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Review Article

The laboratory mouse and wild immunology

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SUMMARY

The laboratory mouse, Mus musculus domesticus*, has been the workhorse of the very successful laboratory study of mammalian immunology. These studies – discovering how the mammalian immune system can work – have allowed the development of the field of wild immunology that is seeking to understand how the immune responses of wild animals contributes to animals' fitness. Remarkably, there have hardly been any studies of the immunology of wild* M. musculus domesticus *(or of rats, another common laboratory model), but the general finding is that these wild animals are more immunologically responsive, compared with their laboratory domesticated comparators. This difference probably reflects the comparatively greater previous exposure to antigens of these wild-caught animals. There are now excellent prospects for laboratory mouse immunology to make major advances in the field of wild immunology.*

Keywords *ecoimmunology, fitness,* Mus*, wild*

THE LABORATORY MOUSE AND IMMUNOLOGY

The laboratory mouse – *Mus* (*Mus*) *musculus domesticus* to give it its full name – is the unsung hero of biology. Generation upon generation of such mice have been used in almost every conceivable aspect of biological research. In the same way that animals used in our wars receive medals for bravery, the laboratory mouse should be awarded an honorary Nobel Prize for its contribution to science. Mice have particularly been used in the study of genetics and immunology and their use in immunological research continues to grow. Their scientific utility is that they are mammals and so closely related to ourselves. Their practical attractiveness is that they are small, easy to keep, and breed rapidly.

Laboratory mouse immunology has been hugely successful at discovering and understanding the working network of the mammalian immune system. Using animals from defined genetic stocks, in tightly controlled environments, with ever more complex immune manipulations (including genetic manipulations and knockouts, *etc.*), this work has discovered the bewilderingly complex functioning of the mouse immune system. This has been a triumph of a reductionist biology approach to understand a complex system. The nascent field of ecoimmunology or wild immunology only exists because of the fundamental, reductionist-based approach to mammalian immunology. It is only by knowing how the immune system of a laboratory mouse (and hence other mammals and vertebrates) works that one can even conceive sensible questions of wild animals' immune lives. Laboratory-based mouse immunology tells us what the mouse immune system can do and how it can function. But, it has also taught us that the functioning of the host immune response is utterly context dependent, so that the context of wild animals will profoundly affect their immune function. Wild immunology is therefore trying to understand how an animal's ecology affects its immune function. This is then the next step for immunology, something that started with the laboratory mouse.

TAXONOMY, WILD ORIGINS AND LABORATORY DOMESTICATION

Mus musculus domesticus is widespread throughout the world, now encompassing northern Europe, the Americas, Africa and Australasia, usually living commensally with people. Other subspecies have a more restricted range, for example with *M. musculus musculus* in northern Eurasia, *M. musculus casteneus* in south-east Asia and *M. musculus bactrianus* in India (1). These four subspecies are well recognized although recent genetic evidence continues to

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reveal further complexity (e.g. 2, 3); some authorities recognize *M. musculus* and *M. domesticus* as species, rather than subspecies of *M. musculus* (4). There is an apparently stable hybrid zone in central Europe between *M. musculus domesticus* to the west and *M. musculus musculus* to the east. At least in one part of this zone the *M. musculus domesticus* alleles are more able to introgress than those of *M. musculus musculus* (5).

The inbred strains of mice commonly used in the laboratory (such as C57BL/6, BALB/c) originated from the 1920s onwards with animals taken from the fancy mouse trade and thus come from mixed, but limited, sources (1). The sequencing of the genome of laboratory mice (specifically of C57BL/6) confirmed this mixed ancestry (6) showing that its genome was mosaic. Thus, about two-thirds of the genome has a low level of polymorphism with other laboratory strains, while the remaining third is highly polymorphic compared with other laboratory strains (6). Thus, when comparing C57BL/6 with another laboratory strain, in the low polymorphism regions both strains appear to have inherited this region from the same subspecies, be it from *M. musculus domesticus* or from *M. musculus musculus*. In contrast, across the high polymorphism regions, each strain seems to have inherited this region from a different one of these two subspecies (6). This means that the laboratory mouse is not a simple domesticated version of *M. musculus domesticus*, but a segmented muddle of *M. musculus domesticus* and *M. musculus musculus*, at least.

In the almost 100 years since some of the most commonly used laboratory strains were established, there have been various efforts to incorporate more of wild mouse genetics into strains available for laboratory use (1). Various wild-derived inbred strains have been made based on animals trapped in various parts of the world (from Asia, central Europe to the Americas), many of which are therefore other subspecies of *M. musculus*. These wild-derived inbred strains have been used in genetic mapping (for both immunological and nonimmunological traits), including *via* F1 hybrids made by crosses to already existing strains, such as C57BL/6. Because these wild-derived inbred strains are genetically distinct from the existing laboratory inbred strains, and because the existing inbred strains have a mosaic genome (above), these derived F1 hybrids have very substantial genetic diversity available that can be used in genetic mapping (7).

Clearly, mice have been selected while being domesticated to the laboratory, as has any other domesticated species. This process started with the mice used in the pet trade and then continued in laboratory mice. Laboratory mice will principally have been selected to be good (high and rapid fecundity) breeders, which itself will have selected on a whole suite of life-history and physiological, *etc*. traits. The mouse immune system and its function are unlikely to have been left unselected during this process. Comparison of the food intake, growth rates, *etc.* of wild-caught mice (at least three generations post-capture) and laboratory mice showed that the wild-derived female mice ate less food, grew more slowly and became sexually mature later (by approximately 3 weeks) than laboratory mice (8). The male wild mice also grew less quickly than the laboratory mice, but they reproductively matured at the same rate (8). These findings are consistent with laboratory mice, especially females, having been selected to feed rapidly so as to grow and reproduce quickly.

ECOLOGY

Wild *M. musculus domesticus* is most commonly known living commensally with humans, typically in farm out buildings *etc*. Such populations can be very stable, probably because of the constant availability of food (9) – many small mammals eat approximately half their body weight in food everyday (10). Beyond the absolute availability of food, a mouse's position in an environment can also significantly alter its behaviour, with ecological consequences (11). Animals in these stable, commensal populations rarely move beyond where they are born (except *via* accidental, passive human action), so that only a very small proportion of mice will move more than 25 m in their life – young male mice are those most likely to disperse (12). Within such an environment there are a mosaic of male-defended territories, with each reinforced by urine-derived cues (9, 13). In each territory there is one dominant male, a few subordinate males, several breeding females and some of their offspring (9). Mice can potentially breed continuously (9), but within each territory reproduction is manipulated by signalling among the mice *via* pheromones in their urine. Firstly, females' ovulation is controlled by these pheromones – cues from males accelerate ovulation, and cues from females slow ovulation (9). Females' puberty is also affected by cues from other females (9), and male hormone titres are themselves altered in response to female urine. What all this means is that the reproductive biology of mice within a territory is controlled by these multiple interindividual interactions that effectively temporally control female ovulation and also male reproductive-cueing behaviour (9).

Mice can also live feral in free-living habitats and in these settings they generally live at much lower densities, their positions are less stable, individual's home ranges may be much larger, and more dispersion occurs (9, 12). Much less is known about the social structuring of mice in these settings, but it is probably unlikely that the stable,

or semi-stable, demic structure (above) occurs because the feral populations are much less stable (9). Indeed, in these populations monthly mortality has been estimated at 30%, with 90% mortality over winter (9). Even within commensal populations it has been estimated that about half of all mice born do not join the adult population after weaning (13). A survey of the age structure of wild-caught commensal mice showed that most male mice were less than 28 weeks old (the very oldest male mouse was 62 weeks old); female mice often lived to be older with them commonly reaching 60 weeks of age (the oldest female mouse was almost 100 weeks old) (14).

For mice in either commensal or feral settings they all have to contend with infection from a variety of pathogens. Several studies have surveyed populations of wild mice for the prevalence of a range of infections (15–17). In many cases the sought-for infections have occurred at a high prevalence (suggesting that these wild mice may be reservoirs of infection for laboratory mice) (16), but the effect of these infections in wild mice themselves is not well understood. Comparing these studies also shows that the infections also differ among mouse populations. For example, serological surveys for infection with Sendai virus among wild mice in the north of England (15), Pennsylvania, USA (16), and Thevenard Island, Australia (18) found no evidence of infection, while in south-eastern Australia there was a prevalence of 1·8% (19). In our own study of wild mice from across southern England and Wales between 2012 and 2014 we found a Sendai virus seroprevalence of 51%. More generally, in our survey of eight different infections, we have found that mice are exposed to multiple infections from early in life such that no mouse was infection-free after 5 weeks of age, and that by 4 weeks of age (the approximate time of weaning) most mice had three or four different infections.

For infection with the pinworm *Syphacia* spp. prevalence of infection also varies substantially among populations (20), ranging from 2% in the UK (21) to 67% in Australia (22); we have observed a prevalence of 71% for *Syphacia* spp. among most of our sampled mice, though an absence of this in mice from Skokholm Island, Wales, and from the London Underground.

THE WILD IMMUNOLOGY OF *MUS MUSCULUS DOMESTICUS*

There has been very limited study – in fact just three papers – of the immune function of wild *M. musculus domesticus*. The very first comparison of wild-caught mice (as well as of other wild-caught rodent species) that were then maintained in the laboratory, with laboratory-bred mice, immunized the animals with sheep red blood cells (SRBC) and then assayed the *in vitro* lysis of SRBC by splenocytes from the immunized animals (23). This found that the wild mice caused significantly greater SRBC lysis compared with the laboratory mice (23). In a second study, a comparison of wild-caught (then laboratory maintained) mice with a standard laboratory mouse strain showed that in response to immunization with keyhole limpet haemocyanin (KLH) the wild-caught mice were generally more immune reactive, as shown by greater and more avid anti-KLH antibody responses (24). The wild-caught animals' splenic leucocytes also showed a greater overall activation (measured by flow cytometric analysis), compared with those of the standard laboratory mice (24). In both these studies the wild-caught mice presumably had these immune phenotypes because of the antigenic challenges that they had had before they were caught, something that had not happened to the laboratory strains of mice. There was a very notable degree of interindividual variation in the immune measures among the wild mice, more so than among the laboratory mice (23, 24). These differences were also likely to be due to genetic differences among mice and due to their different prior history (antigenic history, infection, health status, *etc.*). In the third study, natural killer (NK) cells of wild-caught mice (that were then maintained in the laboratory for no more than 7 days) and of laboratory strains of mice were compared (25). This found that the wild-caught mice had NK cells in the peripheral lymph nodes (but the laboratory mice did not) and that the NK cells of the wild-caught mice were in a primed state, compared with those from laboratory mouse strains (25). Further, when the NK cells were stimulated with cytokines the wild-caught mouse NK cells responded to a comparatively greater extent (25). As above, this difference between mice from these two sources was probably because the wild-caught mice had been under sustained microbial exposure during their wild lives, unlike their laboratory-bred, effectively naïve counterparts (25). Together, these three studies show that, perhaps not surprisingly, wild-caught mice have qualitatively different measures of immune function compared with laboratory strains of mice, probably due to the different antigenic exposure histories of the mice from these two sources. The immune system responds to antigen and so wild animals, with their richer antigenic history, will have immune systems that are in a different state than that of naïve, laboratory-bred animals. There was also very substantial variance among the wild animals in their immunological measures, with this both due to the animals differing genetically and in their prior antigenic history, physiological state, *etc.*, factors that are largely standardized among the laboratory-bred mice.

There has also been some analysis of the immune function of wild-derived inbred strains of mice (above). These strains differ in phenotypes of immunological interest, both when compared with each other and when compared with established laboratory mouse strains. For example, among wild-derived inbred mouse strains some are comparatively hyporesponsive to stimulation with polyinosinic–polycytidylic acid (poly(I:C)) [measured as the tumour necrosis factor α (TNFα) produced by peritoneal macrophages following *in vitro* stimulation] compared with C57BL/6, but generally not following stimulation with other molecules such as lipopolysaccharide (LPS), peptidoglycan, CpG, *etc.* (26). This difference was tracked down to the effect of a different allele of the TLR3-coding locus of the hyporesponsive strains, compared with the "normally" responsive strains (26). Some wild-derived inbred mouse strains also showed a resistance to the effect of LPS administration, something that kills C57BL/6 mice (27). This gross phenotypic difference has an immunological basis because the wild-derived mice that were resistant to the effect of LPS administration were comparatively deficient in their macrophages' production of interferon β (IFN-β). The origin of this effect was complex, appearing to be under polygenic control (27). Also, among other wild-derived (but not inbred) mouse strains there was a diversity of B cell responsiveness (but not of macrophage responsiveness), such that some of the wild-derived strains were significantly less responsive than the laboratory strain C57BL/6, while other wild-derived strains were similar to the laboratory strain (28).

Using these wild-derived inbred strains of mice will principally reveal the effects of genetic differences among the mice, be these simple one-locus effects, or more complex effects. Because these wild-derived inbred strains include a number of subspecies of *M. musculus* then this is potentially revealing genetic effects beyond *M. musculus domesticus* itself. Moreover, what these studies show is the rather self-evident fact that the immune phenotype of standard laboratory strains of mice (such as C57BL/6) is just one phenotype from a range of many possibilities. Perhaps inevitably, much of this literature takes it as self-evident that the immune response of the standard laboratory strain is normal and that of the wild-derived mice is reduced or defective (26), but this of course does not recognize that the standard laboratory mouse and its phenotype is just one sample of what exists in the wild.

A number of studies have investigated the genetic diversity of wild mice, specifically of genes of immunological relevance (e.g. 29, 30). These often report variants, or levels of diversity, that are surprising from the perspective of laboratory strains of mice, but often the deeper significance and broader relevance of this genetic diversity and of its functional immunological effect is less clear. However, the approach used in (30) is particularly interesting from a wild immunology perspective. Specifically, in this study different genetic variants in the regulatory region of the *Fcgr2b* gene in wild mice were found, and the most common wild haplotype was then knocked into C57BL/6 mice (30). This knocked-in mouse strain was then used to make detailed study of the molecular genetic and immunological effect of this particular haplotype. This approach was therefore able to go from identifying genotypes in wild mice to assaying their functional effect in the laboratory.

RATS – *RATTUS NORVEGICUS* AND *SIGMODON HISPIDUS* – AN ASIDE

Rats are also common laboratory animals whose immunology has also been studied in the laboratory. Analogously there has also been some study of the immune function of wild rats. Wild rats (*R. norvegicus*) had greater serum concentrations of IgG, IgM and IgE, compared with laboratory-bred rats, and there were more autoreactive IgG antibodies in wild rats, compared with laboratory rats (31). In contrast to the studies with wild mice showing that wild animals were often more immunologically responsive compared with laboratory animals (above), wild rat splenocytes were less responsive to stimulation with ConA, compared with laboratory-derived rat splenocytes, by a number of measures; the exception was the production of interleukin 4 (IL-4), which was significantly greater by stimulated splenocytes of wild rats compared with those of laboratory-bred rats (32). Flow cytometric analysis of cells from wild and from laboratory-bred rats showed a number of differences, but of note was that the wild-caught rats had a comparatively greater measure of activation of their T cells (33). In general the rather few studies of wild *R. norvegicus* show that the wild rats differ immunologically from laboratory strains of rats, with many of these differences also probably due to the previous infection and antigenic exposure of the wild animals, compared with the laboratory strains of rats.

In wild-caught cotton rats, *S. hispidus*, comparisons of measures of humoral and cellular immune function throughout the year showed seasonal changes in these measures, with this possibly being due to density-dependent effects operating within the sampled population (34). In this study there were no laboratory-bred, control animals against which the wild-caught animals could be compared (34). In many species it has been shown that an individual's diet can have profound effects on measures of immune function (35). When wild-caught *S. hispidus* were maintained in enclosures with different (both quantitative and

qualitative) feeding regimes, better-quality food increased the total number of white blood cells, as well as some other haematological values (36), suggesting that some aspects of the immune function of these cotton rats were limited by their natural environment.

Considering these studies of wild mice and of wild rats together, firstly it is remarkable how very, very few studies there have been. Secondly, the measures of the immune responses of the wild animals are recognisably similar to those of laboratory strains. Thirdly, wild animals differ immunologically from the laboratory animals in ways that are probably due to the wild animals having had a history of sustained antigenic exposure – something completely consistent with their wild lives. Fourth, there is significant interindividual immunological variation among the wild animals, which could be due to genetic differences and prior-environmental differences among individuals.

THE CENTRAL QUESTIONS OF WILD IMMUNOLOGY

The central question of wild immunology is how does an animal's immune system and its immune responses contribute to that animal's fitness (35, 37, 38)? Because the immune system and its consequent responses is just one of many physiological systems of an animal, this question can never be divorced from asking how other aspects of an animal's life – for example, physiological investment in reproduction – also contribute to its fitness. Because these and other physiological processes require resources, and because it is thought that animals are often resource limited, then animals have difficult decisions of resource allocation to make, with the consequence that the immune response mounted is often done so under these conditions of resource limitation (35). Thus, our starting question can be refined to what are the optimal immune responses that an animal should make to maximize its fitness? Here, the answer may be counterintuitive, for example that some hyporesponsiveness is optimal because (i) this might avoid immunopathological effects and (ii) that by not responding then limited resources are available for something else (37). Individual animal's lives differ in many ways and therefore what is immunologically optimal will be individual specific. Moreover, because prior functioning of the immune system affects its future function, then this can drive very substantial immunological differences among individuals. This therefore means that questions of wild immunology need to ask about the functional effect of the immune system rather more than measurement of detailed immunological parameters.

IMMUNOLOGY'S NEXT MAJOR CHALLENGE

It is time for the laboratory mouse to get back to the field. The decades of immunological research on mice and the vast repertoire of tools and reagents can – and should – be used in wild immunology. Laboratory-based, reductionist mouse immunology has been working towards this end, for all these years, without realizing what its destiny would be. What sort of studies can, and should, now be done? Clearly the style of study possible in a laboratory and that possible in the field is different, but the challenges of working in the field are not insurmountable hurdles. Ironically, much mouse-based immunological work is carried out with the perspective of understanding human immunology, and in these settings researchers continually move between laboratory-based studies of mice and field-based studies of humans. It is obviously possible to make immunological observations of wild mice that we could not of humans, so the wild immunology study of wild mice is potentially easier than integrated human–mouse studies.

Laboratory-based immunology has explained how the immune system works – that is the networks of signals, checks and balances that define what immunological output results from what antigenic and immunological input. These basic mechanisms are not then what needs to be restudied *per se* in wild animals. We need to find out what is the standard immunological background of wild mice, and we need to redefine normal to wild mice and so stop applying this label to laboratory mice. What we need to know for wild mice is what is the functional immunological output of a mouse in its environment, and what is the effect of this output on its ecology and fitness. This is a hard problem of ecology, not necessarily a hard problem of immunology.

These studies are possible and tractable now. The perfect study would be a longitudinal one of marked wild animals, but where an animal's capture and sampling is random. This has been done very successfully with other small rodent systems (e.g. 39). At each sample we would then want to know what sort of immune responses the animal is making, including both general measures but, with more refined hypotheses, understanding antigen-specific responses would also be key. Repeating this over an animal's short life (hence using sample collection that is non-lethal) would enable a summary of each mouse's immunological life-history course to be described. For the ecology and fitness, at each capture we will want to know about its relative success (thus measuring survival and health, *etc*.). Reproductive success is the key measure of fitness, and here genetics can be used to measure individuals' genetic contribution to succeeding generations. In essence, this is what the long-running study of the St Kilda

Soay sheep has done, so that this has generated a very good understanding of what contributes to a sheep's fitness on St Kilda (40). Wild mouse systems, though, offer considerably greater analytical power both because the necessary immunological characterization is very much more straightforward and because replicate populations can be used with wild mice. The ability to replicate study populations gives very substantial statistical advantages, but it also allows the opportunity to understand how different geographies and ecologies affect how mice use their immune responses.

So far we have considered the two extremes – the laboratory and the wild – but a halfway house of enclosures is possible too. These have the advantage that there are defined animals within the enclosures that, in theory, can be caught and sampled at will (41). The enclosures can be left semi-wild or managed in various ways to perturb the test population. Of course such enclosures allow replication and the use of different treatments. A different type of halfway house is the approach used in (30), where genetic variants of wild mice are knocked-in to laboratory mouse strains for laboratory assay.

So far, such studies of either truly wild populations or of enclosed, semi-wild animals are observational studies, but in both settings the populations can be manipulated to test specific hypotheses. This is where the immunological power of the laboratory mouse can be used for very great effect. Many of the immune manipulations that are standardly used in laboratory immunology can in principle be used with wild animals. This means that some cell populations can be depleted, or supplemented; that certain cytokines or other signalling molecules can be inhibited and that the effect on mice, their ecology and fitness tested. Clearly these would be nontrivial wild experiments, but they would be very powerful experiments. What these approaches would allow is the test of the functional effect of immune system components in a real-world context.

MOUSE GENETICS

Currently large international research consortia are trying to discover the function of all of the mouse genes. This is being done by systematically knocking out genes and then phenotyping the animals in many ways. Mouse knockouts have been used very extensively in immunological research, allowing researchers to disentangle the effects of different cell types and molecules on immune responses and other phenotypes. All this is being done to understand how genes control immunological phenotypes. In the wild there are several, complementary ways in which wild mouse immunogenetics could be studied. Firstly, taking inspiration from human-based genome wide association studies (GWAS), traits of immunological interest could be genetically mapped in wild mice. Simply, wild mice are caught, their relevant immune phenotype is measured, the mice genotyped, and then associations sought between the trait and genotype. This approach is potentially hugely powerful, explaining the genomic architecture underlying the trait in question. The results may be complex, because of epistatic and pleiotropic effects. Further, results may differ among different mouse populations [thus highlighting environmental (E), genetic (G) and also G $\times$ E effects]. However, this complexity is what needs to be embraced. While the one gene, one phenotype paradigm is attractive and tractable, within-genome interactions are as important and complex as those within a mammalian immune system. GWAS-style analysis of wild mice populations is a powerful way to discover the genetic control of immunological traits in the ecological context of a mouse and its immune response. Such analyses can continually move between the field and the laboratory.

These analyses can go a next step too. The relative success of different alleles at loci of immunological interest can be followed in wild populations. This could be a study of already existing allelic diversity in the study populations. Alternatively, alleles present in laboratory strains could be introgressed into wild mice and then released into the wild (or, at least, enclosures) and their population genetic success, as well as the immunological and ecological effect studied in the wild.

The possibilities of what could be done to understand how the mouse immune system is functioning in wild populations, and the effect of this function on the ecology and fitness of wild mice, are endless. For inspiration we should turn to the genome-enabled field biology approach that is currently being used with plants (42). This major programme of work is genetically dissecting and manipulating traits in real-world conditions. By manipulating a trait genetically and phenotypically and then testing the consequent effects on fitness in the organism's natural environment the challenge of modern biology is addressed head on: this is what laboratory mouse wild immunology can now do.

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