Modelling the human immune response: can mice be trusted?

Commentary

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The mouse is now the animal of choice for laboratory-based medical research. Although its contribution to advancing understanding of our inner workings is indisputable, we should acknowledge that mice and humans are tangibly different. This article highlights, and attempts some rationale for, discrepancies between the two species' immune systems.

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Current Opinion in Pharmacology 2001, 1:431–435

1471-4892/01/$ – see front matter

Abbreviations

BCR	B-cell receptor
Btk	Bruton's tyrosine kinase
EBV	Epstein-Barr virus
GC	germinal centre
GSL	glycosphingolipid
IL	interleukin
XLA	X-linked agammaglobulinaemia

Can mice be trusted?

As with people, the answer to the question must be "it depends what you ask them". With the means to genetically manipulate the mouse with increasing elegance, its current role as a powerful research tool is undeniable. However, it seems that, for some, mice are being exploited not so much to model the human condition but more as an end in itself. There is also a trend to extrapolate automatically (and often lazily) findings generated in *Mus musculus* directly to *Homo sapiens* without any concession to the possibility that the two species may have established a few differences since their diversification some 50 million years ago. The purpose of this commentary is to highlight, with a few salient examples, some of these disparities and to moot possible reasons as to why they may have come about.

Whiskers and tails

Apart from whiskers and tails, there are a variety of conspicuous attributes to distinguish mice from us. Our rodent cousin is, for example, 3000 times smaller, grows 100 times faster after birth, and ages 30 times faster after maturity. Its living horizon does not go above 5 cm compared with the physical stature of humans that reaches some 30–40 fold higher; the breathable microenvironment (including microbes, allergens, and pollutants) should thus be very different for the two species. Then there are considerations relating to diet, habitat, survival and reproductive strategies. Surely, just as selection over the aeons will have fashioned and specified what is externally discerned as mouse-ness and human-ness, so will (at least some of) those defining characteristics — together with the alternative lifestyles they impose — have participated in individually shaping each species' internal constitution including, and perhaps especially, their immune system.

The enemy within

Then there is the 'enemy within'. Each species has taken on board, and coexists with, its own stock of bacterial and viral flora. Although many of these will be innately harmless, and some even beneficial, others harbour the potential for catastrophe if not kept in check. In this respect, our symbiotic relationship with the fascinatingly complex — but potentially lethal — Epstein-Barr herpes virus (EBV) highlights a remarkable adaptation between the host and an uninvited guest that not only infiltrates but conceals itself within the very system designed to combat such intrusion. EBV is present in humans the world over. It, or closely related viruses, can be found in all apes of the Old World and was more recently described in primates of the New World [1••]. We are likely, therefore, to have been evolving with EBV for as long as we became a recognisable species some three million years ago.

Needless to say, mice neither harbour EBV nor can be infected with it. It is beyond the scope of this review to detail the complexities of the intricate co-existence that has been established to allow the successful propagation of both humans and EBV. Instead, the reader's attention is drawn to eloquent discourses on the subject by George Klein and Dorothy Crawford [2,3,4••]. Recent studies from David Thorley-Lawson and colleagues [5•,6] are indicating that EBV has elegantly hijacked the selfsame pathways that its target cell, the B lymphocyte, uses to generate immunological memory, allowing the virus to establish itself a secure and lifelong haven within its chosen host. It is almost inconceivable that such sophisticated adaptation is unidirectional; that the human immune system has not itself been refined in the process. This is only one example of the need to adapt and survive — since going our separate ways there will have been numerous other separate fine-tunings of the human and murine immune systems in response to such internal parasitic pressures. Our current tussle with HIV might well be laying the ground for a future symbiotic partnership.

Although we acknowledge that common themes of the immune system have undeniably been preserved — not just among Rodentia and Primates, but probably all mammals — we will now illustrate in detail (with a focus on B lymphocytes and asthma) a few of the discrepancies that highlight the proposition that, perhaps, when modelling the human condition mice cannot always be trusted.

B lymphocytes

Early B-cell development

There are two critical checkpoints through which a pro-B-cell must pass in order to enter the periphery as a mature B cell. Checkpoint one is the production of a functional pre-B-cell-receptor (pre-BCR). Checkpoint two is the production of a BCR (surface immunoglobulin). Failure to pass these results in entry into apoptosis. BCR engagement by antigen at the immature B-cell stage can induce receptor editing, apoptosis, positive selection or even recruit the cell into a T-dependent-antibody response if T-cell help is available [7]. These processes are common to both mouse and man.

Critical differences emerge when the controlling signals involved in B lymphopoiesis are analysed in greater detail. In particular, the requirement for a functional Bruton's tyrosine kinase (Btk) appears much more stringent in man than in mouse. Defects in Btk in man produce, for the most part, X-linked agammaglobulinaemia (XLA), characterised by a block in B-cell maturation occurring at the pro-B to pre-B stage and resulting in very low numbers of circulating B lymphocytes [8]. This block is associated with profound hypogammaglobulinaemia, which typically presents in childhood with repeated infections due to encapsulated bacteria. In contrast, the Xid mouse (X-linked immunodeficiency) and mice with a null mutation in Btk exhibit an immunodeficiency characterised by reduction in B-cell numbers to 50% of normal levels, lack of the $CD5^+$ B-cell subset and decreased serum concentrations of IgM and IgG_3 [9]. This is associated not with global hypogammaglobulinaemia but, rather, with a selective inability to respond to polysaccharide antigens. A similar contrast is seen with the B-cell linker protein BLNK. In humans, defects in this protein produce an XLA-like phenotype but with even fewer circulating mature B cells [10]. Again the murine counterpart has a phenotype similar to X-linked immunodeficiency [11].

Mutations in λ5, a component of the pre-BCR, in humans produce a more severe clinical phenotype [12] compared with λ5 knockout mice, in which immune function improves with time [13]. The cytokine requirements of developing B cells appear to be critically different in mice and men. Defects in the interleukin-7 (IL-7) receptor result in a profound block in B-cell development in the mouse [14], but not in the human, where defects produce a severe combined immunodeficiency with normal B-cell numbers [15].

Differences between mature B cells of mice and people

Mature B cells have been delineated into two major subsets, B-1 and B-2 [16]. B-1 cells are dominant during foetal development of both mice and humans, whereas in adults they represent a minor population that is concentrated particularly in coelomic cavities and associated with the production of autoantibodies. Although initially thought to represent discrete lineages, with evidence gleaned primarily from adoptive transfer studies in the mouse, there now exists a groundswell of opinion that the minority B-1 cell population can be generated from the majority adult B-2 pool of conventional B cells [17•,18•]. The CD5 surface antigen has served as a defining marker for the bulk of murine B-1 cells (termed 'B-1a'), although a small 'sister' $CD5^-$ B-1b subset has been identified. Again, in the mouse, expression of CD5 within the B-cell compartment appears to be mutually exclusive with that of CD23, a marker restricted to conventional B-2 cells. Indeed, it has been shown that whereas crosslinking BCR promotes CD5 induction at the expense of CD23 expression, CD40 ligation downregulates CD5 in favour of CD23 upregulation [19]. This scenario is not recapitulated in the human. In fact, neonatal (cord blood) B cells are characterised by the co-expression of the two 'mutually exclusive' markers, a feature that is echoed in chronic lymphocytic leukaemia where dual CD5 and CD23 positivity is diagnostic of this common B-cell malignancy. Moreover, in humans, CD40 engagement actively promotes the development of this double phenotype amongst both $CD5^-$ and $CD5^+$ B cells [20•]. The functional impact of this interspecies discrepancy has yet to be determined, but advises caution in extrapolating from murine studies to human function with regards to these two important surface receptors.

CD38 was recently identified as the ecto-enzyme, ADP-ribosyl cyclase. Its targeting at the surface of expressing cells by monoclonal antibodies can mobilise intracellular Ca^{2+} with functional consequences that are both cell-type specific and microenvironment specific [21]. Within the human B-cell lineage, high-level expression of CD38 has proven to be a valuable marker for terminal differentiation towards plasma cells. It can also help to distinguish B cells of germinal centre (GC) origin from those residing in the periphery, the latter displaying sparse expression in comparison with the intermediate CD38 levels that characterise GC B-cells [22••]. A diametrically opposing pattern exists in the mouse; thus, initial high-level CD38 expression is actively downregulated as B cells enter a GC reaction and becomes lost on the plasma cells of this species [23].

Another surface molecule that aids the discrimination of GC B-cells from those of a non-GC origin in humans is CD77. Indeed, an exquisitely restricted CD77 expression defines the centroblast subset of GC B-cells and is diagnostic of the associated malignancies Burkitt's lymphoma and follicular-centre cell lymphoma [24•]. CD77 is a neutral glycosphingolipid ([GSL] globotriaosylceramide, Gb3) that serves as a receptor for the Shiga-like toxin of *Escherichia coli* O157. It has also been proposed to associate with CD19 [25] and, upon binding multivalent ligand,

independently promote apoptosis in susceptible cells following its redistribution with BCR into signalling complexes of so-called lipid rafts [26]. Although it is undoubtedly present in the mouse, CD77 has been reported as either being completely absent from murine splenocytes [27] or indiscriminately present at low levels on all B cells of the spleen and lymph nodes [28•]. From studying a spectrum of GSLs and their distribution, Kovacic *et al.* [28•] commented on the "interspecies differences in GSL expression between murine and human lymphocytes" with "human B lymphocytes expressing a more restricted GSL repertoire (compared to the mouse)".

Telomeres – why humans live longer than mice?

Telomeres — the protein and DNA structures that form the ends of eukaryotic chromosomes — are believed to function to stabilise and protect chromosome ends, to determine chromosomal localisation and to regulate cellular replicative capacity. This last property has been the subject of much research with regard to ageing of cells and organisms. A reduction in telomere length with each cell division is proposed to be a cell division counter and, once a preset number of divisions has been achieved, cellular senescence ensues. Telomere shortening can be opposed and even reversed by the expression of the enzyme telomerase. For example, the reduction of telomere length as pre-B-cells progress to naïve B cells is reversed, and telomeres actually grow longer, as naïve B cells become GC B-cells [29].

Murine telomeres are considerably longer than their human counterparts, yet mice have a much shorter life span. A murine telomerase knockout strain of mice was able to reproduce through five generations without any significant biological abnormality, casting considerable doubt on the hypothesis of telomere 'counting' in the regulation of cellular senescence in this species. Indeed, it has been proposed that this mechanism might be disadvantageous for short-lived vertebrates such as the mouse. Wright and Shay [30] have gone so far as to state that extrapolation of data from mouse studies of telomeres to human replicative aging needs very careful interpretation. Data showing differential regulation of replicative senescence in $CD8^+$ T cells in humans and mice bear out their caution. Akbar and colleagues [31••] suggest that telomere lengths in mice are sufficiently long that CD8 memory can be maintained by slow but continuous cycling. In contrast, the shorter telomere lengths of human $CD8^+$ cells would prevent this, requiring additional mechanisms for the maintenance of memory that do not include proliferation. When one considers mechanisms underlying 'life-long' immunological memory to an antigen, whether it be in the T-cell or B-cell compartment, there are bound to be differences between species where there is a greater than 30-fold discrepancy in how long that needs to be.

Mouse models of asthma – or are they?

Asthma represents a major and growing health problem of industrialised nations and the need for good animal models is pressing. Although it is relatively straightforward to induce infiltration of eosinophils and lymphocytes into the lungs of mice — irrespective of the strain or sensitisation and challenge protocols — certain strains with underlying Th2-like or hyperresponsive phenotypes are favoured for use in asthma models. Numerous reports over the past few years have described the 'hallmarks' of asthma in such mice: epithelial damage; microvascular leakage and oedema; and eosinophil activation [32–35]. Because of the success at inducing such phenotypes, the notion that allergic murine models are asthma-like has gained wide acceptance. The advantages of using inbred allergen-responsive mice are obvious but there is the inherent danger, as with all murine models, in assuming that results obtained are pertinent to the human disease. Mouse models of asthma make use of genetically identical animals that have spent their entire life in a pathogen-free environment and are then exposed to a specific antigen under very tightly controlled conditions for a defined period of time. Compare this with the human experience where a genetically out-bred population has been under chronic bombardment by myriad environmental antigens over its entire life. Add to this the role an individual's complex genetic background clearly plays in the way it responds to allergenic challenge, and it becomes almost surprising that any formative information has been generated through murine models of asthma.

Important differences exist between these mouse models of asthma and the human condition. The mere presence of eosinophils in the lungs of allergen-challenged mice is generally interpreted as confirmation of an asthma-like eosinophilic inflammation. However, although eosinophil degranulation is a characteristic feature of asthma and allergic rhinitis in humans, degranulation of eosinophils has not been convincingly demonstrated in the various murine models of these airway diseases, even when marked pulmonary eosinophilia is evident [36]. Interestingly, blood eosinophils isolated from allergen-challenged mice remain non-degranulated *in vitro* in the presence of stimuli such as fMLP (formyl-Met-Leu-Phe) and PMA (phorbol myristate acetate), whereas the same treatment of their human counterparts results in extensive degranulation [37]. Furthermore, in contrast with what is seen in the human disease, pulmonary eosinophils do not appear to infiltrate the airway epithelium of allergen-challenged mice [38,39]. It appears that there are fundamental differences in the regulation of murine and human eosinophil development.

The role of mast cells in murine asthma models is also unclear. The crosslinking of high affinity IgE receptors (FcεRI) on mast cells leading to degranulation, is one of the most important factors in generating the pathology of atopic disorders. In humans, the release of inflammatory mediators from mast cells leads to bronchoconstriction and the influx of inflammatory cells. However, studies with both mast-cell-deficient and IgE-deficient mice have demonstrated that these animals show degrees of bronchial hyperresponsiveness, eosinophilia and inflammation comparable to those of

normal animals [40–42]. These findings in the IgE-deficient mice suggest that the mere presence of IgE is not critical for the development of the murine 'asthmatic' phenotype. It also implies that many of these murine models may be more representative of the human condition of intrinsic, rather than allergic, asthma. Intrinsic asthma is recognised as a form of the disease which typically occurs in older individuals and is related to neither antigenic sensitisation and exposure nor to elevated levels of IgE.

Another hallmark of asthma is epithelial shedding and the epithelial injury repair process plays a major causative role in asthma-like pathology and remodelling. Repair of the airway epithelium starts immediately after infliction of injury and shedding; however, in the mouse there is scant evidence of airway epithelium shedding and restitution following injurous allergenic exposure.

In summary, mouse models of asthma can reproduce some, but not all, manifestations of the human disease. The antigen-driven models are useful in that they allow the dissection of the mechanisms of inflammation; however, the limitations of existing mouse models highlight the need for further development of sophisticated alternatives that more faithfully represent the complex human disease. Even then, intrinsic differences between the species may preclude a dependable recapitulation of this debilitating ailment.

A salutary lesson

IL-5 has for a long time been seen as the 'asthma-relevant' cytokine. IL-5 levels in the serum and tissues of asthmatics correlate with numbers of eosinophils in the tissue and these parameters correlate with symptoms [43,44]. IL-5 deficiency abolishes airway hyperreactivity, eosinophilia and lung damage in mice [32]. A monoclonal antibody has been made to neutralise IL-5 and in mouse models of asthma it removes IL-5, reduces eosinophil counts, and dramatically improves the bronchial hyperreactivity that mouse allergists correlate with asthma [45]. On the basis of these results, large amounts of money were invested by the pharmaceutical industry into an anti-IL-5 treatment for asthma. The first clinical trial was performed at the Brompton Hospital and the results published in the *Lancet* [46••]. Certain caveats need to be applied (the dose given may have been too low or given over too short a period of time) but in this study IL-5 levels and eosinophil counts went right down — nothing happened to the asthma-outcome measures.

Epilogue

Since retired schoolteacher Abbie Lathrop first began breeding mice for research [47], the mouse has dominated biomedical exploration and breeding of mice is now a multi-million dollar industry [48]. We know so much about mouse biology that it sometimes seems mice are getting the best deal from medical research programmes (in particular, see [49]). This calls to mind a passage from Douglas Adams' *Hitch Hiker's Guide to the Galaxy* [50], when the final beneficiaries of the 10 million year long Earth experiment were revealed: "The stuff with the cheese etc was just a front. It wasn't we who were doing experiments on mice, it was mice who were experimenting on us!".

Dedication

This article is dedicated to the memories of Noel Ling and Graham Bird, both very 'human' immunologists in the fullest sense of the word.

Acknowledgements

We thank the numerous colleagues who contributed ideas and anecdotes to this commentary even though pressures of space prevented the inclusion of all of them. In particular Chris Buckley, Chris Bunce, Dorothy Crawford, Bill Cushley, Leopoldo Flores-Romo, George Klein, Allison Lang, Janet Lord, Kenneth Nilsson, John Pound, Mike Salmon and Ludwik Trejdosiewicz. The work of JG and GG is supported by a Medical Research Council (UK) Programme Grant. John Gordon is an MRC Non-Clinical Research Professor. Mark Larché is a National Asthma Campaign Senior Research Fellow.

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