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IMMUNOLOGY INTRODUCTION

Review series on helminths, immune modulation and the hygiene hypothesis: Nematode coevolution with adaptive immunity, regulatory networks and the growth of inflammatory diseases

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Any high-school student asked to produce an example of symbiosis in nature would probably be able to explain that this had to encompass mutual benefit to the two species and might then cite plover birds plucking the leeches from the Nile crocodiles. Some, under the influence of the movie *Finding Nemo*, might even mention the relationship between sea anemones and clownfish. Challenged to explain parasitism, they would explain that this entails harm being done to one of the species rather than mutual benefit, and might well offer the example of human infestation by nematodes. However, in this volume of *Immunology*, we have assembled some of the leading figures looking at interactions between nematode infection and immune regulation.[1–4] The hypothesis they explore is that by ridding the human immune system of interaction with nematodes, one loses the potential for key regulatory interactions on which normal immunity may have evolved a dependence. Collectively, the case they assess is as follows: all mammalian wildlife carry nematodes and this relationship is one that reaches back in coevolutionary terms to the first appearance of the adaptive immune system. Hunter–gatherer hominids would have harboured several species of nematodes. This coexistence is thought to have had a substantial impact on the development of regulation of adaptive immunity, as discussed here by Jan Bradley and colleagues. That is, through interactions of nematode gene products with the immune system, notably modulation of dendritic cell function and the establishment of regulatory T-cell networks. There is also, of course, a substantial skewing of immunity in favour of T helper type 2 (Th2) cytokines. The case is made that the loss of this tuning of human adaptive immunity by nematode gene products in the developed world over the past two generations has removed one of the driving cogs of human immune regulation. Indeed, one of the authors, Graham Rook, goes so far as to use the term 'pseudocommensal', rather than parasite. Compelling evidence has been presented, both in the articles here and elsewhere, for the relationship between this change in immune set-point and the growth in inflammatory diseases in the developed world. This encompasses autoimmune conditions such as multiple sclerosis and type 1 diabetes (as discussed in the following pages by Anne Cooke), as well as a massive increase in allergic disease. The list of diseases includes those which, though all involving immune–inflammatory dysregulation, span those of excessive Th2 immunity and those of excessive Th1/Th17 immunity, so earlier incarnations of the 'hygiene hypothesis' in which a key mechanism is loss of Th1/Th2 equilibrium must be an oversimplification. More recent studies emphasize the role of regulatory T cells.[5] Specific evidence for the relationship between nematode infection and protection from allergy and autoimmunity comes from epidemiological studies as well as from mouse models. Ed Pearce and colleagues here review current concepts on the molecular mechanisms operating at the level of dendritic cell programming.

The articles gathered together here argue persuasively that removal of nematode products from human immunity has consequences for the regulation of inflammatory disease. However, it would be a dangerous and Western-centric jump from there to nostalgia for parasitic infestation as a 'good thing'. For much of the developing world, parasitic disease imposes a massive burden of morbidity, whether in terms of enhanced susceptibility to human immunodeficiency virus and tuberculosis or through retarded infant growth and development.

Clearly, the challenge to immunologists is to understand in molecular terms the components of nematode genomes with capacity to induce regulation and consequently those with biotherapeutic value, without having to endure the ignominy of Sally Mae Wallace from Mississippi from whom a 37-foot (11.3-m) worm was removed. Interestingly, however, Sally is quoted as saying 'I just knew I had the record. I was really filled with joy'.

References

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