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Explaining variable costs of the immune response: selection for specific versus non-specific immunity and facultative life history change

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The cost of the immune response is variable and may provide a sufficient selective pressure to produce adaptations that minimise those costs under high infection prevalence. Here, using invertebrates as a model, I suggest two possible mechanisms that maintain variation in responses that covary with costs. First I propose that infection prevalence should balance costs through the selection of optimal patterns of "specific" and "non-specific" immune pathways concomitantly expressed in the immune response. Second, I propose that life history adjustments (e.g. earlier reproduction in response to infection) could have been selected to minimise the cost of successful immune responses and consequently may result in the maintenance of costly immunity.

The immune system of animals is the last line of defence against parasites and three lines of evidence suggest it is costly. First, when expressed at high levels it is often traded off against other fitness parameters (Kraaijeveld and Godfray 1997). Second, mounting an immune response has been demonstrated to impose condition dependent fitness costs (Ilmonen et al. 2000, Moret and Schmid-Hempel 2000). Third, producing an immune response often involves the release of cytotoxic chemicals that are harmful to the host (Nappi and Vass 1993, Sugumaran et al. 2000). However, the cost of an immune response to a standard challenge has been shown to be variable (reviewed by Zuk and Stoehr 2002 and Schmid-Hempel 2003). For example, in the blue tit, *Parus caeruleus*, vaccinated with diphtheria-tetanus vaccine Råberg et al. (2000) found a reduction of the nestling-feeding rate whilst Svensson et al. (1998) did not detect any significant increase in basal metabolic rate. In bumblebees, the survival cost to an immune response under starvation conditions was strongly affected by the colony origin from which the insects were (Moret and Schmid-Hempel 2000). The reason for this variation is not clear but could result from selection of optimal immune responses from different levels of infection (Jokela et al. 2000). Because immune defence is an important trait in hosts, selection should act to minimise costs in populations facing high parasite pressure. Here, using invertebrates as a model, I propose two non-exclusive mechanisms by which variation of the cost in the immune response may be maintained. First, since the invertebrate immune response against microbial pathogens involves the simultaneous action of specific (effective against a narrow range of microbes) and non-specific (effective against a wide range of microbes) defences (Gillespie et al. 1997), their relative expression should shape the cost of the whole immune response. The cost of the immune response is then balanced against infection prevalence, which should select for optimal patterns of relative expression between specific and non-specific immunity. Second, facultative life history alterations (i.e. shift to earlier reproduction) are known to be adaptive since they minimise the cost of parasitism and may compensate the cost of immune responses once a threshold cost is reached. Such life history responses would maintain variation in cost of the immune response by lightening the selective pressure on costly immune defences that are consequently not counter selected.

Mechanism 1. Specificity and variation in the cost of the immune response

While both vertebrates and invertebrates possess an innate immune system, the acquired immunity based on immunoglobulins does not exist in invertebrates (Hoffmann et al. 1996). To combat microbial infection, invertebrates rely on both constitutive and inducible mechanisms that provide non-specific and specific immunity respectively (Hoffmann et al. 1996, Gillespie et al. 1997). Infection activates multiple systemic re-

sponses, including phagocytosis and encapsulation by haemocyte blood cells (Rattclife et al. 1985, Hoffmann et al. 1996), and accompanying melanisation reactions (Söderhäll and Cerenius 1998). These latter reactions are based on the prophenoloxidase (proPO) cascade, which is a common and generalised response to invasion by a parasite and is non-specifically elicited by critical surface molecules of the microorganism (Söderhäll and Cerenius 1998). The proPO system involves numerous enzymes constitutively synthesised and located both in the haemolymph and in circulating haemocytes (Gillespie et al. 1997, Söderhäll and Cerenius 1998). In addition, the specific recognition of microorganism cell walls induces the production, by the fat body, of antifungal or antibacterial peptides, which are then secreted into the haemolymph (Hoffmann et al. 1996).

The immune response mounted against microbes involves both the non-specific proPO cascade and the specific anti-microbial immune pathway (Hoffmann et al. 1996, Söderhäll and Cerenius 1998). Each of these mechanisms may carry a different cost when activated and their relative expression may shape the cost of the whole immune response for an equivalent efficiency (i.e. rate of parasite cleared per immune response). If these non-specific and specific immune mechanisms are physiologically and genetically independent, they should respond independently to selection, unless trade-offs between these immune pathways and other fitness components constrain the response to selection (Henter and Via 1995, Ferrari et al. 2001). Recent studies have shown a physiological independence between different specific immune pathways (Gottar et al. 2002, Tzou et al. 2002). Specific immune responses to Gram-positive and Gram-negative bacteria in *Drosophila* are based on different and independent recognition and activation processes, which suggest that they may respond independently to selection. In addition, there is no report of a link between the proPO cascade and specific antimicrobial defences, which also suggests independence between non-specific and specific immune pathways. Consequently, variable degrees of expression between these effector systems could be selected by infection prevalence, against which the cost of the immune response is balanced (Frank 2000). Alternatively, if these immune pathways are not independent and that a genetic co-variation exists between them, then variable infection prevalence may select variable degrees of correlated responses to minimize the cost of the immune response.

Under a high prevalence of infection, the systematic use of the proPO system is likely to produce highly detrimental effects to the host because, it produces quinones, phenols and oxygen radicals that are released in the haemolymph and are toxic to the host (Nappi and Vass 1993, Söderhäll and Cerenius 1998, Sugumaran et al. 2000). Such immunopathologic effects might be even more detrimental under stressful conditions (Råberg et al. 1998). Furthermore, the maintenance and synthesis de novo after each infection of the numerous enzymes belonging to the proPO cascade is likely to be costly in terms of nutrients, energy and time until the enzyme background level is reached again. By contrast, specific recognition and defence against microorganisms using antimicrobial peptides may provide an appropriate response with fewer negative side effects. Antimicrobial peptides are specific and act selectively on the parasites without damaging host's tissues (Hoffmann et al. 1996). But they have the disadvantage of a relatively long lag-phase during synthesis in response to infection. Relative to molecular size and for an equivalent efficiency against parasites, the inducible synthesis of antimicrobial peptides might be less costly per unit than the constitutive production of the enzymes of the proPO system (Hoffmann et al. 1996, Söderhäll and Cerenius 1998). Therefore, under a high frequency of infection, a larger participation of specific defences in the immune response would provide the cheapest immunity. In contrast, when the frequency of infection is low, then specificity may carry the cost of maintaining high concentration of various specific recognition factors that are not used (Frank 2000). Therefore, under low rate of infection, a larger participation of non-specific defences in the immune response might have a lower relative cost.

This hypothesis predicts that in geographic areas characterised by a high prevalence of microbial pathogens, the relative strength of the specific anti-microbial response and the occurrence of specific recognition factors should be high while the relative strength of the proPO response and the cost of a single immune response should be relatively low. In contrast, for geographic areas with low microbial prevalence, the strength of the specific anti-microbial response and the occurrence of specific recognition factors should be low while the relative strength of the proPO response and the cost of a single immune response should be relatively high.

Mechanism 2. Life history changes and maintenance of costly immunity

Even when optimised, the cost of an immune response also depends on the strength of the immune challenge and resource scarcity (Moret and Schmid-Hempel 2000). The resulting cost of the immune response is usually confounded with that of parasitism, when combined, these could have a dramatic effect on host fitness. However, hosts exposed to infection can minimise the cost of parasitism by a facultative change of life history e.g. an immediate increase in reproductive effort (Minchella 1985, Adamo 1999). The immune

system was proposed to be a signalling mechanism that alerts the host about a virulent infection threat in such a life history response (Adamo 1999). As an alternative but non-exclusive hypothesis, the cost of the immune response may induce similar life history changes to minimise its negative impact on host fitness. Such a mechanism could help to maintain high investments to immunity that otherwise would have been counter-selected. However, these life history responses also impose a fitness cost (Minchella and Loverde 1981, Agnew et al. 2000). Consequently, selection of a low cost immunity as discussed in the above section might be balanced by the cost of the immune response itself and this of the life history shift. Here, based on recent studies, I examine the assumptions of each hypothesis (signalling mechanism vs cost minimisation) to experimentally distinguish them.

Invertebrate hosts can reduce the magnitude of adverse effects caused by parasites with a facultative change in life history (Minchella 1985, Adamo 1999). For instance, the cricket *Acheta domesticus* increases its rate of egg laying in response to a challenge by the bacterium *Serrata marcescens* (Adamo 1999). The cricket therefore has a chance to compensate for the cost on future reproduction resulting from the infection by an immediate increase in offspring production. In the same study, a similar alteration of reproductive effort was obtained when the cricket was challenged with pathogen ''antigens'' (i.e. lipopolysaccharides – LPS). Here the direct effect of the living parasite was removed. LPS is recognised by the immune system of insects (Hoffmann et al. 1996) and elicits a costly immune response (Moret and Schmid-Hempel 2000). This result suggests that the immune system may be involved in the induction of the life history response in at least two different ways. First, the immune system functions to alert the host of a potential infection by a virulent parasite (Adamo 1999). This hypothesis implies, a priori, that the host might not manage to overcome the parasite attack and only certain parasite recognised as virulent by the immune system will induce the life history response. Second, the cost of the immune response used to combat the infection may induce the life history change to minimise its fitness consequence. This latter hypothesis implies that the infection is at least controlled by the immune system independently of the pathogen origin. Then the life history shift should be independent of the parasite origin but dependent of the environmental conditions (i.e. resource scarcity), which determine the magnitude of the cost of the immune response (Moret and Schmid-Hempel 2000).

In another study, the bumblebee, *Bombus terrestris*, was challenged with *Escherichia coli* LPS, which induced (a) a measurable antibacterial response, (b) a reduction in fitness and (c) an acceleration of the reproductive effort of the colony (Moret and Schmid-Hempel, unpubl.). But the fitness cost and the life history change were only observed when environmental conditions constrained compensation through the setting of demanding concurrent needs (e.g. thermoregulation). Here the induction of the life history response through the activation of the immune system alone was condition dependent. Furthermore, the strength of the immune response measured as the antibacterial response to LPS was similar in both harsh and good conditions. This suggests that it is the cost that is condition dependent, and not the strength of the immune response that induces the alteration of the life history trait. It is likely that without this life history change the fitness cost imposed by the use of the immune system could be more dramatic. However, it is not clear whether the change in life history only results from the cost of the immune response independently of the origin of the parasite recognised. The use of a novel immune elicitor, which induces a similar cost to LPS, could demonstrate whether life history responses result from the cost of immune defence alone.

Conclusion

Here, I identified two mechanisms, which might explain variation in the cost of the immune response. First, variable infection prevalence may create a wide range of variation in the cost of the immune response through the selection of optimal patterns of expression between specific and non-specific defences involved in the immune response. Second, in a more restricted way, life history changes could have lightened the selective pressure on costly immune responses and therefore contribute to their maintenance. However, these mechanisms hinge on the hypothesis that selection should act to minimise costs of immune defence under heavy parasite pressure. This hypothesis needs to be experimentally tested in order to assess the relevance of the mechanisms presented here.

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