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TURNING UP THE HEAT: IMMUNE BRINKSMANSHIP IN THE ACUTE-PHASE RESPONSE

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ABSTRACT

The acute-phase response (APR) is a systemic response to severe trauma, infection, and cancer, although many of the numerous cytokine-mediated components of the APR are incompletely understood. Some of these components, such as fever, reduced availability of iron and zinc, and nutritional restriction due to anorexia, appear to be stressors capable of causing harm to both the pathogen and the host. We review how the host benefits from differences in susceptibility to stress between pathogens and the host. Pathogens, infected host cells, and neoplastic cells are generally more stressed or vulnerable to additional stress than the host because: a) targeted local inflammation works in synergy with APR stressors; b) proliferation/growth increases vulnerability to stress; c) altered pathogen physiology results in pathogen stress or vulnerability; and d) protective heat shock responses are partially abrogated in pathogens since their responses are utilized by the host to enhance immune responses. Therefore, the host utilizes a coordinated system of endogenous stressors to provide additional levels of defense against pathogens. This model of immune brinksmanship can explain the evolutionary basis for the mutually stressful components of the APR.

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INTRODUCTION

THE ACUTE-PHASE response (APR) is an evolutionarily conserved and highly coordinated systemic response to tissue damage, infection, and late-stage neoplasia (Gabay and Kushner 1999; Blatteis 2006). The APR involves numerous changes of plasma protein levels and systemic metabolic, physiologic, and behavioral changes that are induced by proinflammatory cytokines, notably interleukins 1 and 6 (IL-1, IL-6) and tumor necrosis factor (TNF), and associated signaling molecules from damaged/inflamed tissue. Among the proteins produced in the APR (primarily in the liver) are: C-reactive protein; serum amyloid A; components of the complement, coagulation, and fibrinolysis systems; antiproteases; transport proteins; inflammatory and anti-inflammatory proteins; and others. Plasma levels of other proteins are decreased, e.g., albumin. Other components of the APR include leukocytosis, fever, decreased plasma concentrations of iron and zinc, anorexia (reduced appetite), sickness behavior (lethargy, somnolence), the anemia of inflammation (anemia of chronic disease), cachexia associated with muscle protein catabolism and lipolysis with increased plasma lipids, and increased release of catecholamines and glucocorticosteroids (Gabay and Kushner 1999).

The components of the APR have been broadly described in the following functional categories: proteins or responses that have direct antipathogen activity, e.g., C-reactive protein and leukocytosis; products that modulate inflammation, e.g., glucocorticosteroids (Munck et al. 1984); reallocation of resources to mount an effective immune response (Hart 1988; Straub et al. 2010); and host-induced stressors that inhibit pathogens (e.g., fever and iron sequestration). In the latter category, fever is perhaps the best described and it is widely viewed as a host defense. Febrile temperatures have been shown to induce heat shock protein (HSP) synthesis (Ostberg et al. 2002; Singh and Aballay 2006; Tulapurkar et al. 2009), indicating that fever can be a stressor. Experimental and clinical studies have documented fever's role in controlling infections in vertebrates and invertebrates (Adamo 1998; Kluger et al. 1998; Hasday et al. 2000; Blatteis 2006). The suggested benefits of fever include: 1) direct inhibition of pathogenic microorganisms; 2) promoting apoptosis of infected or neoplastic cells; 3) eliciting pathogen heat shock proteins (HSPs) to enhance immune responses; 4) invoking host HSPs that protect against pathogen damage; 5) enhancement of inflammatory/immune cell function; and 6) downregulation of immune responses by promoting apoptosis of lymphocytes and neutrophils (Hasday et al. 2000; Srivastava 2002; Tran et al. 2003; Singh and Aballay 2006; Meinander et al. 2007; Nagarsekar et al. 2008). Of these listed benefits, the first four are based on fever being a stressor.

Along with fever, iron sequestration participates in the inhibition and killing of bacterial pathogens (Weinberg 2009). During the APR, plasma levels of iron are reduced. Iron is a critical micronutrient involving numerous cell functions in prokaryotes and eukaryotes, and is especially important in proliferating cells (Lieu et al. 2001). Although adequate iron is needed for a properly functioning immune system, the host must strike a balance between providing for its own needs and defenses while minimizing access to iron by pathogens (Beard 2001). Lactoferrin, primarily derived from neutrophils, is able to bind and locally sequester iron at inflammatory sites and mucosal surfaces (Weinberg 2009). The importance of iron for bacteria and fungi is highlighted by their production of iron-trapping siderophores that increase the ability of pathogens to compete for this critical micronutrient. Hosts can counteract bacterial siderophores with lipocalin 2, which in turn is inhibited by enzymes of the *iroA* gene cluster in some pathogenic bacteria (Fischbach et al. 2006). In an additional metal withdrawal defense mechanism, iron is pumped out of phagolysosomes into the cytoplasm of neutrophils and macrophages by natural resistance-associated macrophage protein-1 (Nramp1), which resides in the lysosomal membrane (Cellier et al. 2007). Some pathogenic bacteria make receptors that take iron from host iron-binding pro-

teins such as transferrin, lactoferrin, and hemoglobin (Weinberg 2009). When iron is liberated from host iron-binding proteins, bacterial pathogens proliferate and are more likely to become invasive (Sandrini et al. 2010). Thus, it is likely that the systemic sequestration of iron in the APR, primarily via binding to ferritin in mononuclear phagocytes and inhibition of its intestinal absorption, serves to support local deprivation at sites of inflammation (Weinberg 1984; Marx 2002; Schaible and Kaufmann 2004).

Although fever and iron sequestration have been shown to be important in host defense, the function of other stressful components of the APR remains unclear and controversial (Gabay and Kushner 1999). These include hypozincemia and hypomanganesemia, anorexia, cachexia and associated hypermetabolism, sickness behavior, and the anemia of inflammation. Additionally, in sepsis, where the host response to infection is so intense that dangerous self-harm predominates over direct pathogen harm (Bone et al. 1997), other systemic cytokine-mediated stressors become clinically apparent. These include metabolic acidosis, impaired mitochondrial function, and impaired myocardial contractility and respiratory strength. Although mediated directly by cytokines through their receptors, these effects appear paradoxically harmful and thus require an evolutionary explanation.

The problem to be explained is expressed by the following quote from Adamo et al. (2007) in regard to the potential benefits of anorexia in the APR: "It is probably difficult to decrease the availability of nutrients to a pathogen, but at the same time maintain immune function when immune cells require many of the same nutrients" (Adamo et al. 2007:298). More broadly, the question is: "How, and under what circumstances, is it possible for the host to use nonspecific stressors to preferentially harm the pathogens more than itself?" We propose that pathogens (including infected and neoplastic cells) are typically more susceptible to the stresses of the APR than is the host because: a) pathogens are already subjected to the targeted local stressors of inflammation and are thus more vulnerable to additional stress; b) the process of proliferation/growth increases vulnerability to stress; c) altered pathogen physiology associated with invasiveness and virulence increases pathogen stress and vulnerability; and d) HSPs, which protect both host and pathogens from certain stressors, can be used against pathogens by an enhanced host immune response. This differential susceptibility to even untargeted mutual stressors potentially provides the host with an additional system of defenses against pathogens.

In this review we present a new conceptual model for the apparently harmful events of the APR: self-injury and self-deprivation represent an effort by the host to direct relatively more harm to pathogens than to itself. We conceptualize this gamble by the host as a form of immune brinksmanship. Following a discussion of cellular stress and an explanation of the nature of pathogen vulnerability, we address relevant components of the APR, the risks involved in this strategy, and questions raised by the immune brinksmanship model of the APR.

Cellular Stress as a Host Defense

Because stress has the potential to cause damage and even death, under appropriate conditions it can be utilized by the host against pathogens. Stress is compensated by stress responses employed by all organisms and cells to protect themselves and maintain homeostasis. Beyond protection and repair, stress responses act to reduce vulnerability, although at the cost of reallocating resources and reprioritizing functions.

At the cellular level, protective stress responses can be activated by a variety of stressors such as heat, nutrient deprivation, oxidative injury, hypoxia, alterations of pH and tonicity, and toxins of any sort (Kültz 2005). Notable among the cell stress responses are: the heat shock response, which protects proteins (Jäättelä 1999); the unfolded protein response that controls protein synthesis (Zhang and Kaufman 2008); autophagy, which digests cell components for reuse (Karantza-Wadsworth et al. 2007); the hypoxic response, which redirects metabolism away from synthesis/growth and toward survival in hypoxia (Giaccia et al. 2004);

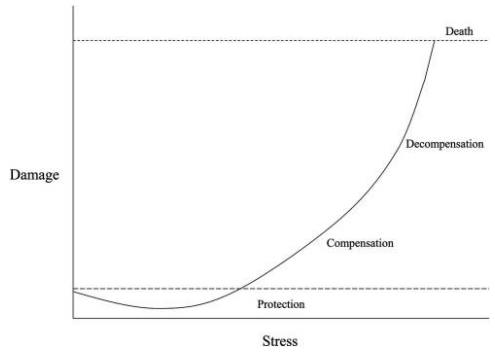

FIGURE 1. SCHEMATIC RELATIONSHIP BETWEEN INCREASING STRESS AND RESULTING DAMAGE WITHIN AN INDIVIDUAL CELL OR ORGANISM

There is an implied time component, in assuming that the increasing stress develops slowly enough that protective stress responses can develop.

the DNA-damage response (Jackson and Bartek 2009); and p53-mediated regulation of the cell cycle to permit repair of DNA damage or to induce apoptosis (Vogelstein et al. 2000; Green and Kroemer 2009). Not surprisingly, there is much overlap in the types of damage that activate the various stress responses as well as considerable linkage among stress responses.

Figure 1 is a representation of a stress-damage curve for a cell or individual organism, with three "zones" corresponding to the level of damage incurred: a zone of protection, a zone of compensation, and a zone of decompensation. Low levels of stress in the zone of protection can activate defenses that can provide protection against sudden, higher levels of the same or even different stressors. This low-dose, protective response has been variously termed "preconditioning," "adaptive response," and "hormesis" (Calabrese 2008). As stress increases on the stress-damage curve, the cell or individual leaves the zone of protection (hormetic zone) and enters the zone of compensation where correspondingly more resources must be devoted to protection/repair to maintain homeostasis. The stress here involves some degree of damage or compromised function, but it is slight enough that homeostasis can be maintained indefinitely given adequate resources. Still more stress causes more damage, leading to the zone of decompensation. Here damage accrues faster than it can be repaired, and homeostasis cannot be maintained indefinitely. In Figure 1, the increasing decompensation is shown with an exponential growth factor greater than 1, with the assumption that, in most instances, the damage feeds on itself as more and more key functional and defense/repair systems fail, ending in death of the cell or organism.

Figure 2 shows how differing stress levels between antagonists (e.g., pathogens versus host) can be utilized to harm the more stressed antagonist. If pathogens are generally more stressed or vulnerable than the host, an induced stress applied to both the pathogens and the host will be more harmful to the pathogens, which will be driven closer to decompensation and death. Additional stress drives pathogens from protective/compensation zones and toward decompensation and death more readily than the host.

Given unequal vulnerability, untargeted systemic stress can be an effective weapon for the less vulnerable contestant. Relevant analogies include international trade sanctions, labor strikes or lockouts (depending on whether labor or management believes it can better handle the stress of lost income), and the military strategy of destroying one's resources in advance of an invading army (a

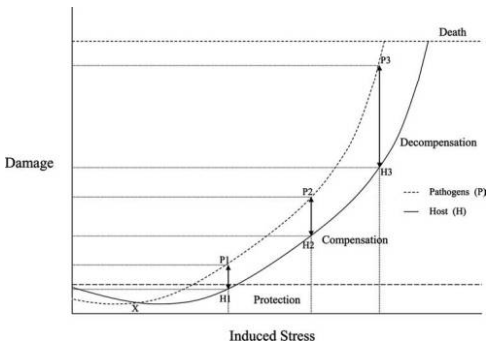

FIGURE 2. EFFECT OF INCREASING STRESS ON PATHOGENS AND THE HOST

If pathogens (dashed curve) are more stressed than the host (solid curve), any additional induced stress (e.g., Points 1, 2, or 3) will cause more damage to the pathogens (P) than to the host (H). Host benefit occurs for every induced stress beyond the crossover point of the two curves (X).

defensive "scorched earth policy"). Military history is replete with battles where bad weather, as an untargeted stressor, has preferentially harmed the more vulnerable army, typically the invading army.

The stress to an infected host comes from the direct pathogen-induced damage/costs as well as the self-induced damage/costs incurred from defense. These defense-associated costs involve the tissue damage or self-harm caused by inflammation locally and by the APR systemically (the focus of this review). Also, the reallocation of resources toward an effective immune response forces the host to pay for lost opportunity costs (e.g., inhibited reproduction/growth) and to take on the risks associated with being stressed, such as susceptibility to predators, additional pathogens, and famine, among others. A host infected due to trauma may also have the stress associated with this direct tissue damage. However, some of the stresses experienced by the host are also borne by pathogens *contained within the host*. Anything that the host can do to selectively transmit this stress to the pathogens and away from its own critical functions can be beneficial.

Why Pathogens Tend to be More Vulnerable to Cellular Stresses of the APR

a) pathogens are subjected to targeted and local stressors of inflammation

Inflammatory cells target pathogens with toxic stressors, notably reactive oxygen and nitrogen species, digestive enzymes, cytotoxic peptides, and apoptosis-inducing ligands. Additionally, inflammatory sites have numerous other stressors, with the greatest stress being further localized to phagolysosomes. As mentioned, neutrophils and macrophages selectively deprive pathogens of iron. Neutrophils and macrophages are profligate consumers of glucose and glutamine, resulting in local depletion of these key nutrients. Glucose is primarily utilized by phagocytes through glycolysis (Cramer et al. 2003), which is energetically wasteful and generates lactate, leading to lactic acidosis (another local stressor). Glutamine is an amino acid that has critical functions in synthesis of proteins, nucleic acids, and glutathione; is a ready energy source; and is needed to mount a heat shock response and prevent apoptosis. Glutamine is needed primarily by proliferating and synthesizing cells, including tumor cells, lymphocytes, bacteria, and fungi; although large amounts are also used by macrophages and neutrophils (Curi et al. 2005; Forchhammer 2007; Boer et al. 2010). Neutrophils take up so much glutamine at sites of infection that they have been considered to be glutamine sinks (Mühling et al. 2007). Additionally, inflammatory sites are notably hypoxic, in part due to respiration by pathogens, local tissue cells, and inflammatory cells. Local edema and altered blood flow associated with sludging and increased hydrostatic pressure impair delivery of O_2 as well as other key nutrients. Thus, inflammatory sites impose stresses that impair and kill pathogens. These include the targeted toxic stressors and the local environmental stressors (which also affect local tissue cells and infiltrating inflammatory cells).

b) pathogen proliferation/growth increases vulnerability

Cells are most vulnerable to damage during proliferation and growth. DNA is particularly susceptible to damage during replication and in mitosis (Kültz 2005), and newly forming proteins typical of growing cells are particularly susceptible to misfolding and denaturation. Proliferating/growing cells are also vulnerable because of increased needs for energy and materials, especially iron, zinc, glutamine, and glucose. Increased amounts of glucose are used by infected cells (Chillakuru et al. 1991; Ojicius et al. 1998); and tumor cells and other proliferating cells shift to aerobic glycolysis (the Warburg effect), utilizing large amounts of glucose to meet the biosynthetic requirements involved in making daughter cells (Vander Heiden et al. 2009). It has been proposed that avoiding mitochondrial respiration serves to reduce oxidative damage during the vulnerable S phase of the cell cycle (Chen et al. 2007). Thus, proliferating pathogens are susceptible to increased nutrient needs and to the vulnerability of replication and synthesis.

The alternative pathogen strategy is to go dormant, but at the cost of self-limiting the infection and, in vertebrates, providing more time for acquired immune responses to develop.

c) altered pathogen physiology involves pathogen stress and vulnerability

The act of invasion can be stressful to pathogens such as bacteria (Gophna and Ron 2003; Henderson et al. 2006). Motley et al. (2004) found that pathogenic *E. coli* in an intracutaneous air pouch infection model expressed a number of stress response genes, including two heat shock genes (although the majority of heat shock genes were not expressed). Invasion involves a change in environmental conditions and a switch from a noninvasive lifestyle. Thus, for extracellular pathogens, invasion at least involves the vulnerability associated with altered gene expression and protein synthesis.

Infected cells (which can harbor and nurture intracellular pathogens) and neoplastic cells are dangerous to the host, and inflammation and the APR can target them. Cell infection and neoplastic transformation, even in culture without an inflammatory environment, lead to "unexpected" alterations of the affected cells' metabolic networks that can induce cell stress responses (Weinstein 2000; Munger et al. 2006; Minami et al. 2007). For instance, malarial parasites compromise the functionality of infected erythrocytes by exporting hundreds of different proteins, thereby causing remodeling of erythrocyte membranes, the cytoskeleton, and nutrient transport systems (Boddey et al. 2010). Likewise, viruses typically inhibit host cell protein synthesis, apparently by activating stress responses, while permitting synthesis of viral proteins (McInerney et al. 2005). Despite these alterations and stresses, infected and neoplastic cells are able to survive and even continue proliferating by virtue of activation of their own stress responses and inhibition of apoptosis (Rohde et al. 2005; Calderwood et al. 2006; McLean et al. 2008). Nevertheless, the more a cell is compromised by alterations and stresses, the stronger the proapoptotic inputs; and, in turn, the stronger the antiapoptotic inputs must be if the cell is to survive. These altered cells are closer to the apoptotic threshold than are normal cells, as seen in the high apoptotic rates in many tumors (Foster 2000) and in prominent cell death at sites of viral infection. That tumor cells are closer to the apoptotic threshold than normal cells is part of the basis for tumor cells being preferentially killed by nutrient restriction (James et al. 1998). In rats, even the minor stress of overnight fasting led to a cyclic increase in hepatocyte apoptosis, with feeding the next day leading to an increase in hepatocyte proliferation (Grasl-Kraupp et al. 1994). Altered cells, being more stressed, are closer to decompensation and death; and Raffaghello et al. (2008) documented this differential stress susceptibility by showing that a brief period of nutritional stress followed by a strong oxidant stress or chemotherapy preferentially killed tumor cells rather than normal cells.

d) pathogen stress responses enhance immune responses

Although stress responses provide protection both to host cells and pathogen cells, the HSPs produced by pathogens can be used against them by the host (Srivastava 2002). Because HSPs function intracellularly by binding to other proteins to prevent misfolding and to protect them from being denatured, the presence of extracellular HSPs indicates both stress and cell damage. The proteins bound by the extracellular HSPs provide further information about the nature of the stress. A number of receptors on various immune cells can respond to HSPs and/or to HSP-bound cellular proteins as signals of danger to enhance inflammatory and immune responses, such as cytokine release and immune cell activation. HSPs in stressed cells (including infected cells and tumor cells) can migrate to the cell surface for targeting by natural killer cells and cytotoxic T lymphocytes. Additionally, HSPs, even from bacteria, can carry antigens into antigen-presenting cells and deliver them to major histocompatibility complex (MHC) class I and II molecules for presentation to cytotoxic T lymphocytes and helper T lymphocytes (Tobian et al. 2004a,b). Evolution-

arily, the host's ability to use pathogens' HSPs for immune enhancement was a straightforward host adaptation, both because HSPs readily bind to other proteins as part of their natural function and because their presence indicates stress (Srivastava 2002).

Stressed host cells also express ligands for natural killer group 2D (NKG2D) on the cell surface. Natural killer cells and cytotoxic T lymphocytes use these ligands to recognize stressed cells, notably infected and neoplastic cells, as targets to be killed (Bauer et al. 1999).

How Relevant Components of the APR Function in Immune Brinksmanship

Understanding the adaptive function of the metabolic, physiologic, and behavioral components of the APR has been a challenge, especially since they seem so counterintuitively harmful. Most of the attention has been directed toward explaining fever and sequestration of iron, which are in line with our model of cell stressors for immune brinksmanship. Other potentially harmful components of the APR are addressed below.

zinc sequestration

Like iron, zinc is a critical metal ion essential for numerous cell functions in both pathogens and hosts, being especially important in cell proliferation (Vallee and Falchuk 1993). Like iron, its plasma concentration is generally decreased in the APR, although there is no restriction of intestinal absorption of zinc in the APR (Hempe et al. 1991). The reduced plasma levels of zinc are primarily due to sequestration in the liver and, to a lesser extent, in the bone marrow and the thymus (Cousins and Leinart 1988). Although an extensive literature emphasizes the importance of adequate zinc for a properly functioning immune system, particularly for cell-mediated immunity (Dardenne 2002; Prasad 2007; Wintergerst et al. 2007), the protective effects of zinc sequestration have been suggested as early as 1983 (Sugarman 1983). More recently, Kehl-Fie and Skaar (2010) have emphasized the protective value of restricting access of zinc to pathogens. Calprotectin, derived from neutrophils, locally sequesters zinc, thereby inhibiting bacterial and fungal growth (Lulloff et al. 2004; Corbin et al. 2008). Somewhat comparable to Nramp1 for phagolysosomal removal of iron and manganese, ZIP8 is a zinc transporter protein located in the lysosomal membrane of macrophages that removes zinc from the phagolysosome during phagocytosis (Begum et al. 2002; Kehl-Fie and Skaar 2010). LPS and mycobacterial cell walls cause upregulation of ZIP8 expression in macrophages (Begum et al. 2002), which has the effect of removing zinc from the phagolysosome containing the pathogen. T lymphocytes also express ZIP8 within their lysosomal membranes, which is upregulated in activated lymphocytes (Aydemir et al. 2009). In noting that zinc can inhibit perforin-mediated pore formation (Bashford et al. 1988), Aydemir et al. (2009) suggested that ZIP8-mediated zinc removal at the interface of the cytotoxic T lymphocyte and its target cell promotes perforin-induced pore formation leading to killing of the target cell. Cells are remarkably susceptible to zinc deficiency-induced apoptosis (Chai et al. 1999), and tumor cells are even more susceptible than are normal cells (Yui et al. 1995). The importance of zinc to tumors is shown by the overexpression of ZIP4 zinc transporter in most of the pancreatic adenocarcinomas examined (Li et al. 2007). Additionally, Li et al. (2007), using pancreatic adenocarcinoma cells with forced ZIP4 expression leading to increased levels of intracellular zinc, found increased proliferation of the modified tumor cells in vitro, and markedly increased growth of implanted tumors of these high-zinc cells in nude mice compared to control pancreatic adenocarcinoma cells. Thus, while iron restriction for pathogen control has received far more attention, there is strong evidence for a similar protective role for zinc restriction in pathogen control through its action as a stressor.

manganese sequestration

Although manganese gets considerably less attention than iron or zinc, it is also a

critical metal ion in prokaryotes and eukaryotes (Cellier et al. 2007; Kehl-Fie and Skaar 2010). As with iron and zinc, manganese plasma levels are decreased in the APR (Hällgren et al. 1987). Like zinc, manganese is bound and sequestered by calprotectin derived from neutrophils (Kehl-Fie and Skaar 2010); and, like iron, it is extracted from phagolysosomes by Nramp1 (Cellier et al. 2007).

ANOREXIA

At present, there is no consensus on the adaptive value of anorexia as part of the APR. Inhibited gastric emptying and impaired intestinal absorption accompany anorexia in the APR (Suzuki et al. 2005). Exton (1997) postulated that anorexia may be beneficial by limiting the availability to pathogens of essential trace metals, notably iron; and he presented evidence that dietary restriction can enhance certain immune functions. Adamo et al. (2007), working on the assumption that anorexia during infection is beneficial, found that force-feeding bacterially infected caterpillars with a high lipid diet increased mortality (although force-feeding infected caterpillars with sucrose or water had no effect). They hypothesized a conflict between lipid metabolism and immune function. In what is apparently the only relevant mammalian experiment, Murray et al. (1978) force-fed *Listeria*-infected mice back to their preinfection food intake levels and found that these mice with "good/normal nutrition" had lower survival than did the infected sham force-fed mice. They noted that therapeutic refeeding of undernourished patients with intracellular infections can exacerbate the infection. Previously, LeGrand (2000) proposed that the nutrient restriction from anorexia is a proapoptotic stressor that can be beneficial during intracellular infections and neoplasia by preferentially promoting the removal of infected and neoplastic cells via apoptosis.

In addition, we note that nutrients feed gastrointestinal pathogens as well as host cells. Anorexia may also act to limit intestinal bacterial growth, a useful adjunct in controlling invasive bacterial gut infections. Since the host can temporarily rely on stored energy reserves, anorexia may disproportionately affect gut pathogens and make infected intestinal epithelial cells more susceptible to apoptosis.

CACHEXIA AND HYPERMETABOLISM

A number of catabolic and antianabolic changes associated with increased metabolic rate occur during the APR leading to cachexia or wasting. These include catabolism of skeletal muscle protein with urinary loss of amino acids, altered fat metabolism leading to hypertriglyceridemia and other plasma lipid changes, and insulin resistance (Beisel 1995; Espat et al. 1995). These effects contrast with the energy-conserving changes in starvation such as decreased metabolic rate, increased ketone use for energy, and more efficient use of glucose. This catabolism in the APR, combined with anorexia, has led to the prevailing view that anorexia and cachexia are paradoxical manifestations of malnutrition due to metabolic dysregulation (Beisel 1995; Yeh et al. 2008), especially since it seems that the metabolic demands of mounting a strong host defense should require good nutrition at such a critical time. Khovidhunkit et al. (2004) noted that the high plasma lipids in the APR would be expected to neutralize/inhibit certain viruses and blood-borne parasites, to neutralize lipopolysaccharide (beneficial to the extent that free lipopolysaccharide unassociated with live bacteria is harmful "noise"), and potentially provide nutrients to immune cells. Straub et al. (2010) recently proposed an "energy appeal reaction" model that sees the catabolic state of the APR as an attempt to redirect nutrient energy toward meeting the high metabolic costs of fighting infection. They emphasized urgency and the limited energy resources available to mount a strong immune response, such that noncritical functions should be inhibited. In this regard, they viewed atrophy of nonessential structures and reduced physical and mental energy as beneficial in meeting this energy appeal reaction for the immune system. Although we concur that cachexia involves a protective reallocation of nutrient resources during infection, we suggest that nutritional atrophy of nonessential tissues also encourages

the clearance of infected cells via apoptosis. Thus, while cytokine-induced insulin resistance could make glucose available to immune cells (as suggested by Straub et al. 2010), it simultaneously reduces glucose availability to infected cells. To the extent that the nutritional and metabolic changes that accompany the APR act as systemic stressors (e.g., loss of amino acids from muscle catabolism), the immune brinksmanship model offers a potential mechanism for host benefit.

sickness behavior

Sickness behavior is a notable component of the APR. It encompasses listlessness, malaise, and sleepiness along with decreased feeding; and it primarily involves reduced motivation rather than weakness (Aubert 1999; Dantzer 2001). In the most widely referenced evolutionary explanation of sickness behavior, Hart (1988) noted that the high energetic costs needed for a strong immune and febrile response require extraordinary resources. Accordingly, behavior and metabolism should be directed toward maintaining a high body temperature by means of shivering and huddling and toward minimizing loss of energy and heat (by convection) via reduced foraging/feeding. The "energy appeal reaction" model of Straub et al. (2010) is similar in emphasizing the urgency of controlling the infection and in viewing sickness behavior as an energy-saving mechanism.

The viewpoints of both Hart and Straub et al. see anorexia and reduced food intake (reduced foraging and/or digestive system atrophy) as means of *increasing* nutrient availability over the course of an infection lasting several days to weeks. Although there is merit to much of these "energetic costs of immune response" explanations, their argument that *reduced* feeding results in *increased* available energy is situation-dependent. In a cold and impoverished environment, an injured and infected animal that is struggling to find food might indeed lose energy via foraging. By contrast, a well-provisioned animal in a resource-rich environment (e.g., grazing animals in a lush pasture in bright sunlight) would be expected to easily increase energy stores through foraging with little cost, metabolic or otherwise. Since feeding almost always results in net energy gain, the strategy of anorexia to reduce energy costs is akin to firing tax collectors as a budgetary remedy to reduce a government deficit.

We envision that the extent of a host response should ideally be matched to the pathogen threat in order to minimize metabolic and opportunity costs and self-harm. That is, a slight threat should be countered with a proportionately slightly costly host response, while an intense pathogen threat should be countered by an increasingly commensurate (and costly) response. The strategy of anorexia as a stressor to inhibit pathogens is compatible with this approach, while anorexia as a means of saving energy is not.

Despite this one point of contention between evolutionary views of APR functions, models proposing a redirection of resources during infection are complementary with our model of immune brinksmanship, which utilizes host-induced stressors to help control infection.

anemia of inflammation

The anemia of inflammation (anemia of chronic disease) is another important systemic effect of proinflammatory cytokines. It is not only due to iron sequestration and hypoferremia, but also to reduced responsiveness of erythrocyte precursors to the stimulatory activity of erythropoietin (EPO), to slightly reduced levels of EPO (at least below that expected based on the degree of anemia), and to slightly reduced RBC lifespan (Adamson 2008). Although the anemia of inflammation is generally considered harmful, Zarychanski and Houston (2008) argued that, as a standard cytokine-induced component of the APR, it is beneficial. They suggested that "[d]ecreased bone marrow production reduces nutrient utilization in times of stress" (p. 334) and that anemia could reduce blood viscosity, thereby decreasing work by the heart and improving tissue perfusion. Straub et al. (2010) view the benefit of the anemia of inflammation as saving energy by decreased erythrocyte production and, by causing hypoxia to reduce oxidative metabolism, reducing muscle activity due to fatigue. We suggest that the mild hypoxia associated with the

anemia of inflammation acts as a systemic stressor for immune brinksmanship.

OTHER CYTOKINE-MEDIATED ALTERATIONS

Additional cytokine-mediated changes are clinically important in sepsis and potentially can be utilized as systemic stressors for immune brinksmanship. These include: lactic acidosis associated with a shift to glycolytic metabolism (Tredget et al. 1988); mitochondrial damage and impaired function due to oxidative injury; decreased myocardial contractility; hypotension; and impaired respiratory muscle strength. These seemingly maladaptive effects are likely interrelated. Inflammatory cytokines, notably IL-1 and TNF, induce nitric oxide (NO) synthesis (a signal for vasodilation, hence hypotension) with oxidative stress (Kumar et al. 1999; Combes et al. 2001). Mitochondria are particularly sensitive to oxidative stress (Suliman et al. 2003), such that inflammatory cytokines can lead to further energy deprivation. This cytokine-generated NO production and mitochondrial damage appears to be the basis for the decreased myocardial contractility noted in vitro with the combination of IL-1 and TNF at levels found in septic patients (Kumar et al. 1999; Moe et al. 2004). There are a number of possible mechanisms for decreased respiratory muscle strength seen in sepsis: impaired perfusion due to reduced myocardial function, muscle atrophy associated with cytokine-induced cachexia, and the same type of cytokine-mediated muscle impairment as occurs with reduced myocardial contractility (Hussain 1998). Although these functional compromises could be viewed as energy-saving mechanisms through Straub et al.'s (2010) "energy appeal reaction," they can also be seen as additional endogenous stressors (acidosis, hypoxia, energy deprivation, decreased tissue perfusion) in the host-pathogen conflict.

BRINKSMANSHIP: A RISKY STRATEGY

Up to this point, we have discussed the benefits to the host of creating and using nonspecific stressors to preferentially harm the pathogens. As noted in the name of the model we have chosen, "immune brinksmanship," there are significant risks to this approach, as listed in Table 1, which includes examples of each type of risk. We emphasize that the model supports the common-sense idea that it is better to be relatively unstressed and in good condition before becoming infected.

TABLE 1
Risks of immune brinksmanship

Inadequate homeostatic reserves to win (being more stressed than the pathogens)
Poor nutrition prior to the infection[a]
Impairment of key organ system prior to infection (e.g., chronic heart failure)
Pathogen-induced injury to key organ system (e.g., heart, lungs)
Exposure to other threats (pre-stressing oneself while fighting the initial infection)
Another infection[b]
Predation
Famine
Excessive self-harm
Sepsis, multiple organ dysfunction syndrome, death[c]
Impairment of gut barrier function
Impaired growth or reproduction
Birth defects due to febrile temperatures[d]
Impaired sperm quality due to febrile episodes[e]
Pathogen resistant to specific stressors
Anaerobes not susceptible to hypoxic stress
Borrelia burgdorferi not susceptible to iron restriction[f]

References:
[a](Scrimshaw et al. 1968; Chandra 1976); [b](Muenzer et al. 2006; Renckens et al. 2008); [c](Bone et al. 1997); [d](Edwards 2006); [e](Carlsen et al. 2003); [f](Posey and Gherardini 2000).

The risk of excessive self-harm from an inappropriately exuberant APR suggests the adaptive value of having mechanisms to rapidly reduce self-induced damage. Romanovsky and Székely (1998) noted that cold-seeking behavior/hypothermia is a part of the APR often occurring subsequent to high fever or in sepsis, and they suggested that hypothermia can protect the host from the high energy demands associated with fever. We concur that cold-seeking behavior/hypothermia should be useful in sepsis, where host defenses are more immediately damaging than pathogen offenses, by serving as a means for the host to rapidly reduce endogenous stress to back away from the brink when needed. Other mechanisms likely exist for allowing rapid modulation of host-induced stressors to the most appropriate level.

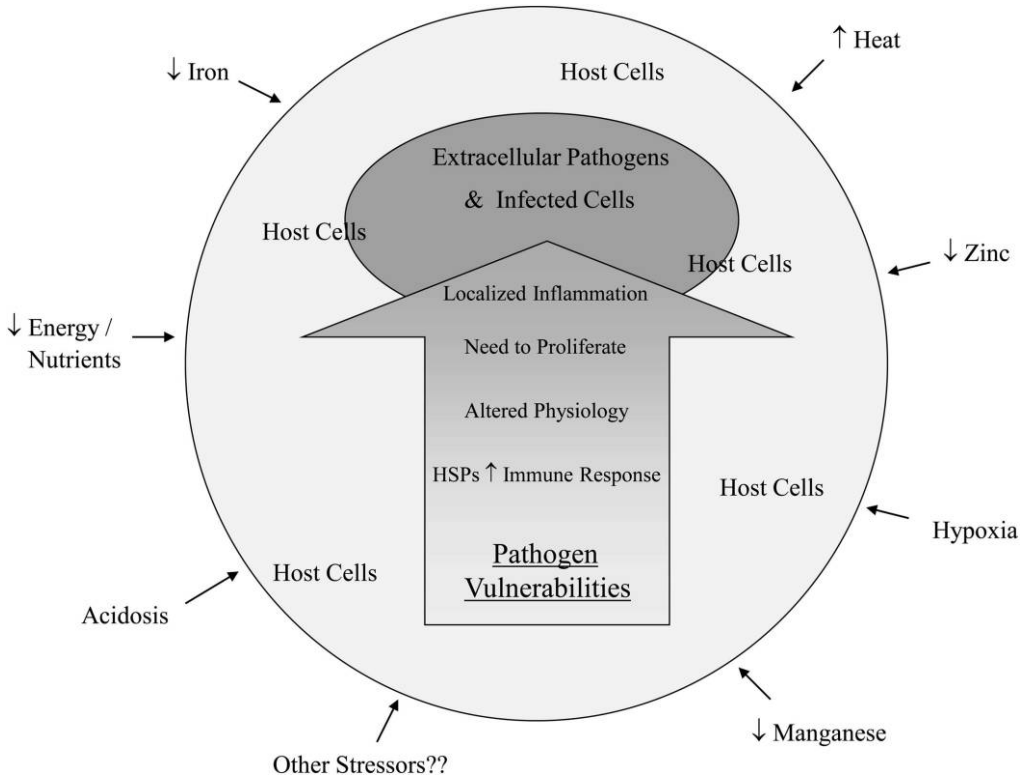

Figure 3. Immune Brinksmanship Model of the APR

Systemic stressors of the APR affect the entire body (outer circle) containing both host cells and pathogens. However, pathogens, being localized to the infected area (dark inner oval), are subject to additional vulnerabilities (listed in the arrow).

Conclusion

Although an ideal host defense against infection would be efficient, highly targeted, and safe to host cells, a number of components of the APR present substantial cellular stresses to the host and appear dangerous and maladaptive. The immune brinksmanship model provides an explanation for the potentially lethal cell stresses of the APR. The systemic stressors of the APR affect all participants: extracellular pathogens, intracellular pathogens, infected or neoplastic cells, local resident host cells in inflamed sites, infiltrating host inflammatory cells, distant host cells, and the host as a whole. The disproportionate vulnerability of infected cells and extracellular pathogens to generalized stress allows the host to benefit by the strategy of immune brinksmanship. Primarily because pathogens are already exposed to and destabilized by localized inflammatory responses at the site of infection, and because pathogens are more vulnerable by the requirement to continually replicate, it typically takes less additional stress for pathogens to reach decompensation and death than does the host. To the extent that the host has the reserves to mount an effective APR and is able to withstand the self-harm that accompanies a sustained APR effort, immune brinksmanship can benefit an individual. In this way, the coordinated network of host-induced cellular stressors that has been shaped by natural selection is a beneficial adjunct to a localized inflammatory response (Figure 3). The immune brinksmanship model assumes that the host has a better chance of winning the contest against invaders

when little stress exists at the outset and reserves are maximized. As a corollary, secondary infections in a host that has already accumulated significant cellular stresses associated with the primary infection may result in failure of immune brinksmanship as a host strategy.

The immune brinksmanship model of the APR leads to a number of questions. To what extent do the various stressors of inflammation and the APR interact? Are some components of the APR more effective in certain situations than are other components? To what extent do the multiple stressors fill gaps in defense (e.g., anaerobic bacteria not being susceptible to hypoxic stress, but perhaps being especially harmed by oxidative stress)? How much synergy is there among the stressors? For instance, Kluger and Rothenburg (1979) found that in culture neither iron restriction nor febrile temperatures had much effect on the growth of *Pasteurella multocida*, but the combination of these stressors had a marked effect on inhibiting bacterial growth. Since the stressors of the APR are host-initiated, to what extent can the host modify and manipulate the various stressors according to the type of pathogen threat? For instance, is it possible to modify fever according to its efficacy against a specific pathogen, as suggested by Adamo (1998) for behavioral fever in crickets? To what extent can the host minimize the effects of these endogenous stressors on itself relative to the pathogens? For instance, despite hypozincemia, zinc levels in the APR are slightly elevated in the bone marrow (Cousins and Leinart 1988), where immune cell proliferation (requiring zinc) occurs. How do exogenous therapeutic stressors (e.g., relatively nonspecific chemotherapeutics or heat) modify the stressors of the APR? And would therapeutic inhibition or enhancement of one or more component of the APR be partially compensated for by other components of the APR (thus making it difficult to document the role of a single component of the APR)?

It is easy to see how a system of coordinated endogenous stressors could have evolved, especially when linked with the recognition of HSPs and their bound peptides as signs of danger. If there were a survival advantage for infected animals to find themselves in stressful situations that also stress their pathogens (e.g., reduced access to food or exposure to excessive heat), the tendency to avoid such stressful situations during infections would diminish. Eventually, there would be a tendency to seek stressful situations upon infection, with further selection acting to internalize and coordinate the stress exposure such that it can maximize pathogen harm while minimizing host harm. Since small incremental selective benefits are compounded from generation to generation, the stressful components of the APR could have evolved and been maintained even with only minor benefit at the individual level.

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