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Relating immune and stress responses to infection resistance and tolerance

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No physiological system exists in isolation; signaling webs link all of our systems and the immune system is no exception. Insect studies have been used to investigate a variety of signaling loops between physiologies like sleep, reproduction, diet and aging. The immune system modifies these physiological systems, and, in turn, alterations in these physiologies, feed back on immunity. Early studies on insect immunity stressed how the immune response is stimulated but as the field matures, these studies are moving towards a description of integrated responses (Lemaitre *et al.* 1996; Shirasu-Hiza and Schneider 2007).

Ecologists describe two routes to maintaining fitness to infections (Raberg *et al.* 2009; Schneider and Ayres 2008). These are resistance and tolerance. Resistance is the ability to limit pathogen growth and tolerance is the ability to limit pathogen damage. For example, a plant that can prevent cows from eating it because it has thorns would be considered resistant because it reduces the threat of cows consuming the flowers. A plant that simply grows new flowers to replace eaten flowers would be tolerant as it has no outright effect on flower consumption.

Physiological changes outside of the canonical “immune system” can affect both of these properties. For example, in the fruit fly, diet restriction reduces resistance against *Listeria monocytogenes* infections but increases tolerance against *Salmonella typhimurium* (Ayres and Schneider 2009). The relationship between these properties is complex and is under active study. Resistance is the most well understood aspect of defense responses and researchers often use proxy measurements of an immune effector to assay a potential resistance response. Examples of this include measuring lysozyme levels, antimicrobial peptide activity or number of phagocytic cells. Work on tolerance is less advanced and we do not have many molecular mechanisms worked out. Instead, we still have to explicitly measure the damage caused by an infection and relate this to the number of microbes present.

Adamo adds another set of links to this signaling web (Adamo 2009). She shows that immune activated crickets produce a stress hormone, octopamine, and that this hormone can

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alter the potential response of the immune system. This communication network establishes a signaling loop where the immune system monitors the stress level of the animal and can also modify the stress level.

Adamo measured the effects of octopamine on potential immune function by measuring the effector lysozyme and the location of phagocytes in the cricket. She argues that this stress hormone signaling loop modifies the immune response in a complex manner that tunes the immune response so that it will function optimally for the existing physiological state. As this is a basic signaling loop in an ancient and conserved system, it suggests that similar events might be working in vertebrates. Note that all of this work was done by testing the potential immune response of the cricket, without measuring the outcome of an infection. The impact of this signaling loop on resistance and tolerance still has to be measured during an actual infection.

The paper states that two physiological systems - the immune and the stress systems - protect an animal from death. These might sound like resistance and tolerance but they are different. Immune systems and stress systems are defined by their method of induction, signaling pathways and effectors. We use these words to describe specific biochemical pathways that have been dissected at a molecular level. In contrast, resistance and tolerance are emergent properties of an animal that can be described independent of the underlying mechanism and are defined by their effects on the health and microbial growth in a host. Resistance and tolerance are properties of a system. We already know that the immune system can affect both resistance and tolerance and the same is likely true of the stress response. These effects can be complicated, such as when an immune response like the production of reactive oxygen species increases resistance (by killing microbes) but decreases tolerance (by killing self). A response that repairs reactive oxygen damage without affecting reactive oxygen levels would be expected to increase tolerance but would have no effect on resistance. This paper provides an example of how the immune system interacts with another physiology to produce a modified immune response that presumably alters resistance and tolerance to a level well suited for that particular environment.

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