Review paper

Integrating Nutrition and Immunology: a New Frontier

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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 (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 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 (Cunningham-Rundles et al., 2005; Klasing, 2007) (Adams and Hewison, 2008; Amar et al., 2007; Calder, 2006; Cohen et al., 2008; Kelley and Bendich, 1996; Klasing, 2007; Kolb, 1997; Kristan, 2007; 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., 2011; 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 response to microbes in invertebrates. We then propose a framework to measure the simultaneous and interactive effects of multiple food components on immune functions. To further characterize interactions between nutrition and immunity, 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.

1. Nutrition and the consequences of immune trade-offs

A common concept in life history theory is that, when resources are limiting, organisms must balance some traits against one another. The idea that disease resistance is costly and is 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) Norris & Evans

2000; 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 to simulate bacterial presence or micro-latex beads to simulate macroparasite infection. 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 microbe 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; 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 increase mortality in *Rhodnius prolixus* bugs when challenged by bacteria (Feder et al., 1997). Nutrition not only affects host resistance to infection but also host tolerance. Disease tolerance is a defense strategy that reduces the negative impacts of the infection on host fitness without reducing the parasite load. The term employed here is different to immunological tolerance (i.e., the process by which the immune system fails to attack an antigen), but rather captures the idea that the costs of the infection can be reduced through reducing the damage caused by the infection and activation of the immune system on host tissues (Ayres and Schneider, 2012; Medzhitov et al., 2012). For example, Ayres and Schneider, (2009) found that during

Salmonella infections, food-restricted *Drosophila* and flies mutant for the gustatory receptor, gr28b, had similar levels of bacteria to wild-type individuals but they lived longer. This result suggested that resistance was unchanged but tolerance was increased.

At a genomic level, dietary restriction induces changes in the expression of several immune genes in *Drosophila* (Pletcher et al., 2005; Pletcher et al., 2002). Molecular studies of the interactions between metabolic pathways and innate immunity have provided a new understanding of the interactions between nutrition and immune defense 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. (Becker et al., 2010) demonstrated that anti-microbial peptides (AMP) in non-infected flies are activated in response to nuclear FOXO activity. FOXO is a transcription factor playing 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). Also, *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)). Becker et al. (2010) found that AMP expression was inhibited in *FOXO* null mutants but enhanced when FOXO was over-expressed. FOXO can directly induce the expression of the peptide by binding to the regulatory region of one of the AMP promoters (i.e., Drosomycin). FOXO interacts with TOR and AMPK (Hay, 2011). Target of rapamycin (TOR) and AMP-Activated Protein Kinase (AMPK) 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). 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; Hultmark, 2003; Lemaitre et al., 1997).

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. 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., 2011).

2. 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) (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 peaked on an intermediate P:C diet (Figure 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 (Povey et al., 2009) found similar results for the African armyworm, *Spodoptera exempta*, infected by the bacterium *Bacillus subtilis*. In addition, as dietary P:C increased, antimicrobial activity, phenoloxidase activity and protein levels in the haemolymph also increased. Larvae injected with a sub-lethal dose of bacteria increased their protein intake relative to control 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 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 defense (see also (Raubenheimer and Simpson, 2009; Singer et al., 2009).

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), and have emphasized the complexity of innate immunity (see also (Hergannan and Rechhart, 1997; Lemaitre and Hoffmann, 2007; Lemaitre et al., 1997). Key questions now are whether these different component mechanisms 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, caterpillars had elevated their antibacterial activity but reduced their phenoloxidase 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 (Cotter et al., 2011). Nutrient-mediated effects on several immune traits were visualized as response surfaces mapped onto nutrient intake arrays for challenged and unchallenged insects. Immune traits were all affected by dietary macronutrient composition (some more so than others), but immune traits peaked at different locations on the nutritional landscape (Figure 2). Hence, no single diet simultaneously optimized all the immune components. It 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).

3. Nutritional interactions between hosts, parasites and mutualists

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 considered 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 the competition for resources with the host. 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; J. Ryder et al., 2007; Nesheim et al., 1978; Smith and Holt, 1996). Because the nutritional requirements of hosts and parasites are likely not to be the same, discovering whether hosts can compensate for infection by altered feeding behaviour may require experimental protocols with more than one dietary treatment.

In a protocol using multiple nutritional treatments, Ponton et al. (2011) showed that mealworm beetles, *Tenebrio molitor*, modify their food intake when infected by cysticercoids

of the tapeworm *Hymenolepis diminuta*. More particularly, 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.

3.2. 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 from commensalism (i.e., one partner benefits and the other is apparently unaffected) to 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 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 SCFAs needs. 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., 2005; Kau et al., 2011; Shin et al., 2011; Turnbaugh et al., 2008; Vijay-Kumar et al., 2010). 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 (Backhed et al., 2004; Hooper et al., 2001). Thus, in vertebrates, the relationship between immunity and nutrition is remarkably intertwined. The presence of microbes is required for many aspects of the immune system to develop at all. Which microbes are present determines the state of the vertebrate immune system by strongly influencing T-cell maturation patterns. The composition of the microbiota is in turn strongly influenced by long-term diet patterns. The increased incidence of modern lifestyle diseases such as allergies, diabetes, inflammatory bowel diseases and obesity to epidemic levels strongly links changes in nutrition, gut microbiota and immune function.(Backhed et al., 2004; Ley et al., 2006; Noverr and Huffnagle, 2004; Vijay-Kumar et al., 2010; Wen et al., 2008).

Gut microbes also play a role in invertebrate biology (Dillon and Dillon, 2003) and digestive process [Brune, 2011 #1962][Lundgren, 2010 #1980], and recently the composition of microbe gut populations has been described in a variety of insect species, including bees (Jeyaprakash et al., 2003; Mohr and Tebbe, 2006), 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). In *Drosophila*, the microbiome regulates host metabolic homeostatic and developmental programs by modulating the insulin/insulin-like growth factor (Shin et al., 2011).

Gut microbiota are also 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; 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 system (Buchon et al., 2009; Douglas, 2010; Feldhaar and Gross, 2008; Kau et al., 2011; Lazzaro and Little, 2009; Ryu et al., 2010; Ryu et al., 2008; Wen et al., 2008). For instance, in mosquitoes, commensals 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 can 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 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; Sorensen 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.

Conclusions

Unravelling the inter-relationship 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 (Figure 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. In particular, insect models do not have the disadvantage of confounding effects due to individual differences in adaptive immune response. Insects possess relatively simple microbial communities, which aids the quantification and manipulation of microbiota. In addition, recent findings concerning *D. melanogaster* intestinal pathology suggest that this model is well suited as a model for the study of intestinal physiology during aging, 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 exist now 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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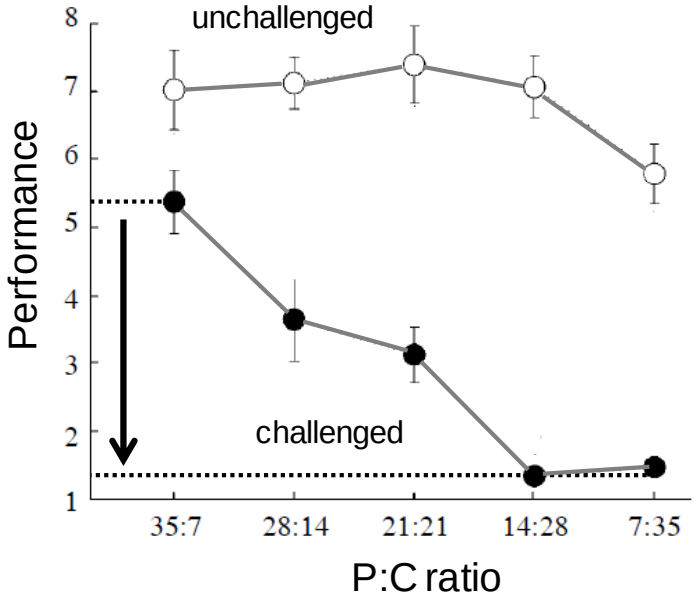
Figure legends

Figure 1: Results from an experiment in which control and nucleopolyhedrovirus infected caterpillars were fed 5 chemically defined diets varying in the ratio and concentration 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 (data from Lee et al. 2006).

Figure 2: Response surfaces showing the effects of protein (P) and carbohydrate (C) intake on the lysozyme activity, PO activity and cuticular melanism for caterpillars that were fed individually 20 diets varying in the ratio and the quantity of P and C (modified from Cotter et al., 2011).

Figure 3: Inter-relationship between host nutrition, host immune function, pathogen population growth, the structure and function of the gut microbiome and host fitness (modified from Ponton et al., 2011).

Figure 1


unchallenged
challenged
Performance
8
7
6
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3
2
1
35:7
28:14
21:21
14:28
7:35
P:C ratio

Figure 2

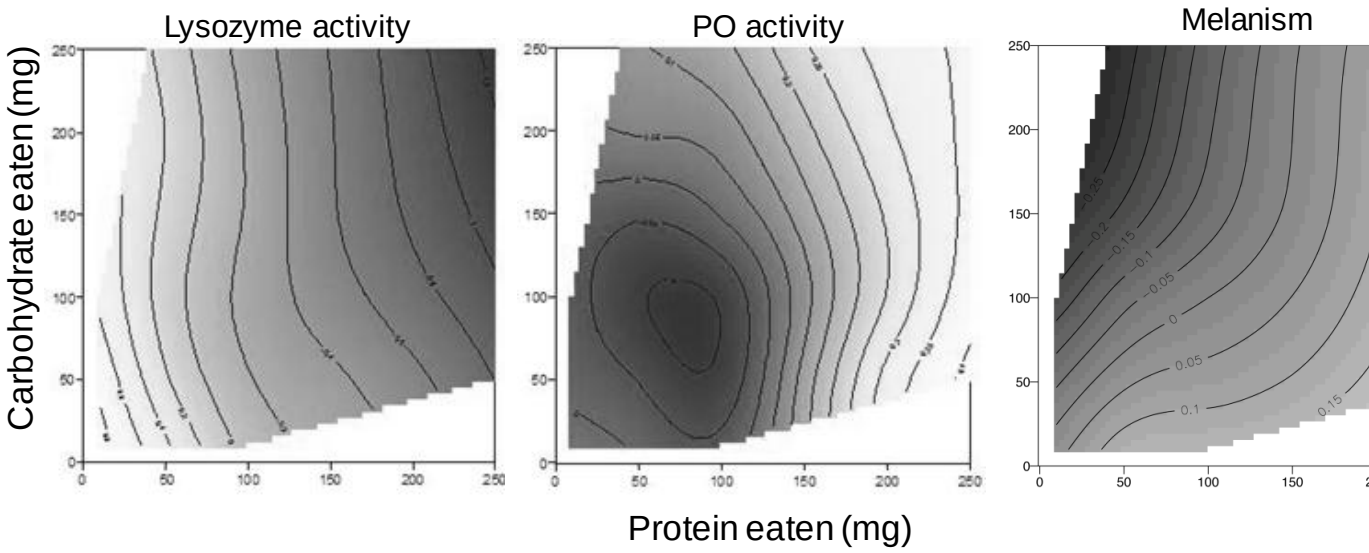
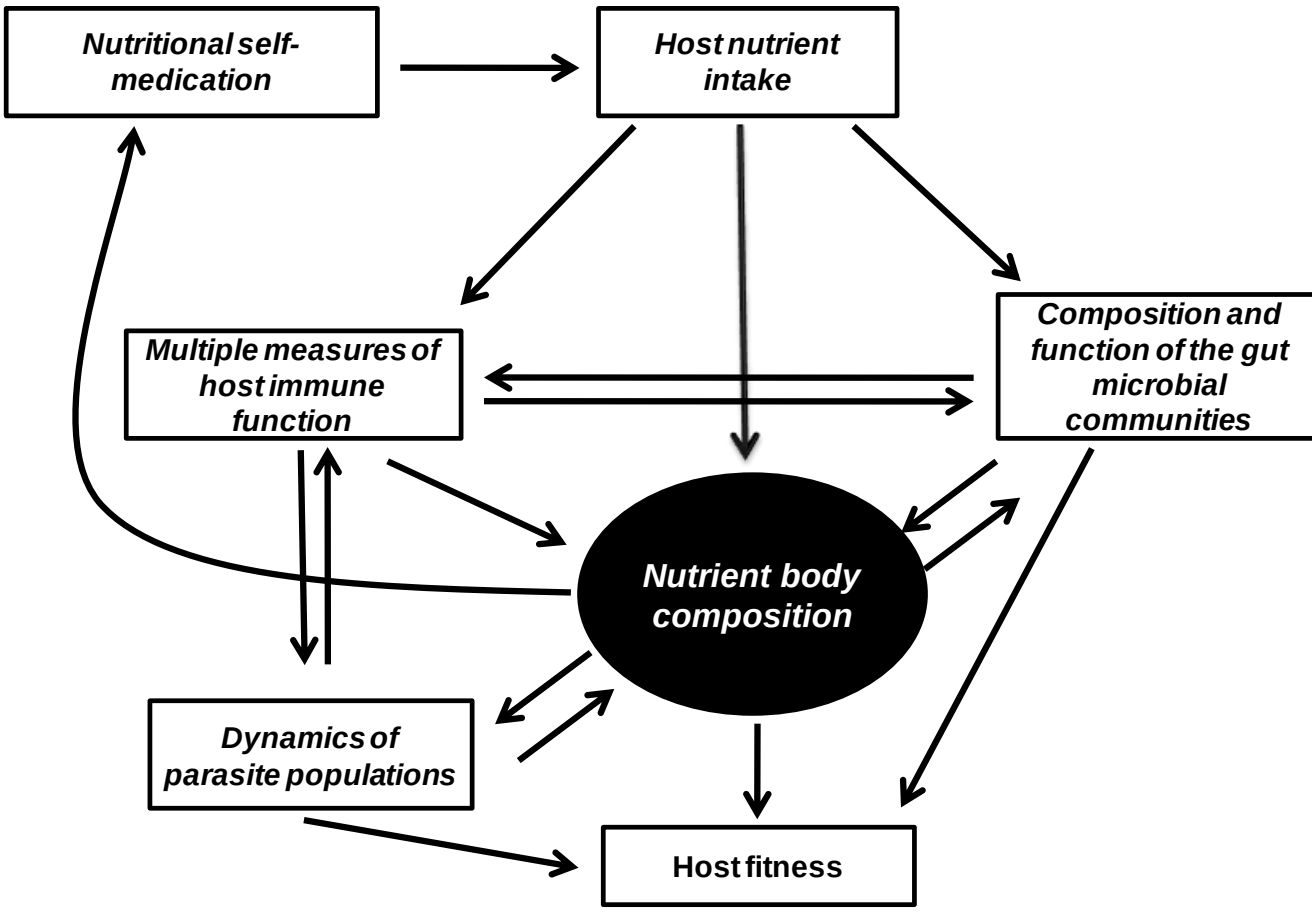

Lysozyme activity
PO activity
Melanism
Carbohydrate eaten (mg)
Protein eaten (mg)
0
50
100
150
200
250
-0.25
-0.2
-0.15
-0.1
-0.05
0
0.05
0.1
0.15

Figure 3


Nutritional self-medication
Host nutrient intake
Multiple measures of host immune function
Composition and function of the gut microbial communities
Nutrient body composition
Dynamics of parasite populations
Host fitness