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BRIEF REVIEWS

Of Mice and Not Men: Differences between Mouse and Human Immunology

Javier Mestas and Christopher C. W. Hughes[1]

Mice are the experimental tool of choice for the majority of immunologists and the study of their immune responses has yielded tremendous insight into the workings of the human immune system. However, as 65 million years of evolution might suggest, there are significant differences. Here we outline known discrepancies in both innate and adaptive immunity, including: balance of leukocyte subsets, defensins, Toll receptors, inducible NO synthase, the NK inhibitory receptor families Ly49 and KIR, FcR, Ig subsets, the B cell (BLNK, Btk, and λ5) and T cell (ZAP70 and common γ-chain) signaling pathway components, Thy-1, γδ T cells, cytokines and cytokine receptors, Th1/Th2 differentiation, costimulatory molecule expression and function, Ag-presenting function of endothelial cells, and chemokine and chemokine receptor expression. We also provide examples, such as multiple sclerosis and delayed-type hypersensitivity, where complex multicomponent processes differ. Such differences should be taken into account when using mice as preclinical models of human disease. ***The Journal of Immunology,*** **2004, 172: 2731–2738.**

Mice are the mainstay of in vivo immunological experimentation and in many respects they mirror human biology remarkably well. This conservation of function is reflected in recent reports on the sequencing of both the human and mice genomes, which reveal that to date only 300 or so genes appear to be unique to one species or the other (1). Despite this conservation there exist significant differences between mice and humans in immune system development, activation, and response to challenge, in both the innate and adaptive arms. Such differences should not be surprising as the two species diverged somewhere between 65 and 75 million years ago, differ hugely in both size and lifespan, and have evolved in quite different ecological niches where widely different pathogenic challenges need to be met—after all, most of us do not live with our heads a half-inch off the ground. However, because there are so many parallels there has been a tendency to ignore differences and in many cases, perhaps, make the assumption that what is true in mice—in vivo veritas—is necessarily true in humans. By making such assumptions we run the risk of overlooking aspects of human immunology that do not occur, or cannot be modeled, in mice. Included in this subset will be differences that may preclude a successful preclinical trial in mice becoming a successful clinical trial in human.

In this review our aim is not to suggest that the mouse is an invalid model system for human biology. Clearly, with so many paradigms that translate well between the species, and with the relative ease with which mice can now be genetically manipulated, mouse models will continue to provide important information for many years to come. Rather, our aim is to sound a word of caution. As therapies for human diseases become ever more sophisticated and specifically targeted, it becomes increasingly important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with examples of therapies that work well in mice but fail to provide similar efficacy in humans (2–7). By focusing on some known differences between mouse and human immunology we hope to spur interest in this area and encourage others to note differences where they occur.

Structure and general characteristics

The overall structure of the immune system in mice and humans is quite similar. As this topic has been recently reviewed in depth (8), we will not go into great detail here. One difference worth noting is that whereas mice have significant bronchus-associated lymphoid tissue, this is largely absent in healthy humans (9), possibly reflecting a higher breathable Ag load for animals living so much closer to the ground.

The balance of lymphocytes and neutrophils in adult animals is quite different: human blood is neutrophil rich (50–70% neutrophils, 30–50% lymphocytes) whereas mouse blood has a strong preponderance of lymphocytes (75–90% lymphocytes, 10–25% neutrophils) (10). It is not clear what, if any, functional consequence this shift toward neutrophil-rich blood in humans has had.

Tyrosine kinase receptor expression on putative hemopoietic stem cells (HSC)[2] shows a reciprocal pattern, with mouse HSC being predominantly c-*kit*$^{\text{high}}$, *flt-3*$^{-}$, whereas human HSC are predominantly c-*kit*$^{\text{low}}$, *flt-3*$^{+}$ (11).

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[2] Abbreviations used in this paper: HSC, hemopoietic stem cells; iNOS, inducible NO synthase; γ_c, common γ-chain; DETC, dendritic epidermal T cells; MS, multiple sclerosis; DTH, delayed-type hypersensitivity; EC, endothelial cells.

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Innate immunity

One of the first lines of defense in higher organisms, and often the only defense in lower animals, is the growing family of antimicrobial peptides, and in particular the defensins. These are important in mucosal defense in the gut and in epithelial defense in skin and elsewhere (12, 13). Neutrophils are a rich source of leukocyte defensins in humans, but defensins are not expressed by neutrophils in mice (14). In contrast, Paneth cells, which are present in the crypts of the small intestine, express >20 defensins (cryptdins) in mice but only two in human, likely reflecting different evolutionary pressures related to microorganism exposure through food intake. There are also differences in processing of defensins (Table I).

The last few years have seen a renewed focus on the field of innate immunology, spurred in large part by identification of the Toll-like family of receptors—the TLRs (15). This field is still relatively young and so far a limited number of differences have been noted between mice and humans (Table I).

There has been considerable controversy as to whether human macrophages express NO. Expression of functional inducible NO synthase (iNOS; NOS2) in mouse macrophages has been clearly demonstrated and iNOS mRNA is readily induced by IFN-γ and LPS (16). However, these same inflammatory mediators have failed to show consistent effects on human macrophages, hence the confusion. Recent work suggests that other mediators, such as IFN-$\alpha\beta$, IL-4 plus anti-CD23, and various chemokines, are actually far more efficient in inducing iNOS in human macrophages (17). However, the controversy is not dead yet (18).

Using different strains of mice a susceptibility locus for CMV infection, *cmv1*, was identified and later shown to encode the Ly49 family of proteins (19). There are at least 14 members and most are expressed on NK and NKT cells, where the majority act as NK inhibitory receptors for MHC I molecules. The Ly49 family is absent in humans, who use the KIR family as NK inhibitory receptors (20). KIR proteins are highly diverged from the Ly49 family and have Ig rather than C-type lectin domains in their extracellular domain; however, similarly to Ly49 they also recognize MHC class I. The ligands for mouse and human NKG2D differ: in humans, NKG2D binds the polymorphic MHC class I-like molecules MHC-I chain-related A, MHC-I chain-related B, and the UL16 binding protein family, whereas in mouse NKG2D binds to H-60 and Rae1β. The significance of these differences to CMV infection and to NK biology in general have not been determined.

Adaptive immunity

FcR represent a link between the adaptive immune system, which generates Ab, and the innate immune system, which can respond to Ab-Ag complexes through capture by FcR expressed on macrophages, neutrophils, eosinophils, mast cells, and dendritic cells. There are several differences in FcR expression between mice and humans. In humans, FcαRI (CD89) is an important IgA receptor expressed by neutrophils, eosinophils, monocytes/macrophages, dendritic cells, and Kupffer cells (21). Mice lack FcαRI and presumably use alternative receptors, such as Fcα/μR, the transferrin receptor (CD71) and polymeric IgR, which also binds IgM. Humans also express two IgG receptors not found in mice: FcγRIIA and FcγRIIC are closely related single-chain FcR, each of which has a single ITAM motif in the intracellular domain. In contrast, most other FcR associate with ITAM-containing signal transduction subunits (22).

In addition to differences in FcR there are well-known differences in expression of Ig isotypes between mice and humans, and direct correlations between subtypes within classes in each species are hard to make. Mice make IgA, IgD, IgE, IgM, and four subtypes of IgG: IgG1, IgG2a, IgG2b, and IgG3. Interestingly, in the C57BL/6, C57BL/10, SJL, and NOD strains of mice there is no expression of IgG2a, instead these mice express the novel IgG2c (23). Humans in contrast express two subtypes of IgA—IgA1 and IgA2—along with single forms of IgD, IgE, and IgM. In humans there are also four subtypes of IgG: IgG1, IgG2, IgG3, and IgG4; however, these are not direct homologues of the mouse proteins. While different subtypes have differing abilities to bind FcR or fix complement, the differences between mice and humans are not considered significant. In contrast, there are differences in class switching: in mice, IL-4 induces IgG1 and IgE, whereas in humans, IL-4 induces switching to IgG4 and IgE. In contrast, IL-13 has no effect on mouse B cells but induces switching to IgE in humans (24).

There are some interesting differences in B cell development that relate to the roles of several signaling molecules. BLNK (Src homology-2 domain containing leukocyte-specific phosphoprotein-65) is an adapter protein that is rapidly phosphorylated by Syk after cross-linking of the B cell Ag receptor. It then serves as a scaffold for downstream signaling components such as Grb2, Vav, Nck, and PLC-γ. B cell development in mice lacking BLNK is blocked at the pro-B to pre-B transition, resulting in low numbers of IgM$^+$ B cells, but no mature IgM$^{\text{low}}$IgD$^{\text{high}}$ B cells, appearing in the periphery (25). A naturally occurring mutation in the human BLNK protein has been identified that results in a splicing defect preventing protein expression. In this patient there was also a block in the pro-B to pre-B transition; however, there was also a complete absence of B cells in the periphery, suggesting a more severe block in human B cell development than in mice (26).

Similarly discrepant phenotypes have been noted in mice lacking functional BCR-associated tyrosine kinase Btk (27) and in mice lacking $\lambda5$ (28), the L chain component of the pre-BCR (Table I). Differences in mature B cells between mice and humans were recently reviewed (29), and include mutually exclusive expression of CD5 and CD23 on mouse but not human B cell subsets, and CD38 expression on human, but not mouse, plasma cells.

The discrepant phenotypes discussed above for BLNK, Btk, and $\lambda5$ should be treated with some caution as the human diseases usually arise due to mutations in the relevant genes rather than deletions of whole exons as seen in the mouse knockout models. In some cases, however, identical mutations have been found, or created, in mice and the discrepant phenotype remains. This is the case for human XLA and mouse XID, which both involve Btk (30, 31).

The development and regulation of T cells also differs between mice and humans. Thy-1 is a GPI-linked Ig superfamily molecule of unknown function. It is expressed on thymocytes and peripheral T cells in mice and has been widely used as a T cell marker in the thymus. In humans, however, it is only expressed on neurons. The basis of this tissue specificity is suggested to be the presence or absence of an Ets-1 binding site in the third intron of the gene (32).

Table I. *Summary of some known immunological differences between mouse and human*

	Mouse	Human	Notes	Refs.
Hemotopoiesis in spleen	Active into adulthood	Ends before birth		
Presence of BALT	Significant	Largely absent in healthy tissue		9
Neutrophils in periph. blood	10–25%	50–70%		10
Lymphocytes in periph. blood	75–90%	30–50%		10
Hemotopoietic stem cells	c-*kit*$^{\text{high}}$, *flt-3*$^{-}$	c-*kit*$^{\text{low}}$, *flt-3*$^{+}$		11
TLR2 expression on PBL	Low (induced on many cells including T cells)	Constitutive (but not on T cells)	Binds lipopeptides	88
TLR3	Expressed on DC, Mac. Induced by LPS	Expressed by DC. No LPS induction	Binds dsRNA	88, 89
TLR9	Expressed on all myeloid cells, plasmacytoid DC and B cells	Expressed only on B cells, plasmacytoid DC and N	Binds CpG	90, 91
TLR10	Pseudogene	Widely expressed		
Sialic acid Neu5GC expression	Widespread	Absent	Binds pathogens	92
CD33	Expressed on granulocytes	Expressed on monocytes	Binds sialic acids	93
Leukocyte defensins	Absent	Present	neutrophils	14
Paneth cell defensins	Processed by MMP7. Stored pre-processed	Stored as pro-form. Processed by trypsin		94, 95
Paneth cell defensins	At least 20	Two		13
Macrophage NO	Induced by IFN-γ and LPS	Induced by IFN-α/β, IL-4^{+} anti-CD23		17
CD4 on macrophages	Absent	Present		96
Predominant T cells in skin and mucosa	γ/δ TCR (dendritic epidermal T cells—DETC)	α/β TCR		40
γ/δ T cells respond to phospho-antigens	No	Yes		97
CD1 genes	CD1d	CD1a,b,c,d		41
NK inhibitory Rs for MHC 1	Ly49 family (except Ly49D and H)	KIR		20
NKG2D ligands	H-60, Rae1β	MIC A, MIC B, ULBP	NK activating Rs	98
fMLP receptor affinity	Low	High		99
FcαRI	Absent	Present		21
FcγRIIA, C	Absent	Present		22
Serum IgA	Mostly polymeric	Mostly monomeric		21
Ig classes	IgA, IgD, IgE, IgG1, IgG2a*, IgG2b, IgG3, IgM * absent in C57BL/6, /10, SJL and NOD mice, which have IgG2c	IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, IgM		23
Ig CDR-H3 region	Shorter, less diverse	Longer, more diverse		100
BLNK deficiency	IgM$^{\text{high}}$ B cells in periphery	No peripheral B cells		25, 26
Btk deficiency	Normal pre-B and immature B	Blocks pro-B to pre-B transition		28
λ5 deficiency	"leaky" block at pro-B to pre-B transition	Blocks pro-B to pre-B transition		28
CD38 expression on B cells	Low on GC B cells, off in plasma cells	High on GC B cells and plasma cells		29
B cell CD5 and CD23 expression	Mutually exclusive	Co-expression		29
IL-13 effect on B cells	None	Induces switch to IgE		24
Thy 1 expression	Thymocytes, peripheral T cells	Absent from all T cells, expressed on neurons		32
Effect of γ_c deficiency	Loss of T, NK, and B cells	Loss of T, NK, but B cell numbers normal		33, 34
Effect of Jak3 deficiency	Phenocopies γ_c deficiency	Phenocopies γ_c deficiency		31
Effect of IL-7R deficiency	Blocks T and B cell development	Only blocks T cell development		35, 36
ZAP70 deficiency	No CD4^{+} or CD8^{+} T cells	No CD8^{+} T but many nonfunctional CD4^{+}	Related to *syk* level?	37, 38
Caspase 8 deficiency	Embryonic lethal	Viable—immunodeficiency		62, 63
Caspase 10	Absent	Present		62
IFN-α promotes Th1 differentiation	No	Yes	Mutant stat2 in mice	44
Th expression of IL-10	Th2	Th1 and Th2		51
IL-4 and IFN-γ expression by cultured Th	Either/or	Sometimes both		
CD28 expression on T cells	On 100% of CD4^{+} and CD8^{+}	On 80% of CD4^{+}, 50% of CD8^{+}		54
ICOS deficiency	Normal B cell numbers and function, normal IgM levels	B cells immature and severely reduced in number, low IgM	Possibly age-related	55–57
B7-H3 effects on T cells	Inhibits activation	Promotes activation		101–2
ICAM3	Absent	Present	DC-SIGN ligand	103–4
P-selectin promoter	Activated by TNF and LPS	Unresponsive to inflammation		58
GlyCAM	Present	Absent		105
MHC II expression on T cells	Absent	Present		59–61
Kv1.3 K^{+} channel on T cells	Absent	Present	Regulates Ca flux	64, 65
MUC1 on T cells	Absent	Present	Regulates migration?	106
Granulysin	Absent	Present	In CTL	43

(*Table continues*)

Table I. *Continues*

	Mouse	Human	Notes	Refs.
CXCR1	Absent	Present		66, 67
IL-8, NAP-2, ITAC, MCP-4, HCC-1, HCC-2, MPIF-1, PARC, eotaxin-2/3	Absent	Present	Chemokines	66, 67
MRP-1/2, lungkine, MCP-5	Present	Absent	Chemokines	66, 67
IFN-γ effects in demyelinating disease	Protective in EAE	Exacerbates MS		4, 69–70
DTH lesions	Neutrophil-rich	Lymphocyte-rich		73, 74
Constitutive MHC II on EC	Absent	Present		80
EC present Ag to CD4+ T	No	Yes	Memory T only	75–77
CD58 (LFA-3)	Absent	Present	CD2 ligand	82
T cell dependence on CD2-ligand interactions	Low	High		82
CD2-ligand interaction	Lower affinity, with CD48	Higher affinity, with CD58		82
CD40 on EC	Absent	Present		83, 84
Vascularized grafts tolerogenic?	Yes	No		5
Microchimerism induces graft tolerance?	High success rate	Low success (expts. in non-human primates)		7
Passenger leukocytes	Account for graft immunogenicity	Do not account for graft immunogenicity		6

Similar to the development of B cells, mutation of key signaling molecules in T cells has markedly different effects in mice and humans. Several cytokine receptors, including those for IL-2, IL-4, IL-7, IL-9, and IL-15, share a common signaling chain called common γ chain (γ_c). Perhaps not surprisingly, deletion or mutation of this gene, which is on the X chromosome, results in severe immunological defects. Interestingly, these differ between human and mouse XSCID (33, 34). Numerous mutations have been identified in the human γ_c gene that inhibit function, and in most of these cases the result is a dramatic decrease in the number of T cells and NK cells. However, B cell development is normal, although function is impaired, likely due to the lack of T cell help. In marked contrast, B cell numbers are greatly diminished in γ_c-null mice. Given that IL-7R deficiency in mice blocks both T and B cell development (35), but only blocks T cell development in humans (36), it is likely that B cell development in humans is independent of IL-7. The major signal transducer for γ_c is JAK3 and mutation of this gene phenocopies the γ_c mutation in both mice and humans; that is, a lack of T and NK cells in human with the addition of a severe B cell defect in mice (31).

Interesting differences have also been noted in ZAP70-deficient mice and humans. ZAP70 is essential for TCR signaling in both developing and mature T cells, and compromised signaling results in SCID. In humans the defect results in normal numbers of CD4$^+$ T cells and absent CD8$^+$ T cells. However, the CD4$^+$ T cells are nonfunctional. In contrast, an identical mutation introduced into the mouse ZAP70 results in a block in differentiation of both T cell subsets at the double-positive stage (37). It has been suggested that the “leakiness” of the human mutant is due to incomplete down-regulation of the protein tyrosine kinase Syk in human thymocytes, compared with mouse thymocytes (38).

The study of γ/δ T cells has revealed a number of significant differences between mice and humans. T cells expressing γ/δ TCR are found in all organisms that have α/β receptors and yet their function is still largely an enigma (39). Mouse skin contains a large fraction of cells bearing a TCR encoded by a single Vγ and Vδ gene. These Vγ5-Vδ1 T cells appear to be oligoclonal, reside in the epidermis, and are known as dendritic epidermal T cells (DETC). DETC represent the predominant T cell in mouse skin, whereas cells bearing α/β receptors predominate in human skin and are found mostly in the dermis. Indeed, a cell with DETC characteristics has not been identified in humans (40). Human but not mouse γ/δ T cells have been suggested to recognize Ag presented by CD1 molecules—in particular CD1b (41). Interestingly, of the five CD1 molecules found in humans (designated CD1a, b, c, d, and e), only CD1d is expressed in mice (41). Similarly to γ/δ T cells the CD1 family of molecules has been implicated in the pathogenesis of tuberculosis, but their precise role has yet to be defined (42, 43). The differing expression of CD1 genes between mice and humans may well turn out to impact activation of both α/β and γ/δ T cells in tuberculosis, as both subsets can recognize a variety of Ags presented by CD1 molecules.

An often critical component of adaptive immunity is the skewing of T cell differentiation toward Th1 or Th2 phenotypes and this process represents another area of interaction between the innate and adaptive arms of immunity. In humans, the type I IFN, IFN-α, is secreted by several cell types in response to viral infection, including macrophages, and acts on T cells to induce Th1 development. This process is dependent upon STAT4 activation, and its recruitment to the IFN-α receptor by STAT2. In mice, however, IFN-α fails to induce Th1 cells and does not activate STAT4 (44).

The existence of polarized T cell populations was first demonstrated by Mosmann and colleagues (45) and since then has become a guiding principle for T cell activation. While polarization is relatively easy to observe in mice the paradigm has never been as clear-cut in the human system. Th1 and Th2 cells can certainly be found in human disease (46, 47); however, there is a growing recognition that in many diseases clear distinctions cannot be made and that T cells of both persuasions can often be generated simultaneously (48–50). For example, in mice, IL-10 is considered to be a Th2 cytokine, whereas in humans both Th1 and Th2 cells can make IL-10 (51). The response of mice and humans to schistosomiasis is remarkably different. Epidemiological data suggest that a Th2 response involving eosinophils and IgE may be key to combating infection in humans (52), whereas in mice effector cell activation by IFN-γ, a Th1 response, is essential for clearance of the parasite (53).

To become fully activated T cells require both a primary, Ag-dependent signal, and a second, Ag-independent or costimulatory signal. One of the best characterized costimulatory receptors is CD28, which is expressed by close to 100% of mouse $CD4^+$ and $CD8^+$ T cells. In contrast, only 80% of human $CD4^+$ and 50% of human $CD8^+$ T cells express CD28 (54), perhaps accounting for the remarkable efficacy of CTLA-4Ig in blocking T cell activation in mice. It will be interesting to see if expression of the CD28-related costimulatory molecule ICOS segregates with $CD28^-$ T cells in humans. The recent report on the identification of a human ICOS deficiency pointed to a further difference between costimulation in mice and humans. Whereas in mice the loss of ICOS does not affect either the number of mature B cells, their maturation status or their secretion of IgM (55, 56), the loss of ICOS in humans results in a severe reduction in B cell number, maturation status and secretion of IgM (57). Given the critical role of T cell CD40L in T-B interactions it would be interesting to know what the level of CD40L expression was on this patient's T cells and whether expression of this molecule is dependent upon ICOS signaling in humans. Two novel members of the B7 family of costimulatory molecules, B7-H3 and DC-SIGN, have recently also been suggested to have different roles in mice and humans (Table I).

P-selectin is constitutively expressed by endothelial cells (EC) and mediates leukocyte rolling by interactions with specific sugar residues carried by mucins. Interestingly, murine P-selectin can be strongly up-regulated by inflammatory mediators such as TNF and LPS, whereas the human gene is nonresponsive (58). It is interesting to speculate as to whether E-selectin in humans, which is strongly up-regulated by TNF, is the more important selectin on human EC for mediating leukocyte rolling.

Once activated, human T cells express MHC class II molecules whereas murine T cells do not. It has been suggested that human T cells can capture, process, and present Ag and that they express B7 and may therefore help to amplify an ongoing immune response (59, 60). In contrast, Ag presentation by T cells may also promote T cell anergy (61) or activation-induced cell death. It is not clear why this function is nonessential in mice, but it is an attractive hypothesis that it may relate to T cell homeostasis and the requirement in humans for maintaining, in a limited compartment, a greater diversity of memory T cells for a considerably longer period of time than is required in mice. T cell homeostasis requires programmed cell death (apoptosis) of unwanted cells. Caspase 8 and caspase 10 are downstream of death receptors in humans and overlap in some of their functions (62). Mice lack caspase 10 and the deletion of caspase 8 is embryonic lethal. Lack of caspase 8 in humans results in immunodeficiency, suggesting a role for this effector in lymphocyte activation as well as death (63). Greater redundancy in death receptor regulators in humans may relate to the longer lifespan and associated increased risk of developing cancer.

A critical step in activation of a T cell is the generation of a sustained calcium flux. In human T cells the inward flow of calcium ions is balance by an outward flow of K^+, mediated in large part by the Kv1.3 K^+ channel. Inhibitors of this channel very specifically block T cell activation in vitro and are being pursued as novel immunosuppressive agents (64). However, in vivo evidence to support such a function is missing as mouse T cells do not express this channel (65).

The movement of immune cells into and through tissues is coordinated by a huge array of chemokines and chemokine receptors and, not surprisingly, differences have emerged between the murine and human systems. While it is still too early to say definitively what such differences may mean, as there appears to be considerable redundancy built into the system, it is worth noting what is currently known. CXCR1 is present in humans but not in mice (66). The chemokines IL-8 (CXCL8), neutrophil-activating peptide-2 (CXCL7), IFN-inducible T cell α-chemoattractant (CXCL11), monocyte chemoattractant protein (MCP)-4 (CCL13), HCC-1 (CCL14), hemofiltrate CC chemokines-2 (CCL15), pulmonary and activation-regulated chemokine (CCL18), myeloid progenitor inhibitory factor-1 (CCL23), and eotaxin-2/3 (CCL24/CCL26) have all been identified in humans but not in mice. Conversely, CCL6, CCL9, lungkine (CXCL15), and MCP-5 (CCL12) have been identified in mice but not humans (66, 67).

Differences in immune system biology

Multiple sclerosis (MS) provides a fine example of both differences and similarities between mouse and human immunology. MS is a multifactorial disease that appears to have a large autoimmune component (68). Experimental autoimmune (allergic) encephalomyelitis is a widely used model for MS that mimics the demyelination seen in central and peripheral nerves in MS. Several studies have indicated that IFN-γ is protective in experimental autoimmune (allergic) encephalomyelitis as neutralizing Abs exacerbate disease, potentially by blocking induction/activation of suppressor activity (69, 70). It was surprising, therefore that clinical trials were not successful; indeed they were stopped because treatment with IFN-γ was found to exacerbate disease (4). In contrast, studies in mice suggested that blocking VLA-4 ($\alpha_4\beta_1$ integrin)-VCAM-1 interaction might help in MS (71) and this has indeed carried through successfully into human trials (72). These studies highlight how caution is required when extrapolating results from mouse studies to the clinic, but suggest that mouse models can successfully predict some therapies for human disease.

An interesting difference exists in the appearance of delayed-type hypersensitivity (DTH) reactions in mice and humans. In humans, around four hours after Ag challenge neutrophils can be seen forming a "cuff" around the venules. This is followed by a dramatic influx of mononuclear cells, such that by 24–48 h the lesion is mostly mononuclear with a mix of T cells and macrophages (73). Paradoxically, in mice where the peripheral blood has a relative paucity of neutrophils compared with humans, the DTH response tends to be more neutrophil rich (74). In addition, elicitation of murine DTH requires much higher concentrations of Ag than in humans.

There is now considerable evidence that human EC can present Ag to resting memory $CD4^+$ and $CD8^+$ T cells (75–77), whereas in mice, $CD8^+$ T cells can be activated by EC (78), but $CD4^+$ T cells cannot (B. Rosengard, personal communiction). As $CD4^+$ T cell-mediated activation of macrophages is thought to drive human DTH responses the suggestion has arisen that in humans, Ag transport to lymph nodes by Langerhans cells may not be necessary as EC may trigger the recall response at the site of challenge. A teleological argument can be made for the need to present Ag locally in humans but not necessarily in mice. It has been estimated that once a cell enters the lymphatics in humans it takes ~24 h to return to the circulation if it is not retained in a node (79). Based on the higher cardiac output of mice as a proportion of their total blood volume compared with humans (5–10 ml/min, 2 ml total volume in mice; 5 L/min, 5 liter total volume in humans) it is reasonable to suppose that return of lymph is at least as fast in mice as it is in humans. Then it becomes a matter of scale. We calculate that an Ag traveling from toe to an inguinal lymph node in the groin should take ~12 h in humans and 20 min in mice. As the human DTH response begins around 4 h after secondary Ag challenge, it is possible that triggering of recall responses may occur by different mechanisms in mice and humans, involving draining of Ag to lymph nodes in mice, compared with local Ag presentation in humans.

Both human and mouse EC express MHC class I. Most human EC in vivo also constitutively express MHC class II molecules, whereas mouse EC do not (80). Thus, human EC can present Ag to $CD4^+$ T cells, as well as to $CD8^+$ T cells. A major costimulatory molecule on human EC is CD58 (LFA-3), a ligand for CD2 (81). Mice do not have the gene for CD58, which arose by CD2 gene duplication after the two lineages split. In mice the CD2 ligand is CD48; however, the distribution of this molecule differs from that of CD58 in humans, and the two-dimensional affinity for the mouse CD2-CD48 interaction is 40- to 50-fold lower than that for human CD2-CD58 interactions (82). In addition, gene deletion and Ab blocking studies have shown that mouse T cell activation is much less dependent on CD2 interactions than is the case for human T cells. Human EC also express CD40 and the ICOS ligand GL-50, whereas murine EC do not (83, 84).

The Ag presenting ability of human EC may have significant consequences for transplantation. For example, in many rodent models vascularized grafts are tolerizing, whereas such grafts are rapidly rejected in humans (5). Numerous studies have shown that purging mouse tissues of $CD45^+$ cells before transplantation dramatically extends the life of the graft, sometimes even inducing tolerance. In sharp contrast, purging human tissues of $CD45^+$ cells provides no benefit as the grafts are still rapidly rejected (6). In addition, the establishment of microchimerism in mice has been quite successful in inducing tolerance, whereas this has not been the case in humans (7). The implication of these findings is that there are major differences between mice and humans in their responses to grafted tissue, and that this may relate to the Ag-presenting ability of human, but not murine, EC.

Natural selection and the immune system

Most, if not all, of the differences we have noted between mouse and human immunology have likely become fixed during the 65 million years since our divergence because they provide some selective advantage. In all likelihood these adaptations are in response to new pathologic challenges from microorganisms, which have very short generation times and often have high mutation rates (85). In consequence, mammalian MHC molecules and NK cell inhibitory receptors have also evolved rapidly (9, 86). It should also be noted that some changes may be fixed primarily as a result of the nonimmune role of that gene—reiterative use of genes is a well recognized phenomenon during development, a good example being the important nonimmunological role of VCAM in chorioallantoic fusion and placentation (87). Thus, both the immune system as a whole, and some of its individual components (B and T cell repertoires) are shaped by natural selection.

Mice evolved in a quite different environment to humans and have been exposed to different Ags and their immune systems might therefore be expected to have evolved in subtly different ways. Mice not only live in different ecological niches, they are also much smaller and have significantly shorter lifespans. These are not trivial differences—as noted above, leukocyte transit times may be quite different in mice and humans, and a larger, broader repertoire of B and T cells must be maintained for many years in humans (up to 50 mouse lifetimes). Thus many changes may be to accommodate increased size of the organism, to regulate larger and more diverse pools of Ag-specific cells, and to provide greater checks and balances to combat the increased somatic mutation load that longer-lived animals necessarily carry.

Summary

While it is hard to draw global conclusions about the significance of differences between mouse and human immunology, it is worth considering the possibility that any given response in a mouse may not occur in precisely the same way in humans. While caution in interpreting preclinical data obtained in mice is clearly warranted, we believe that with these caveats in mind, mice will continue to be the premiere in vivo model for human immunology and will be absolutely essential for continued progress in our understanding of immune system function in health and disease.

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References

1. Waterston, R. H., K. Lindblad-Toh, E. Birney, J. Rogers, J. F. Abril, P. Agarwal, R. Agarwala, R. Ainscough, M. Alexandersson, P. An, et al. 2002. Initial sequencing and comparative analysis of the mouse genome. *Nature 420:520.*
2. Shepherd, F. A., and S. S. Sridhar. 2003. Angiogenesis inhibitors under study for the treatment of lung cancer. *Lung Cancer 41(Suppl. 1):S63.*
3. Oehler, M. K., and R. Bicknell. 2000. The promise of anti-angiogenic cancer therapy. *Br. J. Cancer. 82:749.*
4. Panitch, H. S., R. L. Hirsch, A. S. Haley, and K. P. Johnson. 1987. Exacerbations of multiple sclerosis in patients treated with γ interferon. *Lancet 1:893.*
5. Sykes, M. 2001. Mixed chimerism and transplant tolerance. *Immunity 14:417.*
6. Wood, K. J. 2003. Passenger leukocytes and microchimerism: what role in tolerance induction? *Transplantation 75:17S.*
7. Monaco, A. P. 2003. Chimerism in organ transplantation: conflicting experiments and clinical observations. *Transplantation 75:13S.*
8. Haley, P. J. 2003. Species differences in the structure and function of the immune system. *Toxicology 188:49.*
9. Pabst, R., and I. Gehrke. 1990. Is the bronchus-associated lymphoid tissue (BALT) an integral structure of the lung in normal mammals, including humans? *Am. J. Respir. Cell. Mol. Biol. 3:131.*
10. Doeing, D. C., J. L. Borowicz, and E. T. Crockett. 2003. Gender dimorphism in differential peripheral blood leukocyte counts in mice using cardiac, tail, foot, and saphenous vein puncture methods. *BMC Clin. Pathol. 3:3.*
11. Sitnicka, E., N. Buza-Vidas, S. Larsson, J. M. Nygren, K. Liuba, and S. E. Jacobsen. 2003. Human $CD34^+$ hematopoietic stem cells capable of multilineage engrafting NOD/SCID mice express *flt3*: distinct *flt3* and c-*kit* expression and response patterns on mouse and candidate human hematopoietic stem cells. *Blood 102:881.*
12. Ganz, T. 2003. Defensins: antimicrobial peptides of innate immunity. *Nat. Rev. Immunol. 3:710.*

13. Ouellette, A. J., and M. E. Selsted. 1996. Paneth cell defensins: endogenous peptide components of intestinal host defense. *FASEB J. 10:1280.*
14. Risso, A. 2000. Leukocyte antimicrobial peptides: multifunctional effector molecules of innate immunity. *J. Leukocyte Biol. 68:785.*
15. Janeway, C. A., Jr., and R. Medzhitov. 2002. Innate immune recognition. *Annu. Rev. Immunol. 20:197.*
16. Bogdan, C. 2001. Nitric oxide and the immune response. *Nat. Immunol. 2:907.*
17. Weinberg, J. B. 1998. Nitric oxide production and nitric oxide synthase type 2 expression by human mononuclear phagocytes: a review. *Mol. Med. 4:557.*
18. Schneemann, M., and G. Schoedon. 2002. Species differences in macrophage NO production are important. *Nat. Immunol. 3:102.*
19. Webb, J. R., S. H. Lee, and S. M. Vidal. 2002. Genetic control of innate immune responses against cytomegalovirus: MCMV meets its match. *Genes Immun. 3:250.*
20. Lanier, L. L. 1998. NK cell receptors. *Annu. Rev. Immunol. 16:359.*
21. Monteiro, R. C., and J. G. Van De Winkel. 2003. IgA Fc receptors. *Annu. Rev. Immunol. 21:177.*
22. Daeron, M. 1997. Fc receptor biology. *Annu. Rev. Immunol. 15:203.*
23. Martin, R. M., and A. M. Lew. 1998. Is IgG2a a good Th1 marker in mice? *Immunol. Today. 19:49.*
24. Snapper, C. M., and F. D. Finkelman. 1999. Immunoglobulin class switching. In *Fundamental Immunology.* W. E. Paul, ed. Lippincott-Raven, Philadelphia, p. 831.
25. Pappu, R., A. M. Cheng, B. Li, Q. Gong, C. Chiu, N. Griffin, M. White, B. P. Sleckman, and A. C. Chan. 1999. Requirement for B cell linker protein (BLNK) in B cell development. *Science 286:1949.*
26. Minegishi, Y., J. Rohrer, E. Coustan-Smith, H. M. Lederman, R. Pappu, D. Campana, A. C. Chan, and M. E. Conley. 1999. An essential role for BLNK in human B cell development. *Science 286:1954.*
27. Satterthwaite, A. B., and O. N. Witte. 2000. The role of Bruton's tyrosine kinase in B-cell development and function: a genetic perspective. *Immunol. Rev. 175:120.*
28. Conley, M. E., J. Rohrer, L. Rapalus, E. C. Boylin, and Y. Minegishi. 2000. Defects in early B-cell development: comparing the consequences of abnormalities in pre-BCR signaling in the human and the mouse. *Immunol. Rev. 178:75.*
29. Gordon, C. J., G. Grafton, P. M. Wood, M. Larche, and R. J. Armitage. 2001. Modelling the human immune response: can mice be trusted? *Curr. Opin. Pharmacol. 1:431.*
30. Thomas, J. D., P. Sideras, C. I. Smith, I. Vorechovsky, V. Chapman, and W. E. Paul. 1993. Colocalization of X-linked agammaglobulinemia and X-linked immunodeficiency genes. *Science 261:355.*
31. Buckley, R. H. 1999. Primary immunodeficiency diseases. In *Fundamental Immunology.* W. E. Paul, ed. Lippincott-Raven, Philadelphia, p. 1427.
32. Tokugawa, Y., M. Koyama, and J. Silver. 1997. A molecular basis for species differences in Thy-1 expression patterns. *Mol. Immunol. 34:1263.*
33. Leonard, W. J. 1999. Type I cytokines and interferons and their receptors. In *Fundamental Immunology.* W. E. Paul, ed. Lippincott-Raven, Philadelphia, p. 741.
34. Fischer, A., M. Cavazzana-Calvo, G. De Saint Basile, J. P. DeVillartay, J. P. Di Santo, C. Hivroz, F. Rieux-Laucat, and F. Le Deist. 1997. Naturally occurring primary deficiencies of the immune system. *Annu. Rev. Immunol. 15:93.*
35. Peschon, J. J., P. J. Morrissey, K. H. Grabstein, F. J. Ramsdell, E. Maraskovsky, B. C. Gliniak, L. S. Park, S. F. Ziegler, D. E. Williams, C. B. Ware, et al. 1994. Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice. *J. Exp. Med. 180:1955.*
36. Roifman, C. M., J. Zhang, D. Chitayat, and N. Sharfe. 2000. A partial deficiency of interleukin-7Rα is sufficient to abrogate T-cell development and cause severe combined immunodeficiency. *Blood 96:2803.*
37. Elder, M. E., S. Skoda-Smith, T. A. Kadlecek, F. Wang, J. Wu, and A. Weiss. 2001. Distinct T cell developmental consequences in humans and mice expressing identical mutations in the DLAARN motif of ZAP-70. *J. Immunol. 166:656.*
38. Chu, D. H., N. S. van Oers, M. Malissen, J. Harris, M. Elder, and A. Weiss. 1999. Pre-T cell receptor signals are responsible for the down-regulation of Syk protein tyrosine kinase expression. *J. Immunol. 163:2610.*
39. Carding, S. R., and P. J. Egan. 2002. $\gamma\delta$ T cells: functional plasticity and heterogeneity. *Nat. Rev. Immunol. 2:336.*
40. Elbe, A., C. A. Foster, and G. Stingl. 1996. T-cell receptor $\alpha\beta$ and $\gamma\delta$ T cells in rat and human skin–are they equivalent?. *Semin. Immunol. 8:341.*
41. Dutronc, Y., and S. A. Porcelli. 2002. The CD1 family and T cell recognition of lipid antigens. *Tissue Antigens. 60:337.*
42. Kaufmann, S. H. 2001. How can immunology contribute to the control of tuberculosis? *Nat. Rev. Immunol. 1:20.*
43. Flynn, J. L., and J. Chan. 2001. Immunology of tuberculosis. *Annu. Rev. Immunol. 19:93.*
44. Farrar, J. D., J. D. Smith, T. L. Murphy, S. Leung, G. R. Stark, and K. M. Murphy. 2000. Selective loss of type I interferon-induced STAT4 activation caused by a minisatellite insertion in mouse Stat2. *Nat. Immunol. 1:65.*
45. Mosmann, T. R., H. Cherwinski, M. W. Bond, M. A. Giedlin, and R. L. Coffman. 1986. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J. Immunol. 136:2348.*
46. Del Prete, G. F., M. De Carli, C. Mastromauro, R. Biagiotti, D. Macchia, P. Falagiani, M. Ricci, and S. Romagnani. 1991. Purified protein derivative of Mycobacterium tuberculosis and excretory-secretory antigen(s) of *Toxocara canis* expand in vitro human T cells with stable and opposite (type 1 T helper or type 2 T helper) profile of cytokine production. *J. Clin. Invest. 88:346.*
47. Romagnani, S. 1991. Human TH1 and TH2 subsets: doubt no more. *Immunol. Today. 12:256.*
48. Allen, J. E., and R. M. Maizels. 1997. Th1-Th2: reliable paradigm or dangerous dogma? *Immunol. Today 18:387.*
49. Gor, D. O., N. R. Rose, and N. S. Greenspan. 2003. TH1-TH2: a procrustean paradigm. *Nat. Immunol. 4:503.*
50. Murphy, K. M. 2003. In search of the CTD. *Nat. Immunol. 4:645.*
51. Del Prete, G., M. De Carli, F. Almerigogna, M. G. Giudizi, R. Biagiotti, and S. Romagnani. 1993. Human IL-10 is produced by both type 1 helper (Th1) and type 2 helper (Th2) T cell clones and inhibits their antigen-specific proliferation and cytokine production. *J. Immunol. 150:353.*
52. Hagan, P. 1993. IgE and protective immunity to helminth infections. *Parasite Immunol. 15:1.*
53. Pearce, E. J., and A. Sher. 1991. Functional dichotomy in the CD4$^+$ T cell response to *Schistosoma mansoni*. *Exp. Parasitol. 73:110.*
54. Lenschow, D. J., T. L. Walunas, and J. A. Bluestone. 1996. CD28/B7 system of T cell costimulation. *Annu. Rev. Immunol. 14:233.*
55. McAdam, A. J., R. J. Greenwald, M. A. Levin, T. Chernova, N. Malenkovich, V. Ling, G. J. Freeman, and A. H. Sharpe. 2001. ICOS is critical for CD40-mediated antibody class switching. *Nature 409:102.*
56. Tafuri, A., A. Shahinian, F. Bladt, S. K. Yoshinaga, M. Jordana, A. Wakeham, L. M. Boucher, D. Bouchard, V. S. Chan, G. Duncan, et al. 2001. ICOS is essential for effective T-helper-cell responses. *Nature 409:105.*
57. Grimbacher, B., A. Hutloff, M. Schlesier, E. Glocker, K. Warnatz, R. Drager, H. Eibel, B. Fischer, A. A. Schaffer, H. W. Mages, et al. 2003. Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. *Nat Immunol. 4:261.*
58. Pan, J., L. Xia, and R. P. McEver. 1998. Comparison of promoters for the murine and human P-selectin genes suggests species-specific and conserved mechanisms for transcriptional regulation in endothelial cells. *J. Biol. Chem. 273:10058.*
59. Barnaba, V., C. Watts, M. de Boer, P. Lane, and A. Lanzavecchia. 1994. Professional presentation of antigen by activated human T cells. *Eur. J. Immunol. 24:71.*
60. Denton, M. D., C. S. Geehan, S. I. Alexander, M. H. Sayegh, and D. M. Briscoe. 1999. Endothelial cells modify the costimulatory capacity of transmigrating leukocytes and promote CD28-mediated CD4$^+$ T cell alloactivation. *J. Exp. Med. 190:555.*
61. Taams, L. S., W. van Eden, and M. H. Wauben. 1999. Antigen presentation by T cells versus professional antigen-presenting cells (APC): differential consequences for T cell activation and subsequent T cell-APC interactions. *Eur. J. Immunol. 29:1543.*
62. Tibbetts, M. D., L. Zheng, and M. J. Lenardo. 2003. The death effector domain protein family: regulators of cellular homeostasis. *Nat. Immunol. 4:404.*
63. Chun, H. J., L. Zheng, M. Ahmad, J. Wang, C. K. Speirs, R. M. Siegel, J. K. Dale, J. Puck, J. Davis, C. G. Hall, et al. 2002. Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency. *Nature 419:395.*
64. Wulff, H., P. A. Calabresi, R. Allie, S. Yun, M. Pennington, C. Beeton, and K. G. Chandy. 2003. The voltage-gated Kv1.3 K$^+$ channel in effector memory T cells as new target for MS. *J. Clin. Invest. 111:1703.*
65. Koo, G. C., J. T. Blake, A. Talento, M. Nguyen, S. Lin, A. Sirotina, K. Shah, K. Mulvany, D. Hora, Jr., P. Cunningham, et al. 1997. Blockade of the voltage-gated potassium channel Kv1.3 inhibits immune responses in vivo. *J. Immunol. 158:5120.*
66. Olson, T. S., and K. Ley. 2002. Chemokines and chemokine receptors in leukocyte trafficking. *Am. J. Physiol. 283:R7.*
67. Zlotnik, A., and O. Yoshie. 2000. Chemokines: a new classification system and their role in immunity. *Immunity. 12:121.*
68. Pedotti, R., J. J. De Voss, L. Steinman, and S. J. Galli. 2003. Involvement of both "allergic" and "autoimmune" mechanisms in EAE, MS and other autoimmune diseases. *Trends Immunol. 24:479.*
69. Lublin, F. D., R. L. Knobler, B. Kalman, M. Goldhaber, J. Marini, M. Perrault, C. D'Imperio, J. Joseph, S. S. Alkan, and R. Korngold. 1993. Monoclonal anti-γ interferon antibodies enhance experimental allergic encephalomyelitis. *Autoimmunity 16:267.*
70. Heremans, H., C. Dillen, M. Groenen, E. Martens, and A. Billiau. 1996. Chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice: enhancement by monoclonal antibodies against interferon-γ. *Eur. J. Immunol. 26:2393.*
71. Yednock, T. A., C. Cannon, L. C. Fritz, F. Sanchez-Madrid, L. Steinman, and N. Karin. 1992. Prevention of experimental autoimmune encephalomyelitis by antibodies against $\alpha_4\beta_1$ integrin. *Nature 356:63.*
72. Miller, D. H., O. A. Khan, W. A. Sheremata, L. D. Blumhardt, G. P. Rice, M. A. Libonati, A. J. Willmer-Hulme, C. M. Dalton, K. A. Miszkiel, and P. W. O'Connor. 2003. A controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med. 348:15.*
73. Dumonde, D. C., M. S. Pulley, F. J. Paradinas, B. M. Southcott, D. O'Connell, M. R. Robinson, F. den Hollander, and A. H. Schuurs. 1982. Histological features of skin reactions to human lymphoid cell line lymphokine in patients with advanced cancer. *J. Pathol. 138:289.*
74. Crowle, A. J. 1975. Delayed hypersensitivity in the mouse. *Adv. Immunol. 20:197.*
75. Pober, J. S., M. S. Kluger, and J. S. Schechner. 2001. Human endothelial cell presentation of antigen and the homing of memory/effector T cells to skin. *Ann. NY Acad. Sci. 941:12.*
76. Murphy, L. L., M. M. Mazanet, A. C. Taylor, J. Mestas, and C. C. Hughes. 1999. Single-cell analysis of costimulation by B cells, endothelial cells, and fibroblasts demonstrates heterogeneity in responses of CD4$^+$ memory T cells. *Cell Immunol. 194:150.*
77. Mestas, J., and C. C. Hughes. 2001. Endothelial cell costimulation of T cell activation through CD58-CD2 interactions involves lipid raft aggregation. *J. Immunol. 167:4378.*
78. Kreisel, D., A. S. Krupnick, K. R. Balsara, M. Riha, A. E. Gelman, S. H. Popma, W. Y. Szeto, L. A. Turka, and B. R. Rosengard. 2002. Mouse vascular endothelium activates CD8$^+$ T lymphocytes in a B7-dependent fashion. *J. Immunol. 169:6154.*
79. Freitas, R. 1999. Lymphatic system. In *Nanomedicine, Volume I: Basic Capabilities.* Landes Bioscience, Georgetown, TX, p. 68.
80. Choo, J. K., J. D. Seebach, V. Nickeleit, A. Shimizu, H. Lei, D. H. Sachs, and J. C. Madsen. 1997. Species differences in the expression of major histocompatibility

complex class II antigens on coronary artery endothelium: implications for cell-mediated xenoreactivity. *Transplantation 64:1315.*

81. Hughes, C. C., C. O. Savage, and J. S. Pober. 1990. Endothelial cells augment T cell interleukin 2 production by a contact-dependent mechanism involving CD2/LFA-3 interaction. *J. Exp. Med. 171:1453.*
82. van der Merwe, P. A. 1999. A subtle role for CD2 in T cell antigen recognition. *J. Exp. Med. 190:1371.*
83. Karmann, K., C. C. Hughes, J. Schechner, W. C. Fanslow, and J. S. Pober. 1995. CD40 on human endothelial cells: inducibility by cytokines and functional regulation of adhesion molecule expression. *Proc. Natl. Acad. Sci. USA 92:4342.*
84. Ensminger, S. M., B. M. Spriewald, T. Fischlein, M. Weyand, P. J. Morris, and K. J. Wood. 2003. Mouse endothelial CD40 expression does not play a role during the development of transplant arteriosclerosis. *Endothelium 10:111.*
85. McDade, T. W., and C. M. Worthman. 1999. Evolutionary process and the ecology of human immune function. *Am. J. Human Biol. 11:705.*
86. Martin, A. M., J. K. Kulski, C. Witt, P. Pontarotti, and F. T. Christiansen. 2002. Leukocyte Ig-like receptor complex (LRC) in mice and men. *Trends Immunol. 23:81.*
87. Gurtner, G. C., V. Davis, H. Li, M. J. McCoy, A. Sharpe, and M. I. Cybulsky. 1995. Targeted disruption of the murine VCAM1 gene: essential role of VCAM-1 in chorioallantoic fusion and placentation. *Genes Dev. 9:1.*
88. Rehli, M. 2002. Of mice and men: species variations of Toll-like receptor expression. *Trends Immunol. 23:375.*
89. Heinz, S., V. Haehnel, M. Karaghiosoff, L. Schwarzfischer, M. Muller, S. W. Krause, and M. Rehli. 2003. Species-specific regulation of Toll-like receptor 3 genes in men and mice. *J. Biol. Chem. 278:21502.*
90. Lund, J., A. Sato, S. Akira, R. Medzhitov, and A. Iwasaki. 2003. Toll-like receptor 9-mediated recognition of Herpes simplex virus-2 by plasmacytoid dendritic cells. *J. Exp. Med. 198:513.*
91. Trevani, A. S., A. Chorny, G. Salamone, M. Vermeulen, R. Gamberale, J. Schettini, S. Raiden, and J. Geffner. 2003. Bacterial DNA activates human neutrophils by a CpG-independent pathway. *Eur. J. Immunol. 33:3164.*
92. Varki, A. 2001. Loss of *N*-glycolylneuraminic acid in humans: mechanisms, consequences, and implications for hominid evolution. *Am. J. Phys. Anthropol. 33(Suppl.):54.*
93. Brinkman-Van der Linden, E. C., T. Angata, S. A. Reynolds, L. D. Powell, S. M. Hedrick, and A. Varki. 2003. CD33/Siglec-3 binding specificity, expression pattern, and consequences of gene deletion in mice. *Mol. Cell Biol. 23:4199.*
94. Cunliffe, R. N., F. R. Rose, J. Keyte, L. Abberley, W. C. Chan, and Y. R. Mahida. 2001. Human defensin 5 is stored in precursor form in normal Paneth cells and is expressed by some villous epithelial cells and by metaplastic Paneth cells in the colon in inflammatory bowel disease. *Gut 48:176.*
95. Ghosh, D., E. Porter, B. Shen, S. K. Lee, D. Wilk, J. Drazba, S. P. Yadav, J. W. Crabb, T. Ganz, and C. L. Bevins. 2002. Paneth cell trypsin is the processing enzyme for human defensin-5. *Nat. Immunol. 3:583.*
96. Crocker, P. R., W. A. Jefferies, S. J. Clark, L. P. Chung, and S. Gordon. 1987. Species heterogeneity in macrophage expression of the CD4 antigen. *J. Exp. Med. 166:613.*
97. Kaufmann, S. H. 1996. γ/δ and other unconventional T lymphocytes: what do they see and what do they do? *Proc. Natl. Acad. Sci. USA 93:2272.*
98. Raulet, D. H. 2003. Roles of the NKG2D immunoreceptor and its ligands. *Nat. Rev. Immunol. 3:781.*
99. Gao, J. L., and P. M. Murphy. 1993. Species and subtype variants of the *N*-formyl peptide chemotactic receptor reveal multiple important functional domains. *J. Biol. Chem. 268:25395.*
100. Zemlin, M., M. Klinger, J. Link, C. Zemlin, K. Bauer, J. A. Engler, H. W. Schroeder, Jr., and P. M. Kirkham. 2003. Expressed murine and human CDR-H3 intervals of equal length exhibit distinct repertoires that differ in their amino acid composition and predicted range of structures. *J. Mol. Biol. 334:733.*
101. Chapoval, A. I., J. Ni, J. S. Lau, R. A. Wilcox, D. B. Flies, D. Liu, H. Dong, G. L. Sica, G. Zhu, K. Tamada, and L. Chen. 2001. B7–H3: a costimulatory molecule for T cell activation and IFN-γ production. *Nat. Immunol. 2:269.*
102. Suh, W. K., B. U. Gajewska, H. Okada, M. A. Gronski, E. M. Bertram, W. Dawicki, G. S. Duncan, J. Bukczynski, S. Plyte, A. Elia, et al. 2003. The B7 family member
103. Geijtenbeek, T. B., R. Torensma, S. J. van Vliet, G. C. van Duijnhoven, G. J. Adema, Y. van Kooyk, and C. G. Figdor. 2000. Identification of DC-SIGN, a novel dendritic cell-specific ICAM-3 receptor that supports primary immune responses. *Cell 100:575.*
104. van Kooyk, Y., and T. B. Geijtenbeek. 2002. A novel adhesion pathway that regulates dendritic cell trafficking and T cell interactions. *Immunol. Rev. 186:47.*
105. Crommie, D., and S. D. Rosen. 1995. Biosynthesis of GlyCAM-1, a mucin-like ligand for L-selectin. *J. Biol. Chem. 270:22614.*
106. Correa, I., T. Plunkett, A. Vlad, A. Mungul, J. Candelora-Kettel, J. M. Burchell, J. Taylor-Papadimitriou, and O. J. Finn. 2003. Form and pattern of MUC1 expression on T cells activated in vivo or in vitro suggests a function in T-cell migration. *Immunology 108:32.*