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Review

Integrating nutrition and immunology: A new frontier

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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

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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., Drosomycin) (Becker et al., 2010). In addition, FOXO interacts with Target of rapamycin (TOR) and AMP-Activated Protein Kinase (AMPK) (Hay, 2011), which are key molecules that integrate information on cellular nutritional status by sensing both qualitative and quantitative changes in nutrients, particularly branch-chain amino acids and glucose (Kapahi et al., 2010; Simpson and Raubenheimer, 2009). Finally, disruption of FOXO activity can have different effects on host survival depending on the nature of the infection (Dionne et al., 2006), which probably reflects the fact that infections by different types of pathogens can trigger different immune pathways (Hoffmann and Reichhart, 2002; Lemaitre et al., 1997; Hultmark, 2003).

Such advances in our understanding at the transcriptional level indicate that the interaction between nutrition and immune function is mediated by nutrient signaling pathways that involve more than the monitoring of energy status, but instead monitor specific nutrients and metabolites (see also Duffey and Stout, 1996; Keating et al., 1990; for the effects of secondary metabolites). However, starvation and food deprivation protocols do not usually consider the nutritional composition of experimental foods, or include consideration of the animal's multiple nutritional needs. Identifying the nutrients and, critically, the interactions that modulate immunity remain central challenges for nutritional immunology (Ponton et al., 2011a).

3. Nutritional immunology: taking a multi-dimensional approach

Recent experiments have explored the single and interactive effects of nutrients in the diet on immune function, using experimental designs derived from nutritional geometry (Raubenheimer and Simpson, 1993; Simpson and Raubenheimer, 1993, 2012). In an initial study, Lee et al. (2006) measured the effects of the dietary ratio of protein to digestible carbohydrate (P:C) on *Spodoptera littoralis* caterpillars infected with a nucleopolyhedrovirus (NPV). Susceptibility to NPV infection decreased as dietary P:C rose. In contrast, the performance of control insects, calculated by multiplying survival by average biomass gain per day, peaked on an intermediate P:C diet (Fig. 1). Insects on high-P:C diets had significantly higher levels of constitutive immune function (i.e., antimicrobial activity, encapsulation capacity and total haemocyte count) than those on low-P:C diets. When insects were allowed to self-compose their diet, the ones that survived the viral challenge had demonstrated an increased consumption of protein compared with uninfected controls and those dying of infection. Povey et al. (2009) found similar results for the African armyworm, *Spodoptera exempta*, infected by the bacterium *Bacillus subtilis*; larvae injected with a sub-lethal dose of bacteria increased their protein intake relative to controls in a self-selection test. The results of Lee et al. (2006) and Povey et al. (2009) indicate that dietary protein is a key nutritional component affecting insect immunity (see also Alaux et al., 2010; Fellous and Lazzaro, 2010; Peck et al., 1992), and that caterpillars are able to self-medicate for infection by selecting a dietary composition that best supports immune defence (see also Raubenheimer and Simpson, 2009; Singer et al., 2009).

Innate immunity relies on many different parameters (Hergannan and Rechhart, 1997; Lemaitre et al., 1997; Lemaitre and Hoffmann, 2007) and recent advances in functional genomics and molecular biology have greatly expanded our understanding of the details of the immune mechanisms that enable insects to defend themselves against parasites (Siva-Jothy et al., 2005; Welchman et al., 2009). Key questions now are whether these different components share similar or different nutritional requirements, and whether they compete for limiting host-derived resources (Cotter et al., 2004; Moret and Schmid-Hempel, 2001). Povey et al. (2009) found that as the ratio of protein to carbohydrate in the diet increased, the haemolymph of caterpillars had elevated antibacterial activity but reduced phenoloxidase (PO) activity, suggesting a physiological trade-off between these immune traits. However, an alternative explanation, that the traits simply have different nutritional optima, cannot be excluded from these experiments. That immune components do indeed differ in their nutritional requirements was demonstrated by Cotter et al. (2011) in caterpillars of *S. littoralis* fed one of 20 diets varying in the ratio and amounts of protein and carbohydrate. Nutrient-mediated effects on several immune traits were visualized as response surfaces mapped onto nutrient intake arrays for immune-challenged and non-challenged insects (Fig. 2). These experiments showed that the response surfaces of immune traits were different for challenged and non-challenged insects. For instance, PO activity was strongly affected by protein intake in non-challenged larvae, whilst the immune-challenged larvae showed a significant response to carbohydrate intake only (Fig. 2). In contrast, for lysozyme activity the shapes of the response surfaces for challenged and non-challenged larvae were not significantly different (Fig. 2). Furthermore, for non-challenged larvae the two immune traits (i.e., PO and lysozyme activity) had different nutritional requirements (i.e., they peaked at significantly different locations on the nutritional landscape), but for immune-challenged larvae the response surfaces for the two traits were not significantly different (Fig. 2). Hence, the effect of nutrition on immunity can vary according to the infection status of the individual and the specific immune trait measured, with no single diet simultaneously optimizing all the immune components. It logically follows that the insect could potentially adjust its dietary choices to achieve a nutrient balance that best meets a particular immune challenge (Cotter et al., 2011).

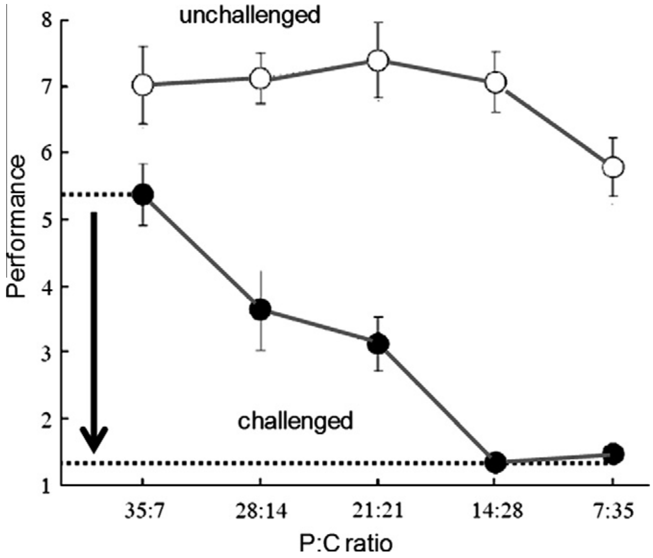

Fig. 1. Performance for control and nucleopolyhedrovirus-infected *S. littoralis* caterpillars fed 5 chemically defined diets varying in the ratio of protein (P) and carbohydrate (C). Performance of the caterpillars was estimated by multiplying the survival by the average biomass gain per day. The arrow indicates performance loss for infected caterpillars when fed on high- and low-P:C diets (modified from Lee et al., 2006).

4. Nutritional interactions between hosts, parasites and mutualists

4.1. Hosts and parasites share the same resources

Hosts are not the only ones facing nutritional challenges. Parasites feed on their host by either hijacking food or feeding on the host's tissues and fluids. The host can, therefore, effectively be con-

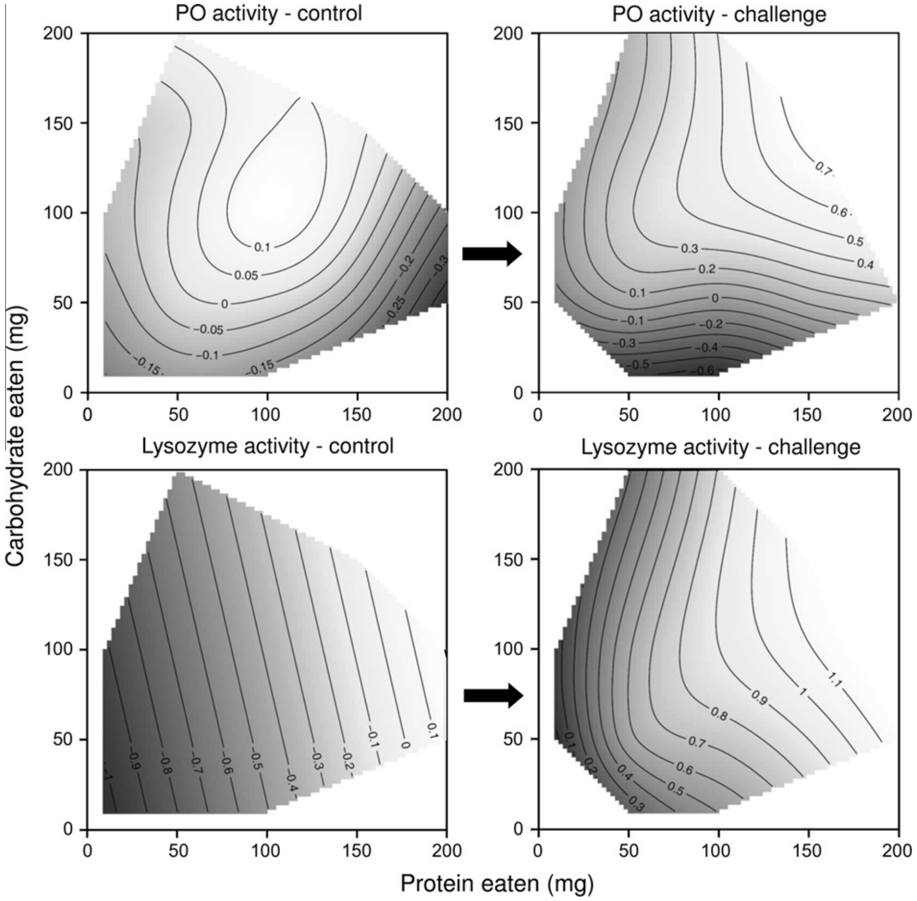

Fig. 2. Response surfaces showing the effects of protein (P) and carbohydrate (C) intake on phenoloxidase (PO) and lysozyme activity for control and immune-challenged (i.e., by piercing the cuticle with a needle dipped in a *Micrococcus lysodeikticus* solution) *S. littoralis* caterpillars. Solid arrows link the two landscapes for each trait. Consumption was recorded for individual insects confined to 1 of 20 diets varying in both the % P and the total amount of P and C. Dark colours indicate low values and light colours high values of each trait (modified from Cotter et al., 2011).

sidered as a parasite growth medium, with nutrient supply influencing not only within-host pathogen population dynamics, but also the degree of pathogenicity of the infection through competition for resources with the host. This sets up possibilities for parasites and pathogens to alter the host's feeding behaviour for their own benefit (Smith, 2007). The host could, in turn, adjust its acquisition of nutrients to alleviate resource competition with parasites and to accommodate the extra nutritional demands of fighting the infection (see above) – if the nutritional environment allows (Bedhomme et al., 2004; De Roode et al., 2008; Ebert et al., 2000; Nesheim et al., 1978; Ryder et al., 2007; Smith and Holt, 1996). Because the nutritional requirements of hosts and parasites are likely to differ, discovering whether hosts can compensate for infection by altered feeding behaviour will require experimental protocols with more than one dietary treatment.

In a protocol using multiple nutritional treatments, Ponton et al. (2011b) showed that mealworm beetles, *Tenebrio molitor*, modify their food intake when infected by cysticercoids of the tapeworm *Hymenolepis diminuta*. Infected insects increased their carbohydrate consumption during the first few days post-infection, i.e. when the parasites are growing and developing into mature forms. Despite consuming more nutrients, infected individuals deposited less body lipid and were less efficient at converting ingested protein to growth. However, infected insects sustained high levels of reproductive output despite the infection, unless confined to foods that were nutritionally dilute. Furthermore, there was no indication that increased carbohydrate intake promoted host immunity. We might then conclude from these results that beetles modified their feeding behaviour to ameliorate the nutritional demands of the infection.

4.2. Microbiota: a key component of nutritional immunology

Interpreting nutritional interactions between hosts and parasites is made significantly more complex by the normal microbial communities inhabiting the host. The normal microbiota encompasses a spectrum of lifestyles including commensalism (i.e., one partner benefits and the other has no net change in fitness) and mutualism (i.e., both partners experience increased fitness). They all receive their nutrition from the host, but may vary in their contribution of nutrients that are integral to host physiology and ecological adaptations (Brune and Ohkuma, 2011; Douglas, 2010). Obligate or primary symbionts (i.e., intracellular mutualists) are vertically-transmitted between hosts and are essential for host survival in resource-limited environments (see for instance Douglas, 1998). Such obligate mutualistic relationships are typically ancient and neither of the partners can survive in the absence of the other. However, most animal-microbial interactions are flexible and facultative, and it is likely that all animals are associated with a complex and ever-changing microbial community that consists predominantly of non-pathogenic, horizontally-acquired bacteria (i.e., facultative or secondary symbionts). The digestive tract of metazoans is particularly rich in such facultative microbes, where their activity may influence nutrient quality and absorption, as

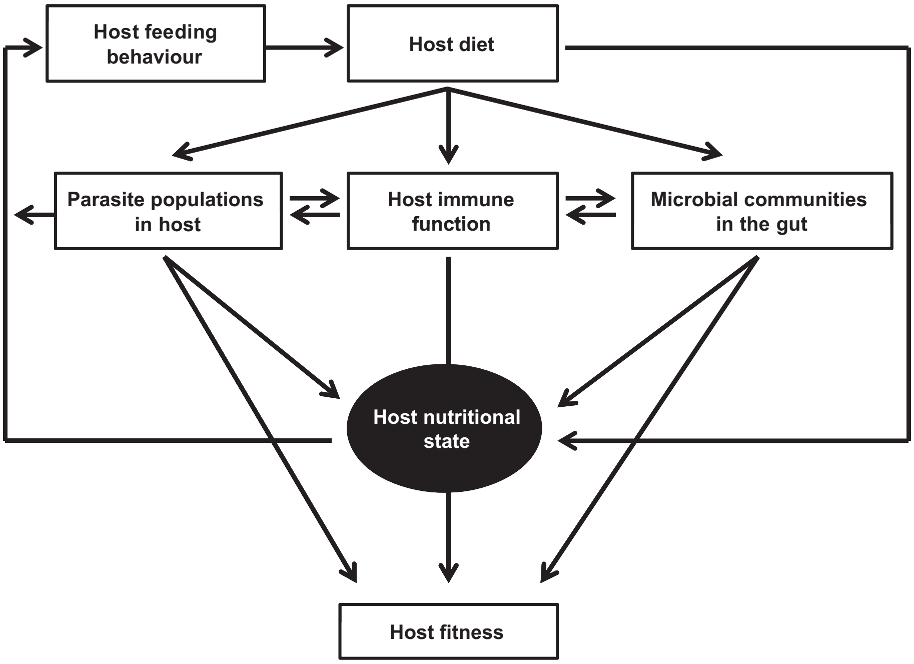

Fig. 3. Interrelationship between host nutrition, host immune function, parasite populations, the structure and function of the gut microbiome and host fitness (modified from Ponton et al., 2011a).

well as immunological challenge. The significance of understanding this is best illustrated in the vertebrates.

The gut microbiota of vertebrates are of particularly high density ($>10^{11}$ cells/ml) and diversity (>1000 species) (Ley et al., 2008). The metabolic activity of this extensive microbial community is comparable to an organ such as the liver and, via conversion of polysaccharides to short chain fatty acids (SCFAs), it directly contributes up to 70% of a vertebrate herbivore's energy needs (Flint et al., 2008). A key point is that in vertebrates this nutritional benefit is an emergent property of the activity of the total microbiota, rather than a benefit derived from one or two primary symbionts. Furthermore, the vertebrate gut microbiota are involved in many other aspects of host health and development (Bäckhed et al., 2004, 2005; Kau et al., 2011; Ley et al., 2006; Noverr and Huffnagle, 2004; Shin et al., 2011; Turnbaugh et al., 2008; Vijay-Kumar et al., 2010; Wen et al., 2008). Analyses of commensal host-microbial relationships in the intestine of mammalian models have identified microbial roles in the regulation of genes in many host systems, including development, differentiation, immunity and metabolism (Bäckhed et al., 2004; Hooper et al., 2001, 2012; Nicholson et al., 2012).

Gut microbes also play a role in invertebrate biology (Dillon and Dillon, 2004; Douglas, 2009; Moran, 2007) and involvement of the gut microbiota in digestive processes is now well acknowledged (Brune and Ohkuma, 2011; Douglas, 2009; Feldhaar, 2011; Kaufman and Klug, 1991). Symbiotic nutritional associations have been particularly well studied in insects with highly restricted diets and, in these systems, nutritional symbionts can be involved in a wide range of nutritional functions from mobilizing stored nitrogen to contributing essential amino acids (Douglas, 2009). Wood feeders, for instance, such as lower termites, harbor complex gut microbial communities that are required for degrading and digesting the cellulose they feed on (see for review Brune and Ohkuma, 2011). Nutritional symbionts are, however, not restricted to insects living on low nutritional value diets. Indeed, insects considered as omnivores can also harbor microbial symbioses that can upgrade their nutritional resources (see Feldhaar et al., 2007). For instance, adults of the beetle *Harpalus pensylvanicus* are considered to be mostly opportunistic feeders; however, they harbor a high density of bacteria in their gut (around 2.5×10^8 per ml gut) including different bacterial strains (Lundgren and Lehman, 2010). Interestingly, beetles deprived of their gut microbiota following antibiotic treatment showed a modified feeding behavior, eating less than non-treated insects when fed on seeds (Lundgren and Lehman, 2010). This result suggests that gut microbiota might be involved in seed digestion in beetles. In *Drosophila*, a fine-scale study of the effects of microbiome perturbations has revealed that microbial symbioses of the digestive tract might regulate host metabolic homeostatic and developmental programs by modulating the insulin/insulin-like growth factor (Shin et al., 2011). The gut microbiota is an essential component of the host digestive process but might be also involved in lots of other physiological mechanisms. Gaining a better understanding of the role of microbes found in the gut of insects, resident or not, is a new challenge. Recently, the composition of gut microbe communities has been described in a variety of insect species, including honey bees (Jeyaprakash et al., 2003; Mohr and Tebbe, 2006), bumblebees (Koch and Schmid-Hempel, 2011a), beetles (Egert et al., 2005; Lehman et al., 2009; Nardi et al., 2006; Zhang and Jackson, 2008), flies (Cox and Gilmore, 2007; Ren et al., 2007; Ryu et al., 2008; Shin et al., 2011; Wong et al., 2011), lepidopterans (Pauchet et al., 2010; Xiang et al., 2006) and termites (Hongoh et al., 2003).

Gut microbiota may also be key to the infection process itself (Boissière et al., 2012; Borriello, 1990; Broderick et al., 2006; Charroux and Royet, 2012; Cirimotich et al., 2011; Harp et al., 1992; Koch and Schmid-Hempel, 2011b; Weiss and Aksoy, 2011; Wilks and Golovkina, 2012). Microbes from the gut can directly interact with parasites through the secretion of inhibitory compounds. Alternatively, the gut microbiota can indirectly affect the development and persistence of parasites by inducing the host's immune response (Buchon et al., 2009; Douglas, 2010; Feldhaar and Gross, 2008; Kau et al., 2011; Lazzaro and Little, 2009; Ryu et al., 2008, 2010; Wen et al., 2008). For instance, in mosquitoes, commensal bacteria can modulate *Plasmodium* infection (Cirimotich et al., 2011; Gonzalez-Ceron et al., 2003; Meister et al., 2009; Pumpuni et al., 1996). Gut bacteria within the mosquito interfere with

Plasmodium development before invasion of the midgut epithelium, by stimulating the production of basal levels of effector molecules that control the proliferation of the bacterial populations as well as *Plasmodium* populations (Dong et al., 2009). Global transcription profiling of germ-free mosquitoes identified a subset of immune genes that were mostly down-regulated, including several anti-*Plasmodium* factors (Dong et al., 2009). In flies, gut microbiota modulate the immune system, and hence presumably susceptibility to invading parasites, by activating the Imd pathway transcription factor Relish (Ryu et al., 2008), which triggers the production of AMPs (Feldhaar and Gross, 2008; Ryu et al., 2008).

Commensal bacterial populations may vary greatly in their persistence, abundance and species composition within the host gut, with a major determinant being host diet composition, notably the macronutrient balance (Faith et al., 2011). Chandler et al. (2011) assessed the importance of host diet and host species in shaping microbiome composition in flies. They showed that whereas taxonomically- and geographically-distant fly populations, collected from various food sources, have very different microbiome compositions, when maintained on the same type of food they developed similar microbiomes. Diet has also been shown to influence the bacterial community in the midgut of larval gypsy moths, *Lymantria dispar* (Broderick et al., 2004) and cotton bollworms, *Helicoverpa armigera* (Xiang et al., 2006). The reasons why host diet has a strong impact on the gut microbial composition are still not well understood (De Filippo et al., 2010; Muegge et al., 2011; Turnbaugh et al., 2009), but presumably reflects a combination of influences on the physical and chemical milieu of the gut (Clissold et al., 2010; Duncan et al., 2008; Faith et al., 2011; Flint et al., 2008; Ley et al., 2008; Sørensen et al., 2010), and effects on immune responses (see above). Also, the diet itself is a vector of commensals, and different diets will provide microbial inoculates of different community compositions. Defining the relationships between diet and the composition and function of the gut microbiome is fundamental to a better understanding the effects of nutrition on immunity and the outcome of host-pathogens interactions.

5. Conclusions

Unravelling the interrelationship between host nutrition, host immune function, pathogen population growth and the structure and function of the gut microbiome is essential to predicting the outcome of parasitic infections (Fig. 3). Ecological immunology has been underpinned by the concept of nutrition-dependent condition, with nutrition influencing immunity, resistance and tolerance to pathogens. Geometric nutritional designs offer a powerful yet tractable approach for studying these interactions, allowing quantitative predictions about the consequences of nutrition on immunity, health and disease. Insects and their pathogens show great promise as model systems in the study of the relationships between nutrition, innate immunity and gut microbiota. They are experimentally amenable to large-scale dietary studies (see for instance Lee et al., 2008), in certain cases offer substantial molecular genetic resources (Chambers and Schneider, 2012), and have an homologous yet simpler immune system to vertebrates (Vilmos and Kurucz, 1998). In particular, insect models have the advantage of lacking confounding effects due to individual differences in adaptive immune responses. Insects also possess relatively simple microbial communities, which aids the quantification and manipulation of microbiota. In addition, recent findings concerning *Drosophila melanogaster* intestinal pathology suggest that this organism might be well suited as a model for the study of intestinal physiology during ageing, stress and infection (Apidianakis and Rahme, 2011). With the advent of nutritional genomics (Afacan et al., 2012; Becker et al., 2010; Fellous and Lazzaro, 2010; Grayson, 2010), opportunities now exist to explore the interaction between nutrients and gene expression and their products to determine the mechanism behind disease development. This will provide significant insights into nutritional regulation of the innate immune system, the gut microbiota and pathogenesis.

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