Journal of Insect Physiology 59 (2013) 130–137

Contents lists available at SciVerse ScienceDirect

Journal of Insect Physiology

journal homepage: www.elsevier.com/locate/jinsphys

Review

Integrating nutrition and immunology: A new frontier

Fleur Ponton [a,b,*], Kenneth Wilson [c], Andrew J. Holmes [b,d], Sheena C. Cotter [e], David Raubenheimer [f], Stephen J. Simpson [a,b]

[a] School of Biological Sciences, The University of Sydney, Sydney, New South Wales 2006, Australia
[b] Charles Perkins Centre, The University of Sydney, Sydney, New South Wales 2006, Australia
[c] Lancaster Environment Centre, Lancaster University, Lancaster LA1 4YQ, UK
[d] School of Molecular Bioscience, The University of Sydney, Sydney, New South Wales 2006, Australia
[e] School of Biological Sciences, Queen's University Belfast, Belfast BT9 7BL, UK
[f] Institute of Natural Sciences, Massey University, Albany, New Zealand

ARTICLE INFO

Article history:
Available online 15 November 2012

Keywords:
Geometric framework
Gut
Immunity
Microbes
Nutrition
Parasites

ABSTRACT

Nutrition is critical to immune defence and parasite resistance, which not only affects individual organisms, but also has profound ecological and evolutionary consequences. Nutrition and immunity are complex traits that interact via multiple direct and indirect pathways, including the direct effects of nutrition on host immunity but also indirect effects mediated by the host's microbiota and pathogen populations. The challenge remains, however, to capture the complexity of the network of interactions that defines nutritional immunology. The aim of this paper is to discuss the recent findings in nutritional research in the context of immunological studies. By taking examples from the entomological literature, we argue that insects provide a powerful tool for examining the network of interactions between nutrition and immunity due to their tractability, short lifespan and ethical considerations. We describe the relationships between dietary composition, immunity, disease and microbiota in insects, and highlight the importance of adopting an integrative and multi-dimensional approach to nutritional immunology.

Contents

1. Introduction

A source of food and somewhere to live are basic requirements for every organism, and achieving these essentials involves interacting with other organisms. By far the majority of these interactions involve microorganisms, and throughout evolutionary history there has been strong selective pressure upon organisms to manage and control these interactions. As a result, key elements of the immune system emerged very early in evolution, including both induced and constitutive defences, allowing an array of complex and effective immune mechanisms (Hamilton et al., 2008; Vilmos and Kurucz, 1998). The function of the immune system is to regulate the full spectrum of interactions with microorganisms; not only the exclusion of organisms that are harmful (henceforth termed parasites) and the clearing of infections, but also limiting the cost of responding to organisms that can be tolerated and allowing (or even encouraging) microbes that are beneficial. Collectively, this means that immune mechanisms are complex and rely on a range of components that are triggered by different types of signals and may be regulated independently (Beckage, 2008; Forsman et al., 2008).

It has long been recognized that the immune response is modulated not only by host (and parasite) genetics, but also by host

* Corresponding author. Address: School of Biological Sciences, Heydon-Laurence Building, A08 University of Sydney, Sydney, New South Wales 2006, Australia. Tel.: +61 2 9036 6262; fax: +61 2 9351 4119.
E-mail address: fleur_ponton@hotmail.com (F. Ponton).

0022-1910/$ - see front matter Crown Copyright © 2012 Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jinsphys.2012.10.011

nutrition (Lazzaro and Little, 2009; Schmid-Hempel, 2011), yet there remain important gaps in our knowledge. Gaining a fuller understanding of the interface between nutrition and immunity is particularly important for three reasons. First, immune function is affected by host nutrition, which may greatly affect the outcome of infection (Lazzaro and Little, 2009; Schmid-Hempel, 2011). Host nutrition influences both constitutive and inducible immune function, with consequences for morbidity and mortality (Adams and Hewison, 2008; Amar et al., 2007; Calder, 2006; Cohen et al., 2008; Cunningham-Rundles et al., 2005; Kelley and Bendich, 1996; Klasing, 2007; Kolb, 1997; Kristan, 2007; Ritz and Gardner, 2006; Samartin and Chandra, 2000; Sorci and Faivre, 2009). Second, nutrition-based interactions are one of the major sources of microbial benefits to animals (Bäckhed et al., 2005; Douglas, 2010; Hooper et al., 2002; Kau et al., 2011; Topping and Clifton, 2001). Third, the host's nutrient digesting and absorbing organ, the gut, is home to the highest density of microbial cells – both beneficial and potentially harmful – and is thus the site of greatest intensity of microbe-animal interactions.

Nutrition is also a complex and multi-dimensional trait, and immunity and nutrition interact via multiple direct and indirect pathways, including the involvement of the host's endogenous microbiota (Chambers and Schneider, 2012; Ponton et al., 2011a; Simpson and Raubenheimer, 2012). The challenge remains to capture these interactions and complexities to better understand nutritional immunology. In this review, several aspects to this complexity are explored. We first give an overview of the effects of nutritional state on immunity and the response to microbes in invertebrates. We then present a framework to measure the simultaneous and interactive effects of multiple food components on immune functions. This section emphasizes how insects provide significant opportunities for capturing the complexity of the relationships between nutrition and immunity (see also Chambers and Schneider, 2012). To further characterize nutritional immunology, we also describe how host nutrition can affect the dynamics of pathogen and mutualist populations, notably the gut microbiota. In each section, we detail findings from recent studies that highlight the importance of adopting an integrative and multi-dimensional approach to nutritional immunology. Our goal is to underline the convenience and flexibility of insect models to better understand the complexity of host-parasite interactions.

2. Effects of nutrition on immunity and parasite resistance in invertebrates

A common concept in life history theory is that, when resources are limiting, organisms must balance the cost of some traits against others. The idea that disease resistance is costly and traded off against other traits, such as reproductive effort and longevity, is fundamental to the field of ecological immunology (e.g. Lochmiller and Deerenberg, 2000; Owens and Wilson, 1999; Schulenburg et al., 2009; Sheldon and Verhulst, 1996; Wilson, 2005). In order to test this hypothesis, immune-related costs must be experimentally distinguished from other pathological processes associated with infection. This internal competition for resources has been illustrated in workers of the bumblebee, *Bombus terrestris* (Moret and Schmid-Hempel, 2000). To generate distinct immune challenges on different nutritional states, fed or starved worker bees were injected with lipopolysaccharides or micro-latex beads to simulate bacterial presence and activate a combination of immune processes such as antimicrobial peptide production and phagocytosis, without the confounding effects of a growing parasite population. The survival of challenged and control bees was then followed. Survival time was reduced for challenged workers that were starved, but not when they were well-fed. This implies that simply activating the immune system (no live microbes were added) uses resources that would otherwise keep the animal alive, but when sufficient resources are available, hosts can compensate for this cost (Moret and Schmid-Hempel, 2000).

As in the previous example, starvation and energy restriction have typically been used to measure the effects of nutrition on immunity (Kristan, 2007; Murray and Murray, 1979). In insects, experimental studies have demonstrated that food deprivation of the host leads to reduced immune responsiveness (e.g. Ayres and Schneider, 2009; DeBlock and Stoks, 2008; Siva-Jothy and Thompson, 2002). For example, short-term starvation resulted in decreased phenoloxidase activity in adult mealworm beetles (Siva-Jothy and Thompson, 2002) and larval damselflies (DeBlock and Stoks, 2008) where the effects of starvation continued up to metamorphosis (see also Campero et al., 2008). Also, low sugar concentrations before or during the blood meal affect the magnitude of the melanization response against *Plasmodium* ookinetes (Koella and Sørensen, 2002; Schwartz and Koella, 2002). The effects of nutrition on individual components of the immune response may ultimately lead to dietary effects on resistance to parasites. For example, an increase in mortality was observed in starved larvae of *Rhodnius prolixus* bugs when challenged by bacteria (Feder et al., 1997). In addition, Ayres and Schneider (2009) showed that mutant phenotypes of flies that eat less than wild-type controls die faster when infected with the Gram-positive bacterium *Listeria monocytogenes*. However, nutrition not only affects host immunity and resistance to infection but also host tolerance. Disease tolerance is a defence strategy that reduces the negative impacts of the infection on host fitness without reducing the parasite load. Disease tolerance is different to immunological tolerance (i.e., the process by which the immune system fails to attack an antigen). It captures the idea that the costs of the infection can be reduced through reducing the damage to host tissues caused by the infection and the activation of the immune system (Ayres and Schneider, 2012; Medzhitov et al., 2012). For example, Ayres and Schneider (2009) found that during infections with the Gram-negative bacteria *Salmonella typhimurium*, food-restricted *Drosophila* and mutant flies (see above) had similar levels of bacteria to wild-type individuals but they lived significantly longer. This result suggests that resistance was unchanged but tolerance to infection by this specific bacterium was increased.

At a genomic level, dietary restriction induces changes in the expression of several immune genes in *Drosophila* (Pletcher et al., 2002, 2005). Molecular studies of the interactions between metabolic pathways and innate immunity have provided a new understanding of the complex relationship between nutrition and immune defence in insects (Castillo et al., 2011; DiAngelo et al., 2009). Mutations of genes in the insulin signaling pathway have considerable effects on immunity. For example, Libert et al. (2008) investigated the effect of the *chico* mutation on resistance of flies infected with either a Gram-negative or a Gram-positive bacterium (*Pseudomonas aeruginosa* and *Enterococcus faecalis*, respectively). *Chico* is an adaptor protein, homologous to vertebrate insulin receptor substrates (IRS). Flies homozygous for the *chico* mutation had superior pathogen resistance to that of wild-type controls and heterozygous siblings. Also, it has been shown that anti-microbial peptides (AMP) in non-infected flies can be activated in response to the nuclear forkhead transcription factor (FOXO) activity (Becker et al., 2010). The forkhead transcription factor plays a pivotal role in adapting metabolism to nutrient conditions and is one of the most evolutionarily ancient downstream effectors of the insulin-signaling pathway (Hay, 2011; Kapahi et al., 2010). In vivo studies indicate that the FOXO-dependent regulation of AMPs is evolutionarily conserved (see also Becker et al., 2010; Garsin et al., 2003; Troemel et al., 2006), and FOXO can directly induce the expression of immune peptides by binding to the regulatory region of one of the AMP promoters (i.e., Drosomy-