenesis field lacked an integrated theory that could account for the role that the host plays in the outcome of infection.

MICROBIAL PATHOGENESIS: THE VIEW FROM THE CLINIC

As we pondered available theories of microbial pathogenesis, we realized they viewed disease causality as a singular event, due either to the microbe or the host. On the microbial side, the view was that microbes were disease perpetrators with virulence factors that acted upon the host to cause disease. This concept led to a substantial scientific effort to identify such factors, although singular factors able to cause disease universally were not found for many microbes. On the host side, immune impairment was viewed as rendering the host vulnerable to microbes that only cause disease in the setting of immune defects (eg, opportunistic pathogens). Although these views were able to explain certain diseases in certain patients, they could not explain others [3]. As we reviewed our own experiences from the lenses of infectious diseases physicians and scientists, we realized that the state of disease was actually only 1 possible outcome of host–microbe interaction. Other important outcomes were the microbial states of colonization, latency, and commensalism. It was also difficult to reconcile the occurrence of disease with commensal microbes such as Candida and Staphylococcus spp. with existing concepts. As clinicians, we realized that patients changed, because they acquired HIV/AIDS, or because they had an indwelling catheter, or because...
they were receiving broad-spectrum antibiotics or immunosuppressive drugs, or because their environment changed [4]. As scientists, we realized that microbes changed too, because they acquired resistance from antibiotic use and misuse, or because their habitat or environment changed. Our knowledge as physician-scientists led us to recognize that, together, patient and microbial change resulted in the emergence of new diseases and unsuspected outcomes of infection, highlighting that microbial virulence requires a susceptible host and is not a stable or singular microbial trait [3, 5, 6].

COPING WITH CHANGE: THE INTERSECTION OF CLINICAL MEDICINE AND BASIC SCIENCE THROUGH THE LENS OF THE DAMAGE-RESPONSE FRAMEWORK

The recognition that patients and microbes could change led to the inevitable conclusion that the outcome of their interaction could change too. Given that not everyone who acquires a microbe gets sick and the state that ensues after infection can vary among patients or within the same patient over time, we reasoned that the common denominator of host–microbe interaction and most relevant factor to assess its outcome should be host damage. This led us to put forth the following DRF tenets, which we view as incontrovertible: (1) microbial pathogenesis is 1 outcome of an interaction between a host and a microbe; (2) the host-relevant outcome of host–microbe interaction is host damage; (3) host damage can stem from microbial factors, host factors, or both. These tenets made it possible to account for the host and the microbe in the pathogenesis of infectious diseases.

THE PARABOLA: INTEGRATING THE HOST INTO THE OUTCOME OF MICROBIAL PATHOGENESIS

The final piece of the DRF came from the insight that there existed a parabolic relationship between host damage and the host response. In this formulation, host–microbe interaction is represented by a point on the parabola corresponding to a certain amount of damage on the Y-axis as a function of the immune response on the X-axis, ranging from weak on the left to strong on the right (Figure 1). The left-hand side of the parabola fit well with the clinical observation that some people are vulnerable to certain infectious diseases because of weak immunity, whereby an inability to control microbial growth may lead to host damage. The right-hand side of the parabola fit with the concept that some infectious diseases, such as toxic shock syndrome and dengue hemorrhagic fever, can be the result of strong, often excessive, immune responses.

THE RIGHT-HAND SIDE OF THE PARABOLA: THE INFLAMMATORY RESPONSE AND INFECTIOUS DISEASES PATHOGENESIS

When the DRF was put forth in 1999, many known examples of inflammation-induced host damage were postinfectious, such as rheumatic heart disease, Reiter’s syndrome, mediastinal fibrosis, and malignancy due to Epstein-Barr virus or herpes simplex virus [1]. The occurrence of severe acute respiratory syndrome (SARS) in 2003 was a transformative moment for the DRF. Clinical and experimental data demonstrated that the immune response to the SARS coronavirus contributed to the severity of this disease. Severe acute respiratory syndrome occurred in young, previously healthy persons. This suggested that the pathogenesis of this syndrome differed from viral diseases that occur in infants and the elderly with weak immunity. The disease process in young persons with SARS was marked by intense pulmonary inflammation and hemorrhage due to immunological damage [7]. This echoed the retrospective discovery that the 1918 influenza virus elicited inflammatory damage [8, 9] and underscores the importance of recognizing the right-hand side of the parabola in clinical practice. For example, cytokine storm plays a central role in the pathogenesis of influenza, dengue, Ebola, and malaria [10–14] and in inflammation-enhanced mortality of young people with pandemic influenza [15]. The right-hand side of the parabola may also provide an explanation for reduced efficacy and greater risk of severe dengue in younger dengue-naive vaccine recipients [16, 17].

FINDING A PLACE ON THE CURVE

Recognition of the importance of inflammation and immunologically mediated damage in the pathogenesis of infectious diseases has led to calls for the use of agents that reduce

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**Figure 1.** The Damage–Response Framework parabola. Host benefit or host damage are plotted on the Y-axis as a function of the host immune response, ranging from weak to strong, on the X-axis. The outcomes of infection represented by the states of commensalism, colonization, latency, and disease are depicted as a function of damage on the Y-axis. The states of commensalism, colonization, and latency can transition to the state of disease due to host or microbial factors [1, 3, 4]. Examples of microbial factors and host factors that can cause host damage are shown.
the inflammatory response in clinical management [18–20]. Although this is a rational suggestion, adjunctive use of anti-inflammatory agents to reduce or proinflammatory agents to augment the immune response has not been reliable or predictably successful. This is because immunotherapy is unlikely to be effective without knowing where on the DRF parabola an individual patient lies. For example, immune adjuvants, such as interferon γ [21], or immunosuppressants, such as corticosteroids [22], did not reliably alter the course of, respectively, HIV- or immune reconstitution inflammatory syndrome (IRIS)–associated cryptococcosis. Steroids may be detrimental in the setting of insufficient fungal control, whereas they may be beneficial in the setting of insufficient control of inflammation. On the other hand, immune adjuvants that augment fungal clearance may enhance inflammation.

The very idea of using corticosteroids in cryptococcal disease reflects a 180-degree change in thinking. The 1999 view was that Cryptococcus neoformans could only cause damage in the setting of weak immunity, whereas the 2017 view is that it can also cause damage in the setting of a strong immune response [23]. Recognition of the latter was driven by clinical observations that antiretroviral therapy initiation in patients with AIDS [24] and antifungal therapy in some patients with solid organ transplants [25] could trigger IRIS-associated cryptococcosis [26], and cryptococcosis in previously normal patients may be associated with aberrant inflammation [27]. This exemplifies the need for immunotherapy to enhance or diminish the immune response to reduce damage as needed in each patient. Unfortunately, this is not currently possible because clinicians do not have readily available data to help them know the kind of damage control their patient needs.

The DRF has the potential to provide clinicians tools to determine whether a patient needs therapy to enhance or to reduce their inflammatory response. This will require scientific advances, such as more robust and complex measures of damage, ways to quantify host damage as a function of the host response, and more robust and complex measures of microbial states. There is also a need to find ways to integrate these measures in clinical practice to correlate clinical states with measures of damage. This will make it possible to develop and select therapies that will move the patient to an appropriate damage-reducing point on the parabola (Figure 2). Although development of measures to place patients on the parabola seems like a daunting task, new platforms may hold promise. For example, machine-learning approaches that incorporate clinical information with host and microbial measures may identify biological surrogates of clinical states of diseases, as described for malaria [28]. Electronic health records and big data platforms that can integrate genetic, immunologic, clinical, microbial, and environmental variables also hold promise as tools to integrate patient and microbial characteristics and identify measures that correlate with defined clinical and microbial states. Even today, clinical parameters, fungal burden, immunologic measures, and cytokine perturbations that correlate with HIV-associated cryptococcosis [29–33] may provide insight into where a patient may lie on the parabola.

**A DAMAGE–RESPONSE FRAMEWORK–INFORMED APPROACH TO COMBATING INFLAMMATION**

Calls to use anti-inflammatory agents, including statins, to dampen the inflammatory response in treatment of influenza, pneumonia, and Ebola [19, 34–37] highlight the central role that the right-hand side of the DRF parabola plays in the pathogenesis of infectious diseases. However, statins may dampen the inflammatory response to influenza vaccine [38, 39] and have other untoward effects. Thus, like corticosteroid therapy in IRIS-associated cryptococcal disease, meningitis, or pneumonia, the anti-inflammatory effect of statins may impede microbial clearance to the detriment of the patient. Thus, it will continue to be difficult to use broad-spectrum or nonspecific anti-inflammatory agents, such as steroids, statins, or cytokine inhibitors, without the ability to place patients on the DRF parabola.

In contrast with nonspecific immune modulators, antibodies are microbe-specific agents with the ability to affect the host response. In fact, the inaugural antimicrobial therapies were sera containing microbe-specific antibodies [40]. Clinical accounts often noted how much better patients felt upon receiving serum therapy. Although antibiotics are powerful antimicrobial agents, most work solely on the microbe without affecting the immune response. In contrast, antibodies can augment the host response. For example, antibody-dependent cellular phagocytosis (ADCP) or cytotoxicity (ADCC) can enhance microbial clearance, and this may dampen inflammation [41]. However, dependence of ADCP and ADCC on activating Fc receptors
may compound the inflammatory response [42] and place the patient on the right-hand side of the parabola. On the other hand, antibodies that dampen inflammation in experimental pneumococcal disease have been identified [43–46]. Clinically, such antibodies could move the parabola down (less damage) and to the left. One mechanism by which they may do so is by promoting cellular microbial uptake and preventing bacterial engagement of host receptors that initiate inflammation [45]. Thus, antibodies are agents that can promote an inflammation-sparing state that benefits the host, as well as augment the immune response [47]. The former could be helpful in pneumococcal pneumonia, a condition that is often marked by inflammation that persists after bacterial clearance. Another way antibodies can dampen inflammation is via direct microbial effects. Antibodies to bacteria, mycobacteria, and fungi that alter microbial transcription, metabolism, or growth have been described [48–51] and may hold promise as therapeutic agents.

**SUMMARY: THE ROAD AHEAD**

The DRF is a conceptually simple and flexible theory that can account for myriad outcomes of host–microbe interaction. When first proposed at the dawn of the 21st century, the DRF was an important conceptual advance because it included host response as a variable in microbial pathogenesis. In addition, it shifted the view of microbial pathogenesis from a singular focus on either the host or the microbe to the outcome of their interaction. Hence, the DRF can explain how the same microbe and host can coexist in a commensal relationship at one time and have a pathogenic relationship at another time. Importantly, the DRF is flexible and can accommodate new information. For example, as noted above, clinical and experimental evidence that immune damage can alter microbial transcription, metabolism, or growth have been described [48–51] and may hold promise as therapeutic agents.

**Notes**

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