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VISIONS AND PERSPECTIVES

The central role of immunity in the symbiotic event referred as parasitism

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Abstract

Several papers have been published on the communications between species, including host-parasite and predator-prey interactions. Here we stress the crucial role of immune system in symbiosis and parasitism. In particular, it appears that during the coevolution between any interacting populations the immune system was selected accordingly to a flexible strategy in order to adapt itself to the needs of the homeostasis, thus allowing the evolution of symbiotic relationships.

Key Words: immune system; symbiotic interactions

Introduction

Accordingly to a traditional view, parasite benefits at the expenses of the host. However even if this is the more diffused situation, cases are reported in which the host alone or both the host and the parasite, survive. What determines the outcome among the existing alternatives? Likely intrinsic and extrinsic factors are involved. The first concerns the characteristics of host and parasite, while the latter may include the environment, the ecological niches in which the interactions take place, etc. Moreover, the relationships parasite-host also are subjected to a basic principle of Eco-Immunology, *i.e.*, to minimize the energy costs of immune responses (Lochmiller and Deerenberg, 2000; Ottaviani *et al.*, 2008).

To explain the evolutive advantage represented by the complex and expensive immune system different models have been proposed, including the trade-off theory. According to Holt and Polis (1997), trade-off theory predicts the coexistence of competition for resources in dynamic populations in which a direct predator-prey interactions occurs allowing a trade-off (transition of energy) which then leads to a partitioning of the ecological niches. In this framework, the worst competitor for the same available resources can find a second source of energy in the best competitor, becoming for instance a predator or a parasite or a symbiont. In symbiotic interactions, the role of the immune tolerance have to be considered. Edwards (2009) suggested that tolerance may be involved in promoting the evolution of mutualism or in its maintenance. Also, tolerance may supply a pathway for autonomy and breakdown of mutualism. Another concept helping us to explain the energy sustainability of immune responses in a host/parasite system is allostasis, that is the process of maintaining stability through deep and transient alterations involving numerous systems (nervous, circulatory, endocrine systems, etc.) (Korte *et al.*, 2005).

Bearing in mind that immune system is devoted to maintain the integrity of an organism through the recognition of self from not-self, a symbiont/parasite must either be recognized as own by the host or escape the host immunosurveillance, for instance by inhibiting the host immune system. In both cases, immune system is a central player. One important point is the role of immune system in defining the demarcation between self and not-self, because harmful and nutritious not-self may be very similar (Ulvestad, 2009). Another important point is that immune tolerance is an important evolutive mechanism that also influences the outcome of the parasitism (Edwards, 2009; Ulvestad, 2009). Indeed, the evolution of the multicellular organisms must have been based on mechanisms resembling the immune tolerance that allows multicellularity where the cells that make up a given organism may not be identical to each other (Ulvestad, 2009). Finally, potential symbionts that can not modulate the host immune system can be “hidden” within specialized structures such as endosymbionts within bacteryocytes (Baumann *et al.*, 2000). Among the most extreme and intimate examples there is the leech symbionts usually harbored in the cytoplasm of mycetocytes that in turn are detected in various

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tissues as the epidermis, salivary glands, gut where help the digestion of the blood meal, providing essential nutrients and prevent colonization by other potentially harmful microorganisms (Graf *et al.*, 2006).

Examples of strategies adopted in the interaction between host and parasite/symbiont

For a parasite is fundamental to escape the host immune system. In this context it has been demonstrated that the parasitic trematode *Schistosoma mansoni* is able to elude the immunosurveillance of the host, the mollusc *Biomphalaria glabrata* (Duvaux-Miret *et al.*, 1992). The release of adrenocorticotropic hormone by the immunocytes of the parasite is converted by neutral endopeptidase 24.11 to α-melanocyte-stimulating hormone, a molecule that inhibits the adherence and locomotory activity of *B. glabrata* immunocytes as it has also been observed for human polymorphonuclear cells and monocytes.

Fig. 1 Light microscopy. Semithin section of the body of the larva (L) surrounded by a thick "serosa" (evidenced area, harrowheads).

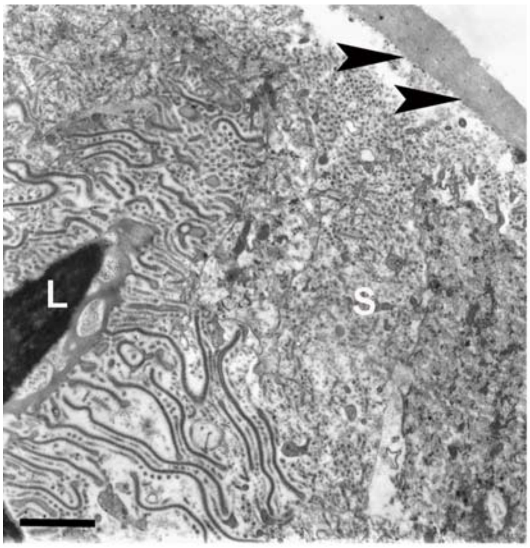

Fig. 2 TEM image of "serosa" lining the parasitoid larva (L) surface. Serosal cells (S) are coated by thick fibrillar basal membrane (arrowheads) (Bar = 0.5 µm).

A complex approach is used in another host/parasitoid system, *i.e.*, *Heliothis virescens*/*Toxoneuron nigriceps* where the parasitoid wasp *T. nigriceps* injects in the host, eggs and maternal fluids (venom, calyx fluid with polydnaviruses and the ovarian proteins) provoking severe damage to the immune and neuroendocrine systems of *H. virescens* larva. During the early phase of parasitization it has been demonstrated that humoral host prophenoloxidase system is rapidly and temporarily switched off and this neutralization is paralleled with a depression of host cellular defense (Ferrarese *et al.*, 2005; Falabella *et al.*, 2011). In addition the parasitoid shows the concurrent presence of active and passive immunoevasive strategies in order to better insure the survival of the progeny. *T. nigriceps*, from the embryo stage up to the moult of first-instars larva, is protected by a persisting extra-embryonic membrane, the "larval serosa" (Figs 1-3). This complex structure fulfills different functions contributing both to the immune evasion, acting as a barrier for macromolecules and to the nutritional exploitation being able to hydrolyze and absorb nutrients (Grimaldi *et al.*, 2006). When the developing parasitoid looses this own protection, it completes the development adopting a molecular mimicking strategy sequestering host hemolymph components close to its body surface (Ratcliffe *et al.*, 1985; Strand and Peck, 1995; Brivio *et al.*, 2010).

A different modality resulting in the same effect is the unique manipulation adopted from several Strepsiptera that for avoiding host immune responses complete their grow in a "bag" derived from the host epidermal tissue. *Stichotrema dallatorreanum* wraps itself with *Segestidea defoliaria defoliaria* tissue; thus, due to this camouflage, the endoparasite is recognized as self. This strategy has been reported as a good example of host/parasitoid coevolution (Kathirithamby *et al.*, 2003; Kathirithamby, 2008).

A complete different strategy is documented by the endosymbiotic prokaryotes. Endosymbiosis is common in insects, with more than 10 % of insect species that depend on intracellular bacteria for their development and survival (Baumann *et al.*, 2000). The endosymbiotic bacteria are transmitted maternally and during the embryogenesis reach specialized cells called bacteriocytes (Fig. 4), cells that derive from the hemocyte line, the plasmatocytes (Sacchi *et al.*, 1989; Sacchi, 2004; Heddi *et al.*, 2005). Sometime the bacteriocytes form a specific organ, the bacteriome, an outgrowth of the insect's gut (Anselme *et al.*, 2006). It has been found that aphid bacteriocyte expresses three transcription factors: Dll, En, and Ubx or Abd-A. These transcription factors play important roles during later stages of insect development (Braendle *et al.*, 2003). Furthermore, it has been found a relationship between bacterial virulence and host immune defense, indeed an overexpression of PGRP gene family is detected in the bacteriome tissue of the host (Haddi *et al.*, 2005; Anselme *et al.*, 2006), as well as the induction of antibacterial peptide genes outside of bacteriome (Anselme *et al.*, 2008).

Last but not least, the studies on the bacterium *Wolbachia pipientis* must be remembered. *Drosophila melanogaster* is protected from RNA viruses when infected by the intracellular bacterium *W. pipientis* (Hedges *et al.*, 2008). In particular, the antiviral activity of *W. pipeintis* is exerted in two different ways: i) the bacterium interferes with the virus infection cycle provoking a delay in the virus accumulation resulting in a host resistance to virus infection; ii) *W. pipeintis* infection protects the flies increasing the host tolerance to virus infection (Osborne *et al.*, 2009).

In this context, Eberl (2010) coined the term of "superorganism" to define the new functional entity composed by host and symbiotic microbiota where they crosstalk with the immune system in order to maintain the homeostasis of the "superorganism".

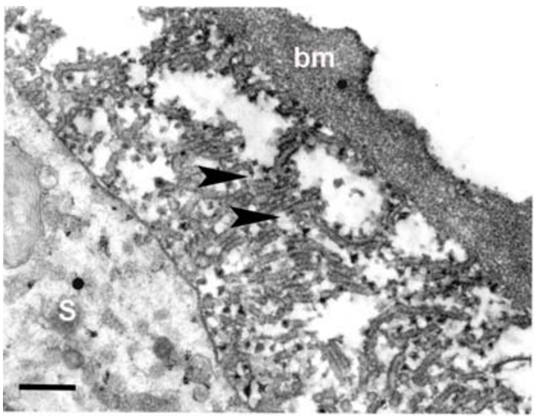

Fig. 3 TEM image of "serosa". In the detail serosal cell (S) shows pressed microvilli (arrowheads) and a coat of thick basal membranes (bm) (Bar = 1 μm) (Courtesy Dr. Grimaldi A, Department of Biotechnology and Life Science, University of Insubria, Varese, Italy).

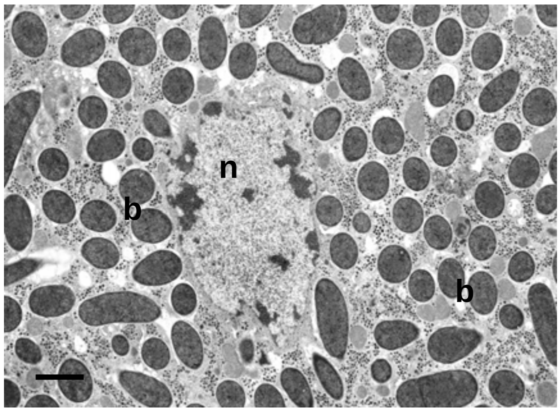

Fig. 4 TEM image of a bacteriocyte from the fat body of the insect *Blattella germanica* (n, nucleus; b, bacteria) (Bar = 1.2 μm) (Courtesy Prof. Sacchi L, Department of Animal Biology, University of Pavia, Pavia, Italy).

Conclusive remarks

On the whole we can stress the following points:

i) Coevolution can occur between any interacting populations, for instance between prey-predator, host-pathogen, etc. This event is very important because this association provokes selective pressures of one on the other participants resulting in different effects on their fitness inducing benefits;

ii) The immune system is crucial for the success of the symbiotic interactions. Furthermore, it emerges an apparent paradox because the defense system recognize not-symbiotic bacteria, while, likely the gut local immune response, avoid a permanent systemic response to the commensal bacteria (Anselme *et al.*, 2008);

iii) The immune system is not a killer, but a system that adapts itself to the needs of the homeostasis, including the symbiotic events (Eberl, 2010).

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