For reprint orders, please contact:
reprints@future-drugs.com

The expanding field of evolutionary immunology: 'The Impact of the Environment on Innate Immunity: At the Defence Frontier – The Biology of Innate Immunity'

22–27 April, 2007, Universitätszentrum Obergurgl, Ötz Valley, Austria

Gráinne H Long[†] *and Andrew F Read*

[†]*Author for correspondence*

University of Edinburgh, Institutes of Evolutionary Biology & Immunology and Infection Research, School of Biological Sciences, Edinburgh, EH9 3JT, UK; Tel.: +44 131 650 5484; Fax: +44 131 650 6564; grainne.long@ed.ac.uk

Expert Rev. Clin. Immunol. 3(4), 459–461 (2007)

Nestled at 2000 meters in the Austrian Alps, the meeting on evolutionary immunology was held at Universitätszentrum Obergurgl, Ötz Valley, Austria, on 22–27 April, 2007. Molecular immunologists want to understand immune mechanisms and, therefore, focus on the signaling cascades, effector molecules, specific receptors and cells that are responsible for host defense. By contrast, evolutionary ecologists who are interested in immunity try to explain variation in host defense and the ecological and evolutionary consequences of this variation.

The premise behind this conference was to bring the two approaches together. It built on two previous meetings on ecological immunology. The first, held in Sheffield, UK, in 2001, focused on how immunity relates to fitness and was largely attended by ecologists. The second, in Plön, Germany, in 2004, was the first to try to bridge the gap between immune molecules and ecology by bringing molecular and ecological immunologists together. Thanks to generous sponsorship from the European Science Foundation (ESF) and der Wissenshaftsfonds (FWF), the 2007 meeting continued along this exciting interdisciplinary path, focusing largely on invertebrate immunity; a follow-up meeting is planned for 2009. Approximately 120 participants talked, ate and drank together for 5 days in the confines of a single center. It is clear that the area is moving very fast and the interests of the reductionists are beginning to overlap with those who study the whole organism. Increasingly, the overlap looks like it will be mutually beneficial.

Immunological mechanism(s) meet whole-organism phenomenology

Until very recently, the absence of T and B cells in invertebrates has been taken as evidence that invertebrate immune defenses are nonspecific and lack memory. However, by the Plön meeting in 2004, whole-organism experimentation by evolutionary ecologists was pointing to functional specificity and memory in several invertebrate species. Mechanisms that might account for these phenomena were lacking. At this year's meeting, it was clear that molecular immunologists now have some very strong candidate mechanisms. For instance, in *Anopheles*, *Drosophila* and now *Daphnia* (the water flea), the Down syndrome cell adhesion molecule (Dscam) has numerous splice variants with very high combinatorial potential, which could enable specific immune recognition with properties analagous to vertebrate antibodies (Dieter Schmucker, Harvard University, MA, USA; George Dimopoulos, John Hopkins University, MD, USA; and Daniela Brites, University of Basel, Switzerland). This finding opens up the exciting possibility that invertebrates and vertebrates may have evolved different methods of carrying out pathogen-specific responses.

Studies in fresh-water snails have revealed that a diverse family of fibrinogen-related proteins (FREPs) are upregulated in the hemolymph in response to pathogen challenge and consist of immunoglobulin superfamily domains that can undergo alternative splicing and further diversification at both genomic and mRNA levels. Thus, FREPs may represent a mechanism in snails that is capable of diversifying molecules involved in internal defense (Sam Locker, University of New Mexico, USA). Nimrod C1 has been identified as a putative phagocytosis receptor in *Drosophila* plasmatocytes, with genomic analysis, indicating that it evolved rapidly, which suggests that it is under strong diversifying selection (Dan Hultmark, Umea University, Sweden). The capacity of *Drosophila* to distinguish between microbes (e.g., between Gram-positive and Gram-negative bacteria) may depend on the specific type of peptidoglycan-recognition receptor (PGRR) (Bruno Lemaître, Centre National de la Recherche Scientifique [CNRS], France; and Ecole Polytechnique Federale de Lausanne [EPFL], Lausanne, Switzerland) and may represent a crude mechanism of specificity in invertebrates. Thus, it seems that our current picture of invertebrate immune systems is edging closer to that of vertebrates in terms of their common use of somatically diversified receptors that can respond quickly to antigenic changes in pathogens (e.g., Dscams) and germ line-encoded receptors directed against conserved pathogen-recognition molecules (PGRRs).

10.1586/1744666X.3.4.459

ISSN 1744-666X

The general consensus at the meeting was that all of these candidate mechanisms will turn out to be the immune machinery involved in immune specificity and memory but it was also agreed that, as yet, none have been nailed down conclusively as immunological effectors. It is hard to imagine that this will not have been carried out by the 2009 meeting. There was also more evidence of transgenerational priming – the transfer of specific immunity from parent to offspring (Ben Sadd, Eidgenössische Technische Hochschule [ETH], Zürich, Switzerland; Simon Fellous, Imperial College, Silwood Park, UK). The underlying mechanisms remain to be elucidated; a leading candidate is the maternal provisioning of eggs with specific antimicrobial peptides. What might be harder to clarify by 2009 is the extent of the fitness advantage that is provided by invertebrate immune specificity and memory. Is it a critically important mechanism used by invertebrates to deal with pathogen exposure or just an intriguing sideshow?

Environmental modulation of immune responses

Host immune responses are not static; rather they are subject to substantial environmental modulations. For example, various environmental stresses (Bodil Hernroth, Göteberg University, Sweden; Gerrit Joop, ETH, Zurich, Switzerland; Otto Seppälä, University of Jyväskylä, Finland; and Stefanie Slos, Catholic University of Leuven, Belgium), including chemical contamination (Tipahnie Monsinjon, Université du Havre, France) and temperature changes (Jirvanichpaisal Pikul, Uppsala University, Sweden) can significantly affect host immunity. The importance of life stage in determining host immune response was also highlighted (Tina Trenczek, University of Giessen, Germany; and Karen Lesser, University of California, CA, USA). Intuitively, one might expect some types of mechanism to work well under some conditions (e.g., in the very young or at cold temperatures), compared with others (e.g., in older life stages or at higher temperatures). It is a small step to imagine that particular pathways will be switched on and off in a condition-dependent manner. It remains to be determined just how misleading it is to study immunity under standardized laboratory conditions. It is not out of the question that the rapid progress in unraveling invertebrate immune mechanisms is, in fact, only scratching the surface.

A similar possibility emerged from the empirical demonstrations that, similar to vertebrates, invertebrates also have compartmentalized responses, with local versus systemic responses (Mike Siva-Jothy, University of Sheffield, UK; and Bruno Lemaître; CNRS, France/EPFL, Switzerland). Does immune response efficacy and the outcome of pathogen challenge vary with different routes of pathogen challenge? If so, do standardized laboratory protocols need to be more varied?

Evolution of immunity in nature

Would it be possible to predict in advance when particular pathways are likely to be turned on? When should constitutive responses be favored and when should responses be inducible? Many of the evolutionists at the meeting clearly thought that we can do more than simply describe mechanisms of immunity. For instance, a common folklore is that longer-lived organisms should invest more heavily in immune defense, since they are more likely to become infected in the first place and more likely to encounter the same pathogen again. Mike Boots (University of Sheffield, UK) demonstrated mathematically that this could be true but need not be. Long-lived organisms have to pay the fitness price of constitutive defenses for all their (long) lives and, if acquired immunity wanes relatively rapidly (as it might for long lived invertebrates), animals might be better investing in behaviors that reduce exposure, rather than investing in immune defense.

Developing such conceptual frameworks necessitates stepping into the real world. Using *Daphnia*, Dieter Ebert (University of Basel, Switzerland) emphasized the ecological function of immunity by measuring the Darwinian benefit of pathogen resistance in the wild. Studies on *Drosophila* in the wild and in laboratory settings (Brian Lazzaro, Cornell University, NY, USA) help explain why genetic variation in resistance is maintained, even though selection should rapidly purge variation.

New approaches to immune discovery

Canonical immunologists largely use conventional molecular techniques for immune gene discovery, such as genome microarrays and quantitative reverse-transcription PCR of candidate immune marker genes (George Dimopoulos). However, evolutionary biologists are using alternative approaches for gene discovery, including molecular population genetics (Darren Obbard, University of Edinburgh, UK; Frank Jiggins, University of Edinburgh, UK; and Tim Sackton, Cornell University, NY, USA) and quantitative trait-loci mapping (Tom Little, University of Edinburgh, UK). These approaches essentially reveal patterns of selection and/or selectable variation in immune function and, thus, have the potential to reveal previously undiscovered immune genes and those important in nature.

Conclusions & perspective

During the meeting, it was sometimes hard to escape the feeling that the canonical immunologists thought that pathway elucidation was real science and that all else, at best, was an entertaining amusement, whereas the evolutionary ecologists were frustrated with the purists' attention to mechanistic detail. But, at other times, it was really obvious that much can be learned by meaningful iterative interactions. Studying immunity relevant to the natural setting is clearly possible and may reveal far more when synergized with laboratory models. In the same vein, a deeper understanding of the molecular basis of host–parasite interactions not only provides new tools for ecologists but also seems to be providing mechanistic credibility to what the whole-organism biologists were saying invertebrate immunity could do.

If the pace of current discoveries is anything to go by, it looks like invertebrate immunity is going to turn out to be much more than the impoverished cousin of vertebrate immunity.

Affiliations

- *Gráinne H Long*
  Post-doctoral Researcher, University of Edinburgh, Institutes of Evolutionary Biology & Immunology and Infection Research, School of Biological Sciences, Edinburgh, EH9 3JT, UK
  Tel.: +44 131 650 5484
  Fax: +44 131 650 6564
  grainne.long@ed.ac.uk
- *Andrew F Read*
  Professor of Natural History, University of Edinburgh, Institutes of Evolutionary Biology & Immunology and Infection Research, School of Biological Sciences, Edinburgh, EH9 3JT, UK
  Tel.: + 44 131 650 5506
  Fax: + 44 131 650 6564
  a.read@ed.ac.uk