Cathelicidins Link the Endocrine and Immune Systems

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DOI 10.1016/j.chom.2010.04.002

Cathelicidin peptides play key roles in host responses to infection. Radek and colleagues (2010) demonstrate that the nicotinic acetylcholine system, activated during stress, suppresses production of mouse cathelicidin, increasing host susceptibility to the pathogen *Staphylococcus aureus*. This suggests a distinct way by which the endocrine system regulates innate immunity.

Homeostasis is the ability of an organism to regulate its internal environment so as to maintain a relatively constant state that permits cells to function normally in the face of external and internal perturbations. The concept of homeostasis is critical to understanding human biology and physiology, and humans, like other animals, utilize their (neuro)endocrine system to regulate this process. The endocrine system consists of two central "command" organs, the hypothalamus and pituitary, and a variety of distributed effector organs, including the thyroid, adrenal, and reproductive organs. The hypothalamus and pituitary monitor input from a variety of receptors that serve to monitor the body's internal milieu, integrate this information with neuronal input from the brain, and turn on or off the effector organs in response to this input. The analogy of a heating circuit is often used to illustrate the basic principles of the endocrine system. The system consists of a "thermostat" (the hypothalamus) that establishes a specific physiological "set point," maintaining body temperature at 37°C. As body temperature fluctuates, it is monitored by the thermostat for drift from the set point. When the temperature drifts too far, heating or cooling effector systems (under control of the pituitary) become active and help return the temperature to a value within the acceptable range of drift from the set point.

The endocrine system has a strong neural component that, in humans, originates from a region of the brain called the hypothalamus. The hypothalamus integrates both neuronal input from the brain and physiological input from the body and uses this information to establish set points through the pulsatile release of regulatory hormones. For example, pyrogenic molecules such as IL-1β, IL-6, and bacterial lipopolysaccharide (LPS) induce fever by acting directly on neural cells in the hypothalamus, reprogramming the temperature set point to a higher value (Blatteis et al., 2000). The pituitary gland receives input from the hypothalamus regarding set point targets, and it, in turn, decides which effector organ to turn on in the event that a monitored parameter has drifted significantly from the set point. For example, thermoregulation can involve alterations in thyroid stimulating hormone (TSH) secretion, with the thyroid gland as an effector system, whereas changes in stress state use adrenocorticoid-releasing hormone (ACTH) targeted to the adrenal gland, which, in turn, alters production of stress hormones, including catecholamines and cortisol (an endogenous corticosteroid).

In addition to homeostasis, the endocrine system also regulates allostasis, or the ability to re-establish homeostasis in the face of external stressors (McEwen, 1998). Whereas homeostatic systems are critical for life and must be maintained within tight ranges, allostatic systems can drift considerably from their set points without harmful consequences, as long as the drift is only temporary (McEwen and Wingfield, 2003). Regulation of allostasis originates from the endocrine system, as well as through direct sympathetic (catecholamine) and parasympathetic (acetylcholine) nerve innervation of key organs. Examples of homeostatic systems include blood oxygenation, pH, and body temperature, whereas allostatic systems include heart rate, blood pressure, metabolism, and salt retention. The concept of the immune system as an endocrine effector "organ" has recently became a topic of discussion in the fields of neurology, endocrinology, and immunology (Rosas-Ballina and Tracey, 2009; Oke and Tracey, 2008; Brogden et al., 2005). Susceptibility to infection has long been known to be affected by the psychological and physiological "stress state" of individuals, and susceptibility to chronic autoimmune diseases shows a similar correlation with stress state. In light of these findings, and as further illustrated in this issue of *Cell Host & Microbe* by Radek et al. (2010), there is mounting evidence that the innate immune system is an effector organ regulating homeostasis and allostasis by a classical endocrine regulatory mechanism (Figure 1A).

The paper by Radek et al. (2010) highlights a new player that integrates the endocrine and immune systems, namely small cationic host peptides termed variously "antimicrobial" or "host defense" peptides. They show that stimulation through nicotinergic acetylcholine receptors plays a role in downregulating tissue levels of cathelicidin (and perhaps other cationic host defense peptides). Cathelicidins, including mouse CRAMP, bovine indolicidin, and human LL-37, are endogenous peptides with a broad range of immunomodulatory and (under appropriate conditions) antimicrobial activities

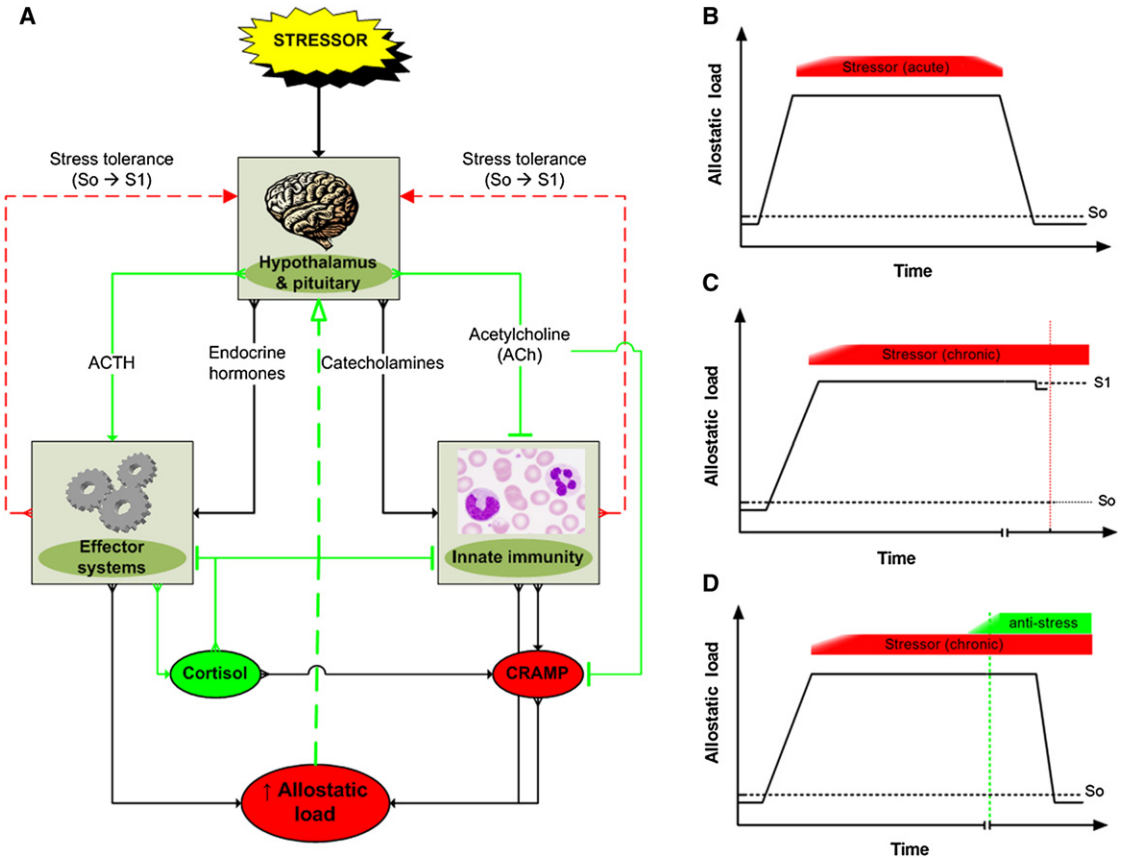

Figure 1. Interface between the Endocrine System and Innate Immunity

(A–D) The relationship between the endocrine system and innate immunity is presented within the framework of the allostasis model of stress response (McEwen and Wingfield, 2003). The human body maintains homeostasis in the face of stressors by increasing allostatic load (A) until the acute stressor is no longer active or significant and the system returns to baseline (B). The system adapts to chronic stressors by changing initial set points (So) to higher values (S1) (A, red pathways), resulting in prolonged production of CRAMP and continuous activation of stress pathways (C). Alternatively, adaptation can occur by engaging anti-stress circuits that utilize cortisol and ACh (A, green pathways), suppressing production of CRAMP and decreasing the allostatic load (D).

(Bowdish et al., 2005). The authors demonstrate that decreased CRAMP production due to endocrine regulation correlates with an increased susceptibility to infection. This finding provides intriguing evidence that the enhanced susceptibility to infection present in chronic stress states might be due to dysregulated cathelicidin production associated with cholinergic system activity that is ultimately maladaptive.

This work is a significant advancement in understanding endocrine regulation of innate immunity on multiple fronts. First, whereas the endocrine system is known to regulate the production of host defense neuropeptides during infection (Brogden et al., 2005), Radek et al. (2010) demonstrate that CRAMP is regulated in a similar manner, providing an important interface between the endocrine and immune systems. Second, Radek et al. raise the fascinating possibility that pathogenic organisms such as *Staphylococcus aureus* exploit these regulatory systems in the process of causing disease. This possibility is consistent with the known ability of *S. aureus* to evade host defense peptides during human infections (Kraus and Peschel, 2008).

When these findings are placed within the larger framework of endocrine control of immunity, acute stress, and subsequent allostatic drift (McEwen, 1998; McEwen and Wingfield, 2003), a cohesive model for the integration of these systems becomes apparent. Stress insults to the host induce increased allostatic load, which is the physiological cost to the organism of maintaining homeostasis during stress (Figures 1A and 1B). The initial allostatic response is achieved, acutely, by the "fight or flight" hormones, norepinephrine/epinephrine, and through immediate production of cortisol, each of which upregulate production of antimicrobial peptides in the skin. When the stress resolves, the allostatic load disappears and the system returns to its homeostatic set point (Figure 1B).

In situations wherein stress to the organism is nonresolving (i.e., chronic), the host endocrine system selects an appropriate response. One response involves the acceptance of a continuing elevation in allostatic load (Figure 1C), either through desensitization or set point modification, ultimately resulting in the development of chronic disease states (McEwen, 1998). In line with this form of adaptation, enduring upregulation of the production of LL-37 has been associated with chronic dermatological inflammatory diseases such as psoriasis (Lande et al., 2007) and atopic dermatitis (Ong et al., 2002). In a second type of response

(Figure 1D), the host upregulates anti-stress circuits that counterbalance allostatic systems, e.g., the anti-inflammatory cholinergic and glucocorticoid pathways. Prolonged activation of these adaptive systems ultimately becomes maladaptive, leading to immunosuppression and increased susceptibility to infectious diseases, a model that is further substantiated here by Radek et al. (2010).

Significantly, this paper demonstrates the specific means and receptor types by which the cholinergic systems regulate cathelicidin production in the skin. This opens many new avenues for therapeutic intervention in inflammatory and infectious conditions triggered by states of chronic stress. For example, overproduction of cathelicidins implicated in psoriasis could be attenuated by the topical application of a designer nicotinic agonist; whereas, conversely, underproduction of cathelicidins could be reversed by topical applications of cathelicidins (or other host peptides) or by designer nicotinic antagonists as part of anti-infective strategies. Clinical trials of known inducers of host defense peptides (vitamin D and sodium butyrate) in the context of infection are already underway, and thus proof of principle of this approach is already being established. In the world of increasing global resistance to conventional antimicrobial agents and increasing prevalence of auto-inflammatory conditions, this type of "thinking outside the box" will become increasingly critical in the prophylaxis and treatment of human infectious and inflammatory diseases.

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*B*attling *I*mmune *K*inases in Plants

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DOI 10.1016/j.chom.2010.04.003

As part of innate immune signaling, plants employ a suite of receptors, kinases, and resistance proteins to recognize pathogen-derived effector proteins. In this issue of *Cell Host & Microbe*, Zhang et al. provide evidence refining the link between multiple layers of defense signaling in response to bacterial pathogen infection.

Recent studies have highlighted the molecular-genetic arms race between the plant immune system and pathogen virulence effectors (reviewed in Chisholm et al., 2006 and Jones and Dangl, 2006). In particular, pathogen effectors often target the plant immune response network (Boller and He, 2009), and in return, plants refine and expand their immune system to defend against pathogens. In this issue of *Cell Host & Microbe*, Zhang et al. (2010), present evidence that several related *Arabidopsis* cytoplasmic receptor kinases, exemplified by botrytis-induced kinase 1 (BIK1) (Veronese et al., 2006) and AvrPphB susceptible (PBS1) (Shao et al., 2003), are cleaved by AvrPphB, a cysteine protease effector from the phytopathogenic bacterium *Pseudomonas syringae*. BIK1 turns out to be particularly important for plant immune responses, illustrating an excellent example of the utility of pathogen effectors as molecular probes in identifying new components of the plant immune system. This work also provides new insights as to how plants recognize the virulence action of AvrPphB and use it against bacterial infection.

Innate immune signaling in plants is initiated as a consequence of the recognition of specific pathogen-associated molecular patterns (PAMP) by cognate plasma membrane-localized pathogen recognition receptors (PRRs). Collectively referred to as PAMP-triggered immunity (PTI) (Chisholm et al., 2006; Jones and