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Phylogeny, longevity and evolution of adaptive immunity

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Abstract. Adaptive immunity is commonly viewed as a unique vertebrate feature. A misleading view on vertebrate longevity compared to non-vertebrate animals together with oversimplification of ‘invertebrate’ phylogeny sometimes serves for justifying the limitation of adaptive immunity exclusively to vertebrates. However, here we emphasise that the borderline for differentiation between ‘innate’ and ‘adaptive’ immunity may be fuzzy and artificial. In each taxon, the feature of bearing a particular immunological mechanism should reflect its costs and benefits in a given ecological context. Hence, in invertebrates with a long lifespan some kind of acquired immunity could be expected. Indeed, several recent studies support this view. We therefore stress that the definition of ‘adaptivity’ of immune response should reflect the system function instead of a certain molecular mechanism adopted. If these altered criteria are considered then several pieces of recent evidence indicate that the adaptive immunity in animals might have arisen several times independently and in very different forms.

Key words: acquired immunity, evolutionary immunology, immunological priming, innate immunity, invertebrates

Introduction

Evolutionary immunology is a challenging and rapidly developing branch of immunological research. Various recent reports from very different fields of immunology provided an interesting background for a polemic on the sense of differentiation between ‘innate’ and ‘adaptive’ immunity (Akira et al. 2001, Flajnik & Du Pasquier 2004, Schmid-Hempel 2005, Sun & Lanier 2009, Hanington et al. 2010) concluding that current categorization of immunity into strict subsets may be in fact artificial. Firstly, the adaptive immunity is not independent on the innate immunity and these two ones form together a single functional unit (Akira et al. 2001). Secondly, the cells of the adaptive immunity originate evolutionarily as well as developmentally from the same basis as some of the innate immunity cells (Sun & Lanier 2009). Unfortunately, debating this issue immunologists sometimes unconsciously sink into a

misleading oversimplification of animal phylogeny and biology proposing that adaptive immunity might have evolved only in vertebrates because these are more complex and live longer than invertebrates (see e.g. Sun & Lanier 2009). The imperfection of this view can be found again in artificial categorisation. To reveal this pitfall we need to focus on three questions: 1) Can metazoans be divided into ‘higher’ vertebrates and ‘lower’ invertebrates? 2) Are invertebrates less complex and do they have a shorter lifespan? and 3) Is ‘adaptivity’ of immunity a unique vertebrate feature?

Animals ‘lower’ and ‘higher’

Many authors (see e.g. Sun & Lanier 2009, Savan et al. 2009, Kiss 2010) divide organisms intuitively into ‘higher’ and ‘lower’ ones, with amniotic vertebrates representing the highest degree. Although this differentiation is often utilised by many authors only

in a rhetorical fashion, it may bring much confusion into the debate with researchers from non-zoological biological disciplines. Animal evolution did not form a single line from 'lower' forms to the 'higher' ones. The situation much more resembles a tree and what we currently see are leaves at the very tips of branches with an equal distance (representing time) from the root (common ancestor). Thus, there is no cause to consider arthropods or various molluscs as 'lower' than vertebrates. Although vertebrate unique features are beyond any doubt, 'invertebrate' taxa are represented in all major animal branches and thus they do not form any monophyletic group with common traits differentiating them from vertebrates (Goloboff et al. 2009).

Body complexity and lifespan

Animal body features (including immunological traits) result from ecological requirements of the organism and constraints borne from the evolutionary past. Forming a highly heterogeneous group ranging from sponges to cephalopods (Loker et al. 2004) the body complexity of invertebrates is difficult to judge. Nevertheless, it is clear that organisms with a long lifespan can be found in all major animal taxa including the invertebrate ones (Bodnar 2009). Some invertebrates of various phylogenetic groups (including molluscs, arthropods and echinoderms) live even longer than several decades or actually more than a hundred years (reviewed e.g. in Bodnar 2009, Abele et al. 2009). In fact, the 374-year-old specimen of a bivalve mollusc *Arctica islandica* represents the oldest individual animal ever reported (Schone et al. 2005). These organisms must be equipped with a highly functional immune system capable to react on pathogen pressure changes. Besides, longevity is only a relative term, depending on the comparison with some other process in focus. If, for instance, the course of infection is short and the probability of repeated infection high, then even short-living organisms may live long enough to require some kind of memory in their immunological protection (Little & Kraaijeveld 2004). Thus, there is no reason to presuppose that adaptivity (*sensu lato*) of immune responses is restricted only to vertebrates because of their longevity. On the contrary, some kind of adaptive immunity can be predicted in any animal lineage with a sufficiently long lifespan to benefit from quick recovering from repeated infections (Boots & Bowers 2004).

Non-vertebrate 'adaptive' immunity

Vertebrate adaptive immunity results from two basic features of the lymphocyte cellular lineage – the specificity enabled by the variability of their receptors

and the immunological memory (Cruse & Lewis 2009). Mammals as well as birds, reptiles, amphibians, fish and chondrichthyans possess adaptive immune cells (lymphocytes) of two types: T cells and B cells (Litman et al. 1999). Both of these cell lines express receptors of the immunoglobulin family that are generated by a process of somatic rearrangement. These are diverse in function and are named T-cell receptors (TCRs) in T cells and B-cell receptors (BCRs) in B cells. In immature cellular stages of either of these two lines several of the original multiple V, D and J segments of TCR or BCR genes are randomly cut out of the DNA by activity of recombination activating genes (RAGs) to form a receptor with an individually specific sequence at the binding site. Despite species-specific differences in gene composition, segment architecture and precise rearrangement mechanism (in some taxa also the gene conversion is involved, Eason et al. 2004, in BCRs the somatic hypermutation takes place, Litman et al. 1999) this type of variability generation in adaptive immune cells is preserved across all jawed vertebrates from chondrichthyans to mammals (Cannon et al. 2004). Although the mechanism of somatic variability generation described above can clearly be distinguished from germ-line encoded variability known in innate immunity (e.g. Vinkler & Albrecht 2009), as mentioned in the introduction, it is currently not completely obvious what the attributes for differentiation between 'innate' and 'adaptive' immunity are (e.g. Flajnik & Du Pasquier 2004, Sun & Lanier 2009). If 'adaptivity' were judged strictly on the basis of somatic RAG-mediated-rearrangement of V, D and J segments in immunoglobulin receptor genes, then adaptive immunity would be very probably the apomorphy of jawed vertebrates; this exact mechanism of immune receptor repertoire generation has not been found anywhere outside this evolutionary lineage (Litman et al. 1999, Fugmann et al. 2006, Rolff 2007). Nevertheless, if the very ability to produce a highly variable and specific receptor repertoire capable to detect evolutionary unknown structures is evaluated, then several examples of 'adaptive' immunity can be given also in some other taxa. For instance, the variable lymphocyte receptor (VLR) repertoire in jawless vertebrates (lamprey, Pancer et al. 2004, and hagfish, Pancer et al. 2005) is created by a mechanism of gene conversion. The somatic rearrangement is based in this case on differential insertions of diverse leucine-rich repeat cassettes into an incomplete VLR genes. The structure of VLRs therefore resembles the structure of some innate immunity receptors such as Toll-like receptors but it is unrelated to the structure

of the typically 'adaptive' immunoglobulin molecules such as TCRs or BCRs (Hsu 2011). Thus, by a very different molecular solution, a palette of specific lymphocyte receptors comparable to jawed vertebrate adaptive immunity is gained. Current results suggest that perhaps functionally related molecules may be formed by a dissimilar mechanism of diversification also in invertebrate deuterostomian taxa. Although the precise function of echinoderm 185/333 molecules remains unknown, basic evidence indicates their involvement in immune function (see Buckley et al. 2008). Interestingly, the expressed proteins exhibit high-level variability differentiating mRNA sequences from their putative genome DNA. Buckley et al. (2008) have proposed that genetic diversity created in this system by frequent recombinations of individual gene elements may be further increased by posttranscriptional editing favouring transition substitutions. Other examples can be found even in more distant (protostomian) animal lineages. In insects (and perhaps also in other arthropods) Down syndrome cell adhesion molecules (DSCAMs) represent an important compound of immunological perception. A mutually exclusive alternative splicing of a single-copy DSCAM locus containing a large number of variable exons has been shown to create a huge diversity of the receptor molecules (*Drosophila* and *Anopheles* immune cells may express over 30000 protein isoforms; Watson et al. 2005, Dong et al. 2006, Crayton et al. 2006). Fibrinogen-related proteins (FREPs) are pattern recognition receptors that are common to mammals as well as many invertebrate taxa (Adema et al. 1997, Dong & Dimopoulos 2009). In molluscs, however, a relatively high level of somatic polymorphism has been revealed in the immunoglobulin superfamily domain of some of these molecules (Zhang et al. 2004). Thus, hemocytes are diversified, for instance, with respect to FREP3 variant expression (Hanington et al. 2010). Although the precise mechanism of the somatic diversification of these saccharide-binding lectins is still unclear, it seems that the diversification is based on source sequence recombination and point mutations (Zhang et al. 2004, Hanington et al. 2010). Moreover, Hanington et al. (2010) have recently provided evidence showing that FREP3 is a molecule involved in snail resistance to trematode infections and possesses opsonic properties increasing the efficiency of phagocytosis. Hence, at least in these taxa an additive and not germ-line encoded variability in immunologically active molecules is developed. This variation might be, perhaps, somehow connected with the histocompatibility allereaction observed in

some invertebrate lineages (De Tomaso et al. 2005, Nicotra et al. 2009).

Another hallmark of the adaptive immunity (imparting it the synonymous name 'acquired immunity') is its memory. Immunological memory of antigen-specific cells enables in vertebrates a faster and more effective immune response after repeated stimulation of the immune system with the same or related pathogen. However, also outside the vertebrate taxon has the phenomenon of acquired resistance been known for quite a long time (Lie & Heyneman 1979). Immunological memory, i.e. increased resistance to parasites upon secondary exposure (termed often in invertebrates as immunological priming) has been reported in various species of cephalochordates (Wang et al. 2009), arthropods (Kurtz & Franz 2003, Schmid-Hempel 2005, Johnson et al. 2008) and molluscs (Hanington et al. 2010). Hanington et al. (2010) have shown that snails *Biomphalaria glabrata* may become resistant to trematode infection by their pre-sensitization with irradiation-attenuated, homologous trematodes. Upon secondary infection these snails displayed a significant increase in FREP3 transcription, which might suggest functional involvement of this lectin in the immunological protection. In insects a pathogen-specific immunological memory was demonstrated, for example, in bumblebees *Bombus terrestris* (Sadd & Schmid-Hempel 2006), fruit flies *Drosophila melanogaster* (Pham et al. 2007) and red flour beetles *Tribolium castaneum* (Roth et al. 2009). Moreover, other recent results also indicate that some kind of immunological memory may persist throughout the complex succession of metamorphoses present in the life-cycles of insects (Thomas & Rudolf 2010). Here, nonetheless, the antigen-specific nature of the memory remains to be proven as insects may also benefit in repeated infections from a long-lasting antimicrobial response which is not pathogen-specific (Moret & Siva-Jothy 2003).

This brief list of recent findings is by no means exhaustive and apparently there still remains much to be resolved and clarified (Little & Kraaijeveld 2004, Schmid-Hempel 2005, Hauton & Smith 2007). In most of the cases mentioned we still need more complex information on the mechanism of the molecular diversity generation or on the function of the resultant proteins. Yet, even these examples illustrate that it might have been too early to assign adaptivity of the immune response as a unique vertebrate feature. Our knowledge of the immune system function in non-vertebrate taxa is currently on a much lower stage than in vertebrates. In fact, most of the results regarding

the invertebrate immune function still come from short-living model species such as *Drosophila* (Loker et al. 2004) and, on the contrary, many long-living invertebrate taxa (such as, e.g., various shellfish and cephalopods) remain unstudied. Therefore, potentially many more examples of the 'adaptive' immunological traits than those mentioned above may wait for their description.

Conclusion

To achieve a correct insight into the ongoing evolutionary processes, immunologists will need to evade the traditional anthropomorphic view on animal phylogeny. Based on the current knowledge this view is erroneous and in nature we do not find any 'higher' and 'lower' organisms. If we miss this point, we may achieve misunderstanding resulting from oversimplification. The vertebrate immune system is by no means 'better' than others. It is different. It may be more complex than some others because different are also the costs and benefits of bearing particular protective immunological mechanisms in individual taxa, depending on their ecological context (Little & Kraaijeveld 2004, Boots & Bowers 2004). Evolution of immune system responds to the organism requirements utilising the pre-existing components. Only nowadays we surprisingly start to reveal the extensive variety of solutions of basically identical host needs (Litman et al. 2005). If we want to compare

vertebrates with other phylogenetic groups objectively, we should pay more attention to the life strategies of the species investigated. If we wish to find parallels to vertebrate immunity evolution, perhaps larger, mobile and long-lived taxa (as e.g. cephalopods) may be worth of investigation. As highlighted e.g. by Sun & Lainer (2009) the contemporary definition of adaptive immunity together with the resulting cell categorization may be artificial. In non-vertebrate taxa different terms are used for principally identical functional features than in vertebrates (such as 'immunological priming' for immunological memory). But is this categorization necessary? When shifting current immunological paradigms we should also consider the possibility that the adaptive immunity might have appeared several times independently and in very different forms. This altered view might promote a more detailed immunological research outside the vertebrate taxon.

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