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Review Article

Immune Relevant and Immune Deficient Mice: Options and Opportunities in Translational Research

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Abstract

In 1989 ILAR published a list and description of immunodeficient rodents used in research. Since then, advances in understanding of molecular mechanisms; recognition of genetic, epigenetic microbial, and other influences on immunity; and capabilities in manipulating genomes and microbiomes have increased options and opportunities for selecting mice and designing studies to answer important mechanistic and therapeutic questions. Despite numerous scientific breakthroughs that have benefitted from research in mice, there is debate about the relevance and predictive or translational value of research in mice. Reproducibility of results obtained from mice and other research models also is a well-publicized concern. This review summarizes resources to inform the selection and use of immune relevant mouse strains and stocks, aiming to improve the utility, validity, and reproducibility of research in mice. Immune sufficient genetic variations, immune relevant spontaneous mutations, immunodeficient and autoimmune phenotypes, and selected induced conditions are emphasized.

Key words: biomedical research; experimental conditions; genetic background; genetic variation; immune system diseases; inbred strains; mice

Introduction

The main advantages of using mice in research include (1) their small size and very prolific nature, (2) the numerous commonalities existing between mice and humans in terms of physiology and pathobiology, (3) the well-characterized genomes and immune responses, and (4) the availability of advanced technologies for genetic and other experimental manipulations.[1,2] Despite the advantages, there is ongoing controversy surrounding the reproducibility and translatability of mouse models of disease.[3–5] Given the immune diversity within the human population, a perfect model relevant to all humans may be neither an achievable nor a reasonable expectation. However, it is possible to strive for relevant and reproducible translational models and to expect experimental designs to address specific research questions. Criticisms of mouse models (mouse blaming) are not always justified. Many factors contribute to study outcomes and reproducibility. These include genetic diversity; microbial, husbandry, and other environmental factors; experimental interventions; etc.[2] Increasing the awareness of the immunobiological variations among inbred mice and their substrains as well as other factors that may impact immune responses in mice will help improve both the validity and reproducibility of mouse-based research. Attention to these aspects is warranted in experimental design, data interpretations, and reporting of research on immunity, disease, and therapeutic interventions.[6,7]

This review aims to provide a useful compendium of resources and references for those investigators who seek to familiarize themselves with key concepts of mouse immunology

and translate those notions into the experimental setting. The most relevant sources of immune diversity of the laboratory mouse are here emphasized with a focus on immune sufficient genetic variations, immunologically relevant spontaneous mutations, autoimmune phenotypes, and selected induced immune deficiencies.

Mouse Nomenclature

Accurate mouse nomenclature is mission critical to scientific communication.[8–10] Nomenclature "rules" for mice genes, strains, and substrains were recommended by scientists to the scientific community in the 1940s and 1950s. The first committees on standardized genetics nomenclature[11] and on standardized strain nomenclature for mice[12] included Nobel laureate George Snell. Early publications provided guidelines for gene and strain nomenclature, a list (database) of strains and substrains, and a list (database) of abbreviations for the researchers or institutions maintaining the mice.[12] The list of abbreviations became the "laboratory codes" (lab codes) that are currently curated by ILAR (http://dels.nas.edu/global/ilar/lab-codes) and are available to producers and researchers at no charge. The lab code identifies the mouse source and becomes part of its name. The 1963 revision includes a listing of named genes, including histocompatibility alleles for many of the common strains. Subsequent committees updated the guidelines and included lists of inbred strains, substrains, and known genetic variants.[13–19] These publications are enlightening regarding the history and research use of contemporary mouse strains. They indicate recognition by the scientific community of the research implications of genetic and phenotypic variations, and reflect scientists' concerns for accurate communication in published research. In 1972, a recommendation was published for standardized nomenclature for outbred stocks of laboratory animals of various species.[20] These recommendations gained traction for mice and rats, but far less for other species. Current gene nomenclature "rules" for mice (International Committee on Standardized Genetic Nomenclature for Mice: http://www.informatics.jax.org/mgihome/nomen/strains.shtml), rats (Rat Gene Nomenclature Committee: https://rgd.mcw.edu/nomen/nomen.shtml), and human genes (HUGO Gene Nomenclature Committee: http://www.genenames.org/) are available online. Guidance for mouse strains, genes, alleles/mutations as well as tutorials and assistance can be accessed from Mouse Genome Informatics Nomenclature sites (http://www.informatics.jax.org/mgihome/nomen/gene.shtml). Recommendations for reporting animal research include correct nomenclature because it communicates key research-relevant elements of the strain or substrain history and genetics, genetic modifications, backcrossing or intercrossing, and other information.[21–23]

Inbred Mouse Strains: Immune Relevant Genotypes and Phenotypes

The immune sufficient common inbred mouse strains are genetically well characterized, with genome projects on more than 30 strains.[24,25] Divergent susceptibilities of inbred strains to infections, diseases, and tumor rejection were recognized early in strain development. Characterization of these variations has exposed research-relevant Th1 or Th2 biases, diversity in major histocompatibility complex (MHC) haplotypes, natural killer (NK) cell repertoires, hemolytic complement (complement component 5 or C5) activity, and toll-like receptor (TLR) function, among others.[7,26,27] Table 1 and Supplementary Table 1 summarize some of the well-characterized immune relevant variations among immune sufficient common inbred mouse strains. Investigations on how penetrance and expressivity of immune phenotypes vary across different genetic backgrounds have enabled the discovery of key strain-related genetic modifiers that specifically enhance or suppress the manifestation of immunological disorders. This genetic source of diversity can be ultimately ascribed to a number of possible genetic alterations/variations including polymorphic alleles, unique quantitative trait loci (QTL) intervals, or specific haplotypes.[28–36] The influence of the inbred genetic background pervades many if not all the experimental contexts considered in this review.

Immune Relevant Variations Among Substrains

Substrains with quite similar names harbor important genetic (and other) variations that are increasingly recognized.[55,74–76] C57BL/6N and C57BL/6J substrains diverged in 1951, so acquisition of mutations among colonies inbreeding at different sites is unsurprising. As illustrated in Table 2, some immune relevant genetic variations among C57BL/6 substrains include a *Nlrp12* mutation in C57BL/6J mice and a *Dock2* mutation in C57BL/6NHsd mice from certain colonies.[55,77] The *Nlrp12* gene primarily controls neutrophil chemotaxis in response to bacterial invasion. C57BL/6J mice carry a missense, loss of function mutation ($Nlrp12^{C57BL/6J}$) and are more susceptible to certain bacterial infections compared with other C57BL/6 substrains harboring the wild-type *Nlrp12* allele.[55,73] More concerning may be when mutations arise within a substrain (of the same name) with colonies maintained at different sites. The $Dock2^{Hsd}$ mutation was revealed when reduced splenic marginal zone B cells and increased numbers of CD8+ T cells were identified in C57BL/6NHsd (and derived mutant mice) relative to other C57BL/6N mice.[77–79] Subsequently, Envigo tested their mice and reported that this mutation ($Dock2^{Hsd}$) was present in 6 of their 19 C57BL/6NHsd colonies (http://www.envigo.com/assets/docs/c57-customer-communication-2-final-9jun16.pdf). Many research programs maintain in-house colonies of genetically engineered animals and "wild-type" background strains that warrant genetic quality assurance (QA) testing and breeding strategies to minimize effects of random mutations and genetic drift. (https://www.jax.org/jax-mice-and-services/customer-support/technical-support/breeding-and-husbandry-support/colony-planning; https://www.taconic.com/quality/genetic-integrity/colony-management/).

Influence of Genetic Background

Influences of background strain(s) warrant consideration when working with spontaneous or genetically engineered mutations. Many genetically engineered mice (GEM) have mixed or undefined genetic backgrounds that can affect research results. When spontaneous or experimentally induced mutations are transferred congenically from the line of origin onto a different (generally inbred) background strain, penetrance and expressivity of the phenotype may be positively or negatively affected by the recipient genome as well as by remnants of the "donor" genome (i.e., chromosomal regions flanking the mutant allele included in the congenic interval).[87–90]

In immunodeficient strains, genetic and phenotypic contributions from background strains have research implications that may not be well known to those who are new to working with these mice. An internet search for commercially available immunodeficient mice bearing the $Prkdc^{scid}$ (*scid*) or $Foxn1^{nu}$ (nude or *nu*) mutations returns more than 20 strains of each on

Table 1 Selected Immune Relevant Genetic Variations in Common Inbred Mouse Strains

	Gene symbol															
Mouse strain	***Ahr***	***Ctse***	***Hc***	***Il2***	***Il12b***	***Mx1 Mx2***	***Naip5***	***Nlrp***	***Nlrp12***	***Oas1b***	***Sirpa***	***Slamf***	***Slc11a1***	***Tcrb-v8***	***Tlr4***	**TH-bias**
A/J	*b-2*	N/A	Hc^0	N/A	N/A	Ø	S	R	N/A	Ø	N/A	N/A	R	N/A	N	2
AKR/J	*d*	N/A	Hc^0	N/A	N/A	Ø	N/A	R	N/A	Ø	N/A	N/A	R	N/A	N	1
BALB/c	*b*	N	N	N/A	N/A	Ø	R	S	N/A	Ø	L29V	2	S	N	N	2
CBA	*b-2*	N/A	N/A	N/A	N/A	Ø	N/A	S	N/A	Ø	N/A	N/A	R	N/A	N	1
C3H/HeJ	*b-2*	N	N	N/A	N/A	Ø	N/A	S	N/A	Ø	N/A	N/A	R	N/A	*Lps-d*	1
C3H/HeN	*b-2*	N/A	N	N/A	N/A	Ø	N/A	N/A	N/A	Ø	N/A	1	R	N/A	N	N/A
C57BL/6	*b-1*	Ø	N	N	N	Ø	R	R	V	Ø	N	1	S	N	N	1
C57BL/10ScCr	N/A	N/A	N	N/A	N	Ø	N/A	N/A	N/A	Ø	N/A	N/A	S	N/A	*Lps-del*	1
DBA/1J	*b*	N/A	N	N/A	N/A	Ø	N/A	N/A	N/A	Ø	N/A	N/A	S	N/A	N	1
DBA/2J	*d*	N/A	Hc^0	N/A	N/A	Ø	N/A	R	N/A	Ø	N/A	2	R	N/A	N	2
FVB/N FVB/NJ	N/A	N/A	Hc^0	N/A	N/A	Ø	N/A	S	N/A	Ø	N/A	N/A	N/A	Ø	N	N/A
MRL/MpJ	N/A	N/A	N	*m1*	N/A	Ø	N/A	N/A	N/A	Ø	N/A	2	N/A	N/A	N	N/A
NOD/ShiLtJ	N/A	N/A	Hc^0	*m1*	N/A	Ø	N/A	R	N/A	Ø	S	2	R	N/A	N	N/A
NZB	*d*	N/A	N	N/A	N/A	Ø	N/A	N/A	N/A	Ø	N/A	2	R	N/A	N	N/A
NZW	N/A	N/A	N	N/A	N/A	Ø	N/A	N/A	N/A	Ø	N/A	2	S	N/A	N	N/A
NZM2410	N/A	N/A	N	N/A	N/A	Ø	N/A	N/A	N/A	Ø	N/A	2	N/A	N/A	N	N/A
SJL/J	*d*	N/A	N	*m1*	P	Ø	N/A	N/A	N/A	Ø	N/A	N/A	R	Ø	N	1
SWR	*d*	N/A	Hc^0	N/A	N/A	Ø	N/A	S	N/A	Ø	N/A	N/A	R	Ø	N	N/A
129	*d*	N	N	N/A	N/A	Ø	R	S	N/A	Ø	N/A	N/A	R	N	N	1

Ahr (aryl hydrocarbon receptor) activates expression of phase I and II metabolizing enzymes (e.g., *Cyp450*) and is important in cellular growth and differentiation; *b1*, *b2* and *b3* alleles are considered metabolically responsive alleles not linked to autoimmunity whereas *d* alleles are metabolically nonresponsive and associated with autoimmune susceptibility.[37–40]

Ctse (cathepsin E) plays a role in antigen processing for MHC class II.[41]

Hc (hemolytic complement) plays a role in innate immune responses; Hc^0 mice are null for this allele.[42,43]

Il2 (interleukin 2) is a key immune signaling cytokine; $Il2^{m1}$ allele has a hypoactive polymorphism in the *Il2* gene.[44]

Il12b (interleukin 12b) polymorphisms (P) have been associated with autoimmune disorders in humans.[45–47]

Mx1 and Mx2 (MX dynamin-like GTPase 1 & 2) play a role in viral resistance; in most inbred mouse strains, these are not expressed.[48,49]

Naip5 (NLR family, apoptosis inhibitory protein 5) plays a key role in early innate immune responses mediated by the inflammasome; allelic polymorphism determines susceptibility to intracellular bacteria ($Naip5^{Lgn1s}$ = sensitive, $Naip5^{Lgn1r}$ = resistant).[50–52]

Nlrp (nucleotide-binding oligomerization domain-like receptors aka NOD-like receptor proteins) has a key role in pathogen-associated molecular patterns detection.[53]

Nlrp12 (NACHT, LRR and PYD domains-containing protein 12) has an important role in inflammasome and activation of caspase 1; it also controls neutrophil chemotaxis in response to bacterial invasion.[54–56]

Oas1b (2'-5' oligoA synthetase family 1b) plays a role in innate immunity to eliminate viral RNA; most inbred mouse strains carry the susceptibility allele that encodes for a nonfunctional protein.[57]

Sirpa (signal-regulatory protein alpha); in BALB/c mice it has a single polymorphism in the IgV domain (L29V), which enhances binding to human CD47, decreasing macrophage phagocytosis; in NOD mice, the increased affinity for human CD47 is driven by a deletion of 2 amino acids in domain 1.[58,59]

Slamf [signaling lymphocytic activation molecule (SLAM) family] plays a role in self-tolerance;[60] haplotype 2 is associated with autoimmune susceptibility.[61–63]

Slc11a1 [solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1] transporter that regulates iron homeostasis and impacts on the ability to control intracellular pathogens by phagocytes.[64]

Tcrb-V8 (T cell receptor beta, variable 8) plays a role in auto-immune disease susceptibility; in some strains, this is not expressed and is associated with increased susceptibility to autoimmune disease.[65–67]

Tlr4 (Toll-like receptor 4) has a role in innate immune responses, in particular responses to LPS;[68–70] the mutant alleles $Tlr4^{Lps\text{-}d}$ *and* $Tlr4^{Lps\text{-}del}$ are not functional.

Th-bias; mice have TH-1 and TH-2 biases in their immune responses.[71,72]

N/A, no data; N, wild type (normal); NOD, nonobese diabetic; Ø, not expressed nonfunctional or hypofunctional gene product; P, polymorphism; R, resistance polymorphism; S, sensitive polymorphism; V, variable.

inbred or non-inbred backgrounds, some with quite similar names but with immune variations relevant to their genetic backgrounds (and with quite different costs that can influence purchasing decisions).[91–93] Variation in "leakiness" in *scid* mice on different genetic backgrounds is a well-known example. Leakiness refers to the tendency of *scid* mice to produce some functional B and T cells as they age and are increasingly exposed to environmental antigenic stimuli. Under similar experimental

Table 2 A Few B6 Substrains and Genetic Variations

	B6 Substrain	Source	*Dock2*	*Nlrp12*	*Nnt*	*Snca*	*Mmrn1*	*Crb1*
J	**C57BL/6J**	Jackson	N	Ø	Ø	N	N	N
	C57BL/6J[a]	Charles River	N/A	N/A	Ø	N	N	N
	C57BL/6JOlaHsd	Hsd/Envigo	N/A	N/A	N	Ø	Ø	N
	C57BL/6JRccHsd	Hsd/Envigo	N/A	N/A	N	N	N	N
	C57BL/6JBomTac	Taconic	N/A	N/A	N	N	N	N
	C57BL/6JRj	Janvier	N/A	N/A	N/A	N/A	N/A	N/A
N	**C57BL/6ByJ**	Jackson	N	N/A	N	N	N	Ø
	C57BL/6NHsd	Hsd/Envigo	Some Ø	N/A	N	N	N	Ø
	C57BL/6NRj	Janvier	N	N/A	N/A	N/A	N/A	N/A
	C57BL/6NCrl	Charles River	N	N/A	N	N	N	Ø
	C57BL/6NTac	Taconic	N	N/A	N	N	N	Ø
	C57BL/6NCr	NCI	N/A	N	N/A	N/A	N/A	N/A
References			[77–79]	[55,73]	[80,81]	[82–84]	[82–84]	[85,86]

Adapted/updated from https://www.envigo.com/resources/data-sheets/envigo-68-c57bl6-enhanced-technical-data-sheet_screen.pdf

Dock2 = the protein encoded by this gene belongs to the CDM protein family. It is specifically expressed in hematopoietic cells and is predominantly expressed in peripheral blood leukocytes. The protein is involved in remodeling of the actin cytoskeleton required for lymphocyte migration in response to chemokine signaling. It activates members of the Rho family of GTPases, for example RAC1 and RAC2, by acting as a guanine nucleotide exchange factor (GEF) to exchange bound GDP for free GTP.

Nlrp12 = This gene encodes a member of the CATERPILLER family of cytoplasmic proteins. The encoded protein, which contains an N-terminal pyrin domain, a NACHT domain, a NACHT-associated domain, and a C-terminus leucine-rich repeat region, has an important role in inflammasome and activation of caspase 1, it also controls neutrophil chemotaxis in response to bacterial invasion.

Nnt = nicotinamide nucleotide transhydrogenase; this gene encodes an integral protein of the inner mitochondrial membrane. The enzyme couples hydride transfer between NAD(H) and NADP(+) to proton translocation across the inner mitochondrial membrane.

Snca = alpha synuclein; one in a family of structurally related proteins that are prominently expressed in the brain, particularly in areas associated with learning and adaption. The exact function of alpha synuclein is not yet known.

Mmrn1 = multimerin 1; multimerin 1 is a stored platelet and endothelial cell adhesive protein that shows significant conservation. In vitro, multimerin 1 supports platelet adhesion and it also binds to collagen and enhances von Willebrand factor-dependent platelet adhesion to collagen.

Crb1 = retinal degeneration 8; the *rd-8* mutation is due to a single base pair mutation in the *CRB1* gene. This gene when mutated in humans is linked to macular degeneration and other age-related vision loss. Mice with this mutation are nearly blind by the time they are 8 weeks of age.

N/A, no data; N, wild type (normal); Ø, not expressed, nonfunctional or hypofunctional gene product.

[a]J mice distributed by Charles River in EU

conditions, leakiness is greater on the C57BL/6 and BALB/c backgrounds, low on the C3H/HeJ background, and very low on the nonobese diabetic (NOD) background.[93] Genetic factors contributing to "less sensitivity" to antigenic stimuli (and therefore less leakiness) include TRL4 deficiency in the C3H/HeJ mouse and impaired MHC-dependent antigen presentation in the NOD/ShiLtJ mouse.[94,95] Especially relevant to human xenografts, NOD mice possess a unique signal-regulatory protein alpha (*Sirpa*) polymorphism with higher affinity for the human CD47 that results in a sustained "don't-eat-me" signal and improves engraftment of human cells in NOD-*scid* and NOD-*scid*-derived mice.[58]

Autoimmune-susceptible strains develop spontaneous autoimmune disorders such as immune-mediated (Type 1-like) diabetes and systemic lupus erythematosus (SLE)-like conditions. The proclivity to develop experimentally induced autoimmune conditions, such as experimental autoimmune encephalitis (EAE) and collagen-induced arthritis (CIA), is also greatly influenced by the mouse's genetic background.[31,96–99] The NOD mouse model for Type 1 diabetes (T1D) (e.g., NOD/ShiLtJ and NOD/MrkTac mice) is characterized by the development of a T cell-mediated immune response to pancreatic islet proteins (including insulin and chromogranin) similar to humans with T1D.[100–102] Their diabetic phenotype is polygenic with a significant contribution, as in humans, by their MHC polymorphisms.[44,103–105] NOD mice have a unique MHC class II lacking expression of I-Eα and I-E surface protein, and expressing I-A^{g7}MHC class II allele that is structurally and functionally similar to the human T1D susceptibility allele, DQ8.[106,107] Other contributors to the autoimmune phenotype include a hypoactive variant of their *IL-2* gene ($Il2^{m1}$), *Sirpa* and *Cd93* polymorphisms, lack of C5 (conferred by homozygosity for Hc^{0}), and absence of complement factor H-related protein C (CFHR-C).[43,44,105,108–110] Genetic and phenotypic variations among the NOD substrains have been identified.[111]

Spontaneous lupus-like conditions in mice are associated with mutations such as Fas^{lpr} and *Yaa* and are influenced by genetic background.[28–36] Inbred strains that spontaneously develop lupus-like conditions include MRL/MpJ, BXSB/MpJ, NZB, NZW, NZBWF1 (aka NZB/W), NZM2410, and Palmerston North (PN/nBSwUmabJ).[112,63,113,114]

MRL/MpJ inbred mice are autoimmune prone and spontaneously develop an autoimmune phenotype as they age. A spontaneous mutation in the Fas^{lpr} gene in this strain resulted in the substrain MRL/MpJ-Fas^{lpr}, which develops signs of autoimmunity much earlier in life than the parent MRL/MpJ strain.[115–118] MRL/MpJ-Fas^{lpr} mice have a short lifespan (>50% mortality by 6 months old). They develop lymphoproliferative disease, immune complex glomerulonephritis, lupus-like skin disease, arthritis, and vasculitis.[115,120–123] It has been demonstrated that onset and severity of symptoms associated with the Fas^{lpr} mutation is strain dependent. For example, the Fas^{lpr} mutation results in a lymphoproliferative disease that on MRL/MpJ background is more severe than on the C57BL/6J background, but less severe than on the C3H/HeJ background.[28,29,31,124] In contrast, immune complex pathologies including glomerulonephritis, vasculitis, and arthritis are more severe and initiate earlier with the Fas^{lpr}

mutation on the MRL/MpJ background than on either the C57BL/6J or the C3H/HeJ background. Predisposition to the development of autoimmune and/or lymphoproliferative lesions in these strains has been mapped to a number of possible other genetic variations.[28–36] Interestingly, when compared with C57BL/6J and/or C3H/HeJ mice, the MRL/MpJ strain harbors diverse polymorphic alleles, unique QTL, or specific haplotypes that render this background more susceptible to autoimmune manifestations.[28–32] As an example, low to no expression of CFHR-C in MRL/MpJ may contribute to the immune hyperresponsiveness typical of this strain.[109]

BXSB/Mp mice are a recombinant inbred (RI) strain originating from a cross between a C57BL/6J female and a SB/Le male, also developed by Murphy[125,126] in his work on autoimmune conditions (lab code Mp). They develop a lupus-like disorder that is accelerated in males and is attributed primarily to the Y-associated autoimmune accelerator locus (*Yaa*) of the SB/Le male founder. *Yaa* is a 4-mb translocated region from the X chromosome that includes multiple genes, among which *Tlr7* seems to be the major contributor to the phenotype.[127–129]

NZB mice develop a variety of autoimmune phenotypes characterized by hypergammaglobulinemia with elevated circulating autoantibodies (including anti-DNA antibodies and anti-thymocyte antibodies), Coombs positive hemolytic anemia, and immune complex glomerulonephritis. NZB mice also manifest a lymphoproliferative disorder involving the B1 subset of B cells. This condition progresses to lymphoma/leukemia, with similarities to human familial chronic lymphocytic leukemia.[130–134] NZW mice develop autoantibodies and glomerulonephritis, with a female predisposition.[135] F1 hybrid offspring of NZB females and NZW males (also referred to as NZB/W) develop a life-limiting autoimmune condition characterized by high levels of antinuclear antibodies, hemolytic anemia, proteinuria, and progressive immune complex glomerulonephritis that is more severe in females.[136–138] NZB/W autoimmune phenotypes map to multiple susceptibility loci, including *Sle*, *Lbw*, and *Wbw* loci and polymorphisms in *Tnf*, *Nkt2*, and *Cd93*, and are linked to a low to no expression of CFHR-C.[110,111,139]

NZM2410 mice (New Zealand Mixed strain 2410, e.g., NZM2410/J https://www.jax.org/strain/002676) derive from NZB/W backcrossed to NZW mice then selected for lupus-like nephritis deaths and inbred. They bear the NZW histocompatibility haplotype $H2^z$ (K^u, A^u, S^z, D^z). Males as well as females develop autoimmune glomerulonephritis at an early age, and this strain has been especially useful in mapping lupus susceptibility loci.[138,140–142]

Important Spontaneous Mutations

Supplementary Table 2 gives a comprehensive overview for most of the well-known murine immune relevant mutations that exhibit Mendelian inheritance. Historically, identification of the genetic basis for spontaneous Mendelian (monogenic) phenotypes was attained via forward genetics approaches to confirm that the heritable trait (phenotype) maps to a specific locus. Additional molecular investigations, including sequencing, are applied to define the mutation further.[88,143] An advantage of forward genetics is the relatively unbiased approach that requires no assumptions or hypotheses regarding the molecular basis of the trait or phenotype. An historical and illustrative example in immunology is the characterization of TLR4, first recognized as the main sensor for lipopolysaccharides (LPS) thanks to studies conducted on the spontaneously TLR4 deficient C3H/HeJ mice, and closely related TLR4 sufficient substrains.[95] A null mutation $Tlr4^{lps\text{-}del}$ mapping to the same site was identified later in the C57BL/10ScCr substrain of the C57BL/10 mouse and is now available as C57BL/10ScNJ.[144,68] Similarly, the role of *Foxp3* as an essential transcription factor for the development of regulatory T cell (Tregs) was first revealed via the analysis of mice with the spontaneous scurfy mutation ($Foxp3^{sf}$).[145]

Hereditary immune deficiencies related to spontaneous recessive *scid*, $Lyst^{bg}$ (*bg* or beige), and Btk^{xid} (*xid*) mutations have been valuable in the study of orthologous conditions in humans and other animals.[146] The *scid* and *nu* (nude) mutations have been especially important for their utility in studying engrafted human tissues in the context of xenotrasplantation experiments.[147]

Hereditary hyperimmune or autommune conditions related to spontaneous recessive Fas^{lpr} (*lpr*, lymphoproliferation) and $Fasl^{gld}$ (*gld*, generalized lymphoproliferative disease) mutations in an important cell death pathway have also been informative. Mice homozygous for either mutation develop lymphoproliferative and autoimmune phenotypes. The (recessive) *lpr* mutation at the *Fas* locus compromises the FAS-mediated apoptosis pathway.[115,123,148,149] The (recessive) *gld* point mutation is in the Fas ligand (*Fasl*) locus, and homozygosity for this mutation also compromises FAS-mediated apoptosis. The *gld* mutation arose spontaneously in C3H/HeJ mice, resulting in the C3H/HeJ-$Fasl^{gld}$ substrain.[150,151]

Interactions Among Mutations

Table 3 summarizes genetic and phenotypic characteristics of some of the widely used mice that carry multiple spontaneous immune relevant mutations. Before the advent of modern genetic engineering capabilities, interbreeding to combine multiple hereditary disorders was used to study phenotypic manifestations of gene interactions and to overcome limitations of the single mutation models, particularly in mice used for xenotransplantation experiments.[89] As an example, *scid*-beige mice homozygous for both the $Prkdc^{scid}$ and $Lyst^{bg}$ alleles were generated to combine the impaired B and T cell development of the $Prkdc^{scid}$ mouse with the defective NK cell function associated with the $Lyst^{bg}$ mutation. These mice are not only severely immunodeficient, but they also lack the "leaky" phenotype of the $Prkdc^{scid}$ animals. The cooperation between the 2 mutations remarkably improves xenotransplantation compared with the single mutation in the $Prkdc^{scid}$ mouse.[152,153]

Combinations of multiple mutations have proved useful in understanding the epistatic interactions among immune relevant genes. Double-mutant mice homozygous for both Fas^{lpr} and the $Foxn1^{nu}$ are an example. The congenital T cell deficiency that characterizes the $Foxn1^{nu}$ mutation is sufficient to abolish the autoimmune and lymphoproliferative phenotype associated with the Fas^{lpr} allele. This finding was consistent with the significant abrogation of the phenotype achieved by neonatal thymectomy in MRL/MpJ-Fas^{lpr}/J mice, and provided early support for the hypotheses regarding the T cell dependence of the Fas^{lpr}-associated autoimmune and lymphoproliferative condition.[89,154–157] Other important immunodeficient models featuring combinations of spontaneous and induced mutations along with specific strain-related immune variations are further discussed in a companion article by Simons and colleagues in the present issue of the *ILAR Journal* and include the well-known NSG and NOG mice. Both models carry a slightly different targeted mutation of *Il2rg* combined with the $Prkdc^{scid}$ mutation on different NOD inbred sublines.

Table 3 Overview of Immunologically Relevant Mouse Models that Combine Multiple Spontaneous Mutations

Allelic combination	Background strain/s	Phenotype	References
Fasl^{gld}/*Fasl*^{gld} *Btk*^{xid}/*Y*	C3H/HeJ	*Btk*^{xid} decreases the severity of B cell manifestations associated with *Fasl*^{gld} including hypergammaglobulinemia, generation of anti-DNA autoantibodies and systemic immune-complex disease; no impact on T cell dependent *Fasl*^{gld} phenotype and lymphadenopathy.	89
Fas^{lpr}/*Fas*^{lpr} *Btk*^{xid}/*Y*	MRL/MpJ	*Btk*^{xid} decreases the severity of B cell manifestations associated with *Fas*^{lpr} including hypergammaglobulinemia, generation of anti-DNA autoantibodies and systemic immune-complex disease; no impact on T cell dependent *Fas*^{lpr} phenotype and lymphadenopathy.	89,158,159
Fas^{lpr}/*Fas*^{lpr} *Foxn1*^{nu}/*Foxn1*^{nu}	C57BL/6J	*Foxn1*^{nu} prevents the development of *Fas*^{lpr}-induced lymphadenopathy, unregulated B cell activation, hypergammaglobulinemia, anti-DNA autoantibodies and systemic immune-complex disease (a similar effect is obtained via neonatal thymectomy confirming the T cell dependency of *Fas*^{lpr} phenotype).	89,154–156
Fas^{lpr}/*Fas*^{lpr} *Prkdc*^{scid}/*Prkdc*^{scid}	MRL/MpJ; C.B-17	*Fas*^{lpr} rescues the developmental deficit of thymic T cells associated with *Prkdc*^{scid}; no effect on the B cell deficit caused by *Prkdc*^{scid}.	160
Fas^{lpr}/*Fas*^{lpr} *X*/*Yaa*	MRL/MpJ; C57BL/6J	*Yaa* causes accelerated onset and increased severity of *Fas*^{lpr}-induced autoimmune condition and lymphadenopathy.	161,162
Foxn1^{nu}/*Foxn1*^{nu} *Lyst*^{bg}/*Lyst*^{bg}	C57BL/6J; N:NIH(S)	*Lyst*^{bg} contributes defective NK cells to the T cell-deficient background associated with *Foxn1*^{nu}; reduced NK cell activity does not seem to impact on the engraftment rate and growth of xenotransplanted human tumor cell lines.	89,163
Foxn1^{nu}/*Foxn1*^{nu} *Btk*^{xid}/*Y* or *Btk*^{xid}/*Btk*^{xid}	N:NIH(S)	Defective T (*Foxn1*^{nu}) and B (*Btk*^{xid}) cell function and/or maturation; spectrum of the immune abnormalities is very similar to the one characterizing *Prkdc*^{scid} mutants; severe depletion of both B and T cell domains in the spleen and lymph nodes; limited production of immunoglobulins; females showing high incidence of both lymphomas and ovarian granulosa cell tumors.	89,164–166
Foxn1^{nu}/*Foxn1*^{nu} *Lyst*^{bg}/*Lyst*^{bg} *Btk*^{xid}/*Y* or *Btk*^{xid}/*Btk*^{xid}	N:NIH(S); KSN	Defective T (*Foxn1*^{nu}), NK (*Lyst*^{bg}) and B (*Btk*^{xid}) cell function and/or maturation; high incidence of multicentric lymphoblastic lymphoma; compared to single *Foxn1*^{nu} mutants, improved engraftment rate and growth of xenotransplanted human tumor cell lines.	89,167,168
Dh/*Dh*$^{+}$ *Foxn1*^{nu}/*Foxn1*^{nu}	N:NIH(S)	Combined athymia and asplenia; defective T cell maturation and function; reduced B cell number; hypogammaglobulinemia; increased incidence of spontaneous mammary tumors compared to single-mutant founder lines.	89,169
Lyst^{bg}/*Lyst*^{bg} *X*/*Yaa*	SB/Le	*Lyst*^{bg} attenuates severity and progression of *Yaa*-linked autoimmune condition resulting in prolonged survival and lack of immune complex glomerulonephritis; possible role of *Lyst* in B cell development and activation.	89
Btk^{xid}/*Y* *X*/*Yaa*	BXSB	*Btk*^{xid} prolongs survival and decreases the severity of B cell manifestations associated with *Yaa* including immune complex glomerulonephritis, hypergammaglobulinemia, autoantibody levels and lymphoid hyperplasia.	170
Prkdc^{scid}/*Prkdc*^{scid} *Lyst*$^{bg\text{-}J}$/*Lyst*$^{bg\text{-}J}$	C.B-17	Defective T, B (*Prkdc*^{scid}) and NK (*Lyst*^{bg}) cell function and/or maturation; reduced level of B cell leakiness; possible role of *Lyst* in B cell development and activation.	152,153
Prkdc^{scid}/*Prkdc*^{scid} *Hr*^{hr}/ *Hr*^{hr}	SCID Hairless Outbred (Crl:SHO)	Impaired B and T cell development (*Prkdc*^{scid}) associated with diffuse hair loss/ alopecia (*Hr*^{hr}).	171
Foxp3^{sf}/*Foxp3*^{sf} *Foxn1*^{nu}/*Foxn1*^{nu}	129/RI; BALB/c	*Foxn1*^{nu} prevents the development of *Foxp3*^{sf}-induced autoimmune disease including anemia, multisystemic immune/inflammatory cell infiltrates, hypergammaglobulinemia, lymphadenopathy and splenomegaly (a similar, but less potent, effect is obtained via neonatal thymectomy confirming the T cell dependency of *Foxp3*^{sf} phenotype).	172,173
Foxn1^{nu}/*Foxn1*^{nu} *Map3k14*^{aly}/*Map3k14*^{aly}	BALB/cAJcl; C57BL/6J	Athymia combined with lack of secondary lymphoid organs including lymph nodes, splenic white pulp, Peyer's patches and isolated lymphoid organs; severe immunodeficiency with impaired humoral and cell- mediated immune responses; preserved intestinal γδ-IEL subset; confirmation that thymus and secondary lymphoid organs are not an essential requirement for the development of γδ-IEL.	174

IEL, intraepithelial lymphocytes; NK, natural killer.

Table 4 Induced Immunodeficiencies (Intended Experimental Interventions)

Inducers	Possible Effects on the Immune and Other Systems	References
Physical: irradiation		
γ rays and X rays	Suppression of bone marrow resulting in marrow atrophy and pancytopenia. High dose: decreased splenic and thymic weights; loss of cortical thymocytes; decreased splenic CD4+ and CD8+ T cells; decreased circulating CD3+ cells. Chronic low dose: prolonged life span in mice homozygous for the lymphoproliferation spontaneous mutation (*Fas*^{lpr}); increased CD4+ cells; suppression of IL6 and IL17, and up-regulation of Tregs in CIA mice; suppression of pro-inflammatory cytokines, reduction of CD8+ T cells, and induction of Tregs in murine EAE model. Other: acute radiation syndrome and death in *Prkdc*^{scid} mice and *Prkdc* ^{dxnph}mice (both are highly susceptible to ionizing radiations); radiation induced-thymic lymphoma in both male and female mice on a C57BL/6 background and NFS mice; radiation induced-myeloid leukemia in male RF mice (RF/J, RFM) and male CBA mice (CBA/Ca, CBA/Cne, CBA/H); induction of persistent oxidative stress in murine intestinal epithelium with potential for neoplastic transformation by heavy ion radiations; radiation-induced cataract; increased osteoclast activity and bone loss; radiation nephropathy.	182,237–244
α and β particles	Release of DAMPs; activation of DCs; systemic and long-lasting T cell-mediated antitumor response in tumor-bearing mice; efficacy of α and β emitter-labeled monoclonal antibodies against fungal infections in mice. Other: radiation nephropathy.	245–247
UVB	Immunosuppressed contact hypersensitivity (*Xpa* deficient mice); inhibited intra-tumor migration of NKs and CD8+ T cells (*Xpa* deficient mice); depressed delayed hypersensitivity in immunized mice; enhanced contact hypersensitivity and skin graft rejection in mice with dermal Langerin+ DCs. Narrowband (NB)-UVB: increased intestinal Tregs, and decreased severity of inflammatory lesions in mouse models of allogeneic GVHD.	248–254
UVA	High dose: increased IFNγ, IL12, and heme oxygenase; inhibited increment of IL10 from UVB exposure. Medium dose: NO-mediated depletion of epidermal Langerhans cells; impaired development of skin memory CD8+ T cells in a mouse model of contact hypersensitivity.	255–258
Chemical agents		
Endogenous and exogenous glucocorticoids	Direct and receptor-mediated immunosuppression: attenuated DC activity; decreased DC number (apoptosis, tissue redistribution); enhanced inflammation; thymic atrophy (decreased DP thymocytes); dampened T cell activation (interference with TCR signaling); suppressed responses of TH1 and TH17 cells; reduced immunoglobulins. Other: osteopenia, decrease in bone formation rate and mineral apposition rate in skeletally mature and young mice; osteoporosis in CD-1 mice (mouse model of glucocorticoid-induced osteoporosis); cleft palate in A/J mice.	259–265
Cyclophosphamide (CYP; Cytoxan)	Direct immunosuppression: depletion of CD8+ resident DCs in murine spleen and lymph nodes, with subsequent decrease in Treg suppressive function; neutropenia; depletion of suppressor or regulatory T cells in diabetic NOD mice. Other: enhanced antitumor efficacy by promoting proliferation/activation of adoptively transferred B and T cells after CYP-induced lymphodepletion in mice; reduced diversity of the fecal microbiota; hemorrhagic cystitis in C57BL/6 and DBA/2 mice; chronic cystitis in DBA/2 (CYP model of bladder pain syndrome); short root lengths and early apical foramen closure during molar root development in ICR mice; suppressed osteoblastogenesis and osteoclastogenesis in C57BL/6 male mice.	266–273,200
5 FU	Direct immunosuppression: depletion of MDSCs, and stimulation of TH17 cells, IL17 production by CD4+ T cells, and tumor growth; no altered levels of circulating B, T, and NK cells.	207,208
Tacrolimus (FK506)	Receptor-mediated immunosuppression: immunosuppressive effects on CD4+ T cells; marked tumor-promoting effect (topical tacrolimus) with decreased CD4/CD8 ratio; reduced inflammation in models of allergic rhinitis, conjunctivitis and arthritis. Other: nephrotoxicity.	211–215
Cyclosporin A (CsA)	Receptor-mediated immunosuppression, reversible inhibition of T cell proliferation and proinflammatory immune reactions; blockage of all the changes resulting from intercellular signaling and cross-talk between DCs to T cells.	209,210

Continued

Table 4 Continued

Inducers	Possible Effects on the Immune and Other Systems	References
Rapamicin	Receptor-mediated immunosuppression: Inhibition of mTOR: suppressed T cell activation, proliferation, and development of FoxP3+ cells; suppression of DC maturation, B cell activation, neutrophil chemotaxis and uptake of antigen by APCs. Other: increases lifespan.	274,275
Busulfan; Treosulfan	Direct immunosuppression: Busulfan: highly myelosuppressive, minimally immunosuppressive; diminished NK cell activity; late-stage (residual) bone marrow injury; stimulation of neuroinflammation through MCP-1. Treosulfan: high persisting myeloablation in BALB/c mice; more effective depletion of splenic B and T cells.	276–280
Physical: Surgical		
Thymectomy	Thymectomy (post-natal day 2-5): autoimmune hemolytic anemia, thyroiditis, gastritis, oophoritis, orchitis, and prostatitis at puberty due to lack of Tregs.	232
Splenectomy	Systemic immune unresponsiveness; absence of tolerance after ocular injections of antigen in F4/80-deficient mice; retardation of tumor growth in melanoma-bearing mice.	281–285,236
Biological agents		
Anti-thymocyte globulin (ATG)	Depletion of naïve T cells; less effective on memory T cells in NOD mice. Prevention of autoimmune encephalomyelitis through expansion of myelin antigen-specific Foxp3+ Tregs in a murine EAE model.	283,229
β-1,3-Glucan	Increased IL2, TNFα, IL17, IFNγ, and lymphocytes in mice treated with aflatoxin B1.	284
CpG oligodeoxynucleotides	In murine models of infections: TH1 cytokine expression, activation of DCs, NK, and B cells. Combined therapy with monoclonal antibodies: increased NK cell activity.	
Bacterially derived ADP-ribosylating enterotoxins	CT toxin produced by *Vibrio cholera:* secretion of TH2 cytokines, maturation of DCs, generation of Th2 and regulatory T cells, active suppression of TH1 responses. LT enterotoxin from *E. coli*: mixed TH1/TH2 immune response.	230,285,291
Anti-lymphocyte serum (ALS)	Long-term abrogation of autoimmunity in overtly diabetic NOD mice.	286
Monoclonal antibody (mAb) therapy	Anti-mouse CD20 mAbs: depletion of mature B cells; reduction of CD4+ T cells, but maintainance of the interactions, functions, and migration of DCs and CD4+T cells; unaffected CD8+ T cell reactivity; absent release of inflammatory cytokines with effects on T cells. Anti-mouse CD4 mAbs: depletion of CD4+ T cells; expansion of CD8+ T cells with an effector phenotype and of tumor-reactive CD8+ T cells; compromised anti-tumor immune memory. Anti-mouse CD8 mAbs: depletion of CD8+ T cells; decreased infiltration of CD4+ cells, neutrophils, and macrophages; downregulation of IL1β, IL6, TNFα, CXCL1, CCL2 and up-regulation of IL4 in a mouse model of wound healing.	287–289

APCs, antigen-presenting cells; CIA, collagen-induced arthritis; CT, Cholera toxin; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; DP, double positive; EAE, experimental autoimmune encephalitis; GVHD, graft-versus-host disease; LT, heat labile toxin; MCP-1, monocyte chemoattractant protein 1; MDSCs, myeloid-derived suppressor cells; NK, natural killer cell; NO, nitric oxide; Tregs, regulatory T cells.

Induced Immunodeficiencies

The mouse immune system can be modulated (regulated or disrupted) intentionally (and unintentionally) through experimental interventions such as exposures to irradiation, chemical compounds, microbial organisms (including virus, bacteria, and their toxins), or biological agents as well as through surgical manipulations. Immune suppression by these means has been especially useful in experiments of engrafted tissues or tumors and to study the immune response against specific infections or neoplasms. Examples from the major categories of intended experimental interventions to induce specific perturbations of the mouse immune system are summarized in Table 4.

Ionizing and Ultraviolet Radiation

Ionizing radiation is a historically important method to suppress or ablate immunity. The peculiar vulnerability of the hematolymphoid tissue to ionizing radiation results in extensive lymphoid depletion and sustained myeloablation. For this reason, ionizing radiation remains an important immunosuppressive intervention allowing the engraftment of xenotransplants/allotransplants, including, for example, tumors or human haematopoietic stem cells for the generation of mice with humanized immune system.[175,176] Sensitivity to irradiation has been linked to the capacity to repair radiation-induced DNA double-strand breaks. Immunodeficient mice harboring the *Prkdc*^{scid} alleles are particularly radiosensitive due to the *scid* mutation

that affects repair of radiation-induced DNA double-strand breaks.[177,178] Susceptibility to irradiation varies among mice, with strains such as the C57BL/6, A/J, and C3H/HeMs being highly resistant and other strains such as BALB/c being highly sensitive.[177,179] A hypomorphic *Prkdc* allele (*Prkdc*^{dxnph}), identified in BALB/c strains, seems to have an important role in BALB/c susceptibility to ionizing radiation.[178,180,181] Some detail on irradiation tolerance, variations, and dosage protocols is available from the sources of mice that are commonly irradiated (https://www.taconic.com/taconic-insights/oncology-immuno-oncology/rodent-irradiation-considerations.html; https://www.jax.org/jax-mice-and-services/find-and-order-jax-mice/most-popular-jax-mice-strains/immunodeficient-mouse-and-xenograft-host-comparisons). In addition to considering strain sensitivity when determining radiation dosage, calibration of the irradiator is also important, as there is considerable decay over time and actual dosage may differ between studies or between irradiators.

Immune-suppressive effects of high-dose γ-irradiation are well known.[182] High-dose γ-irradiation differentially affects the diverse populations of mouse lymphocytes with B cells recognized as more radiosensitive than T cells.[183] Repeated low-dose gamma irradiation also has profound immunomodulatory effects and is linked to a robust Th2 skewing that may mitigate autoimmune conditions that are dependent on a Th1 response. Suppression of pro-inflammatory cytokine production, reduced CD8+ CTLs, and up-regulation of Tregs also have been demonstrated in certain experimental conditions, including CIA and EAE.[184]

Overwhelming infections remain an important cause of mortality of irradiated experimental animals and clinical patients. Mice with defective adaptive immunity including nude, *scid* and NOD *scid* mice can effectively control common opportunistic agents such as Pseudomonads, until myeloablative effects of irradiation or other interventions eliminate their innate immunity as well.[185] Effects of ionizing radiation on other tissues, and on developing or proliferating cells, influence morbidity and mortality of research mice. Radiation impact on developing brain, bone, eyes and teeth as well as on heart, lung, kidney, may complicate interpretation of disease or death related to rejection, GVHD, or other research endpoints.[186–195]

Ultraviolet (UV) radiation effects on local skin immunity are especially relevant to research on photocarcinogenesis or inflammatory skin conditions.[196–198] Effects vary with dose, duration of exposure and wavelength composition.[196–198] UV radiation primarily affects adaptive immunity, and has been used to induce and promote skin photocarcinogenesis, and to modulate the immune response in diverse experimental immunoinflammatory conditions of the skin.[196–198]

Chemicals

Experimental use of chemicals also has been and remains an important method to suppress or ablate immunity. Examples including metals, aromatic hydrocarbons and other environmental contaminants, and antimicrobial agents are summarized in Table 4. Alkylating agents that affect chromosomal DNA through formation of phosphodiesters and DNA-DNA crosslinks, are widely used. Cyclophosphamide (CYP), a cytotoxic alkylating agent used in the treatment of neoplastic and autoimmune diseases, is also exploited to induce neutropenia in the context of infectious disease studies.[199] Mice with impaired granulocyte production and/or leukocyte function secondary to CYP are more prone to develop systemic disease upon experimental infection with environmental opportunists such as *Pseudomonas aeruginosa* or *Cryptococcus neoformans*.[200,201] CYP has both immunomodulatory and immunosuppressive effects.[202] Immunosuppression in mice appears to result from the induction of apoptosis in activated B and T cells as well as NK cells.[203] At low doses, CYP may enhance immune responses to tumor antigens attributed, at least in part, to suppression of Tregs.[204] Similarly, the alkylating agent busulfan is used as conditioning regimen to enhance engraftment of xenotrasplanted hematopoietic stem cells.[205,206] Other important agents include 5-fluorouracil (5FU), which selectively depletes tumor-associated myeloid-derived suppressor cells (MDSCs) promoting the activation of tumor-specific CD8+ T cells.[207,208] Calcineurin inhibitors (CNI), such as tacrolimus and cyclosporine A, directly inhibit Tregs function, by inhibiting peripheral Tregs generation, and less directly by limiting IL2 production, in preventing transplant rejection and to treat a variety of autoimmune conditions.[209–215] Glucocorticoids are important clinically and experimentally for their anti-inflammatory and immunosuppressive effects.[216]

A variety of experimental interventions including hormones, antimicrobials, nanoparticles, etc., have immunomodulatory effects that may not be intended or expected, especially by investigators who are new to using them in mice. For example, estrogens (and synthetic estrogens such as diethylstilbestrol) and androgens have immunosuppressive effects that affect both adaptive and innate immunity.[217–220] Nanoparticles, usually studied as a drug delivery method or biomedical imaging tool (e.g., metallic nanoparticles), are typically taken up by macrophage/monocyte cells and may act either as immunostimulants or as immunosuppressants and may have additional immune effects related to imaging methods such as MRI or μCT.[221] The unique physicochemical characteristics of nanoparticles influence their interactions with host's immune system and determine the overall immunotoxicologic profile.[222,223]

Biologics

Biologics with immune modulating properties have been exploited in the experimental context to target specific functions of the mouse immune system and achieve definite preclinical endpoints.

Antibody-mediated depletion of cell lineage-specific immune effector cells has been used to delineate their roles in innate and adaptive immunity, in rejection, GVHD, and other conditions.[216,224–226] Anti-thymocyte globulin (ATG), is another important immunosuppressive agent that specifically depletes T cells from peripheral blood and lymphoid organs in NOD mice; it is also used in the modulation of graft rejection and autoimmune disorders in mice.[227,228] Glucans, CpG oligodeoxynucleotides (CpG ODN) and bacterial enterotoxins have been used as prophylactic or therapeutic interventions to modify immune responses to infections or vaccination, or to counteract effects of immunotoxic agents (see Table 4).[229,230]

Surgical

Thymectomy or splenectomy are the traditional surgical methods to alter immunity. Thymectomy in neonatal or adult animals has profound effects on T cell development and continues to be an important procedure in studies of T cell ontogeny, tolerance and education. Neonatal thymectomy experiments offered early evidence of the existence of Tregs as these mice develop autoimmune disease shortly after the removal of thymus.[231] Thymectomy is also used to investigate the dynamics

of extrathymic T cell development.[232] However, mice exhibit a relatively high frequency of functional thymic tissue in ectopic locations, especially in close proximity to the thyroid gland (also known as cervical thymus). While ectopic thymi may be small, they can be confounding source of T cells. They are reported to be more common in NOD and BALB/c mice compared to C57BL/6 mice.[232,233]

Splenectomy has been used to study the role of the spleen in infectious disease, peripheral antigen tolerance, and tumor growth.[234] In cancer, some splenectomy studies implicate the spleen in promoting tumor antigen tolerance.[234,235] while others demonstrate a role of the spleen in maintaining an effective antitumor immune response and prevention of metastatic disease.[236]

Induced Autoimmune and Hyperimmune Conditions

Autoimmune diseases arise when there is poor control of self-reactive lymphocytes and cytokine production, or disrupted regulatory T cell and effector T cell balance. While underlying genetic polymorphisms predispose to immune hyperresponsiveness, manifestation of disease often requires additional triggers such as microbial infections, dysbiosis, or tissue damage. Once initiated, cytokines participate in disruptions of immune tolerance by altering the balance between T-effector functions and T-suppressor functions.[290–292] Strain-related variations in innate and adaptive immunity affect penetrance, onset and severity of disease.[7,27,89,293,294] Modifiers such as *Slamf*-haplotype 2 seem relevant to autoimmunity in MRL/MpJ mice and not so relevant on other backgrounds such as BALB/c.[60–62] The complexity of autoimmune conditions in mice has many parallels with human and, because of a more granular characterization of strain genetics, may have much to offer to our understanding of the human conditions and interventions for them.[295,296] Two examples are discussed here.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an immune-mediated destruction of the synovial lining of the joints, with devastating effects on underlying cartilage and bone. Susceptibility to the induction of rheumatoid arthritis-like conditions in mice, using type II collagen-induced arthritis (CIA) or proteoglycan-(aggrecan)-induced arthritis (PGIA), depends on multiple susceptibility alleles and QTL.[96,297,298] The disease in mice and in humans is polygenic and complex. MHC H2 subtypes seem to have more impact on CIA than on PGIA susceptibility, and PGIA susceptibility is influenced by multiple genes.[96,298,299] Strains expressing the H-2^q and the H-2^r haplotypes are most susceptible to CIA. DBA/1 (H-2^q) are sensitive to CIA but insensitive to PGIA. BALB/c (H-2^d) mice are not so susceptible to CIA but are highly susceptible to PGIA.[96,297,299] In contrast, DBA/2 (H-2^d) are resistant to arthritis induction by either method, implicating roles for strain associated modifier genes.[299,300] Non-MHC QTL associated with susceptibility to CIA and/or PGIA localize to regions on mouse chromosomes 2, 3, 7, 15, and 19 that contain multiple candidate genes with known immune functions.[299]

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disorder with a spectrum of disease manifestations. While disease is associated with certain genetic polymorphisms, environmental triggers as well as sex hormones have roles in disease development.[290,301] A spontaneous mouse model of MS has not been identified. But various aspects of MS are recapitulated by experimental autoimmune encephalomyelitis (EAE), classically induced "actively" by immunization with immunodominant myelin epitope components in combination with immunostimulants, or induced "passively" by adoptive transfer of preactivated myelin-specific T cells into naïve mice.[98,302–305]

EAE in mice was first reported in 1975, and the SJL/J and C3H/HeJ strains were identified as susceptible strains.[98,294,302–304,306] SJL/J mice are used to model features of relapsing-remitting MS, and their susceptibility is associated with several polymorphisms, including hyper-responsive IL12 and hypo-active IL2 and IL4.[67,306,307] Additionally, C57BL/6, DBA1, and C3H/HeJ strains also are sensitive to induction of EAE.[98,294,308]

GEM models such as transgenic mice bearing human TCR and T cells targeting myelin-specific antigens (e.g., myelin basic protein) have been informative,[309] as has immune-mediated demyelination associated with infections by Theiler's Mouse Encephalitis Virus, a Picornavirus, in susceptible SJL/J and resistant C57BL/6.[310–312] Demyelination with certain strains of Mouse Hepatitis Virus (MHV), a coronavirus, has been used to model features of MS in susceptible C57BL/6 and BALB/c mice. This is primarily a virus-mediated cytolytic phenomenon, and SJL/J resistance is attributed to their spontaneous mutation in *Ceacam1*, whose protein product is an important receptor for neurovirulent MHV strains.[313–315]

Other Immunomodulators and Unintended Experimental Consequences

Environmental Factors

Table 5 summarizes examples of immune effects of common environmental factors including husbandry conditions, microbiota, as well as effects caused by experimental or therapeutic interventions. These examples illustrate why reporting of environmental and husbandry conditions and specifics of experimental or therapeutic interventions is warranted in scientific publications. Microenvironment refers to the immediate physical environment surrounding the animal such as the cage, pen, or stall. Macroenvironment refers to the physical environment of the secondary enclosure (e.g., a room, a barn, or an outdoor habitat).[323] A multitude of factors in the microenvironment and macroenvironment can be stressors. Stressors activate the hypothalamic-pituitary-adrenal axis, in turn increasing circulating glucocorticoids. In mice, corticosterone is the primary stress-induced glucocorticoid. Corticosterone elevations (and corticosterone-mediated lymphocytolysis) are expected with stressors such as adverse environmental conditions, shipping, handling, social stresses, noise, vibration, etc.[317–319] Responses to stressors also vary with mouse strains.[320,321]

Caging

Common contemporary caging options are open top, static microisolators (filter top cages), and individually ventilated caging. Suspended wire caging is less common today but may be scientifically justified to prevent coprophagy and ingestion of drugs or metabolites in feces. Individually ventilated caging is increasingly available with advantages in terms of barrier protection of the animals, lower bioburden, and cage changing frequency and with concerns in terms of microenvironment temperature, humidity, wind, and dust. Temperature, vibration,

Table 5 Other Immunomodulators, Including Unintended Immune Consequences of Husbandry and Environmental Factors, Clinical and Experimental Interventions

Immunomodulators	Possible Effects on the Immune and Other Systems	References
Environmental factors		
Housing conditions		
Caging	Individual ventilated cages (compared to static microisolator caging): decreased bioburden and risk of intercage infection spread; increased cold stress; decreased circulating leukocytes; decreased intracage ammonia levels and correlated nasal pathology.	322–325
Bedding	Experimentally relevant parameters influenced by the type of bedding: higher intracage ammonia levels with reclaimed wood pulp bedding; corncob bedding associated with decreased efficiency of feed conversion in mice fed a high-fat diet; hepatotoxicity associated with vermiculite and unbleached pulp from pine and eucalyptus; hepatic and mammary carcinogenesis associated with aromatic red cedar bedding; altered estrogen signaling mainly due to BPA residues; corncob bedding associated with increased aggressivity and social stress in females; drastically lower endotoxin levels and bioburden associated with paper bedding.	323,342,352–357,366
Single or group housing and social stressors	Group housing: negative social events associated with lower lymphocyte proliferation; lower level of antigen-specific IgG; granulocytosis; lymphopenia, higher predisposition to tumor development and progression, huddling associated with amelioration of cold stress. Individual housing: decreased antibody production; worsened allergic skin reaction; increased cold stress.	326–330
Environmental enrichment	Reduced stress levels; reduced oxidative stress; enhanced NK antitumor functions; enhanced macrophage chemotaxis and phagocytosis; improved capacity to clear systemic microbial infection; enhanced lymphocyte chemotaxis and proliferation; increased lifespan.	331–336
Temperature and humidity	Thermoneutral housing temperature (26°–34°C): reduced tumor formation, growth rate and metastasis due to increased CD8+ T cells; reduced myeloid-derived suppressor cells and Tregs. Sub-thermoneutral housing temperature (20°–26°C): suppressed immune responses; increased therapeutic resistance of tumor and GVHD severity; suppressed myeloid cells function; alternative activation of macrophages. Elevated humidity: increased bioburden; high ammonia levels due to expansion in urea-converting microflora.	327,328,337–341,473–476
Environmental noise and vibration	Altered tumor resistance; immunosuppression; reduced body weight; reduced fertility.	348–351,477
Inappropriate handling; untrained personnel	Increased risk of infection associated with inappropriate PPE and insufficient sterilization of equipment; pain, discomfort and stress associated with frequent/improper handling.	316
Altered light-dark cycle	Suppressed immune response; decreased splenic T cells; continuous illumination associated with decreased CD8+ and CD4+ cells in thymus and lymph nodes.	343–345
Dim lights	Elevated nighttime light exposure in male mice associated with worsened inflammation and weight gain under high-fat diet regimen.	478
Diet and water modifications		
Caloric restriction	Immune effects: reduced H_2O_2, TNF α, IL6, IL2, IL10, NO, IFNγ; decreased macrophage activation; impaired NK cell function; reduced IgA in small intestine and serum IgG. Other effects: increased lifespan; reduced age-related morbidities.	363,478–483
Protein-energy malnutrition	Impaired proliferation CD8+ T cells; modulation of intestinal IgA responses to rotavirus; increased duodenal γδ IELs; increased production of jejunal proinflammatory cytokines in response to bacteria.	484–486
Prolonged fasting (48–120 h)	Stress response due to activation of hypothalamic-pituitary-adrenal axis; thymic atrophy (apoptosis of cortical DP thymocytes).	487
High-fat diet (in C57BL/6 mice)	Suppression of delayed hypersensitivity; altered intestinal microbiota with stimulation of mucosal immunity; altered systemic metabolomes; inflammation of adipose tissue with release of adipokines, cytokines, and chemokines, and propagation of a chronic inflammatory state (inflamobesity).	488–490

Continued

Table 5 Continued

Immunomodulators	Possible Effects on the Immune and Other Systems	References
Chlorella vulgaris supplementation	CYP-treated mice: reinstated lymphocyte proliferation and macrophage phagocytic activity; stimulation of IL2, IL12, TNFα, IFNγ, NK cell cytotoxicity; decreased splenic necrosis.	491
Polyunsaturated fatty acids supplementation	Dietary DHA and AA associated with improved allergen-induced dermatitis as consequence of increased FoxP3+ T cells, elevated IL10, and decreased TNFα.	492
Water acidification	Switch from normal tap water to acidified water associated with severe and long-lasting stress.	343
Nutritional deficiencies		
Zinc deficiency	Thymic atrophy (loss of DP thymocytes); accelerated lymphopenia with loss of antibody and cell-mediated responses; decreased number of pre-B cells, better survival for pro-T cells and mature DP and CD8+ T cells; increased myeloid lineage in bone marrow.	493–496
Vitamin A deficiency	Decreased ILC3 and antibacterial responses; compensatory expansion in IL-13-producing ILC2 and increased anti-helminth responses; intestine devoid of CD4+ and CD8+ T cells; lower salivary IgA levels and increased serum IgG response in mouse model of influenza; decreased mucosal antigen-specific IgA responses.	497–499
Vitamin D deficiency	VDR-deficient mice: increased mature DCs in skin draining lymph nodes; decreased Th1-cell responses and induction of IL10-producing Tregs.	500
Diet and water contaminations		
Estrogenic endocrine-disruptors	Isoflavones (genistein): thymic atrophy; suppression of delayed hypersensitivity; decreased splenic NK cells; decreased IFNγ in response to bacterial infection. Mycotoxins (aflatoxins, deoxynivalenol, zearalenone): elevated IgA and IgE; kidney mesangial IgA deposits; polyclonal activation of IgA secreting cells; IgA autoantibody. BPA (cages, water bottles): lupus-like syndrome (C57BL/6 mice); allergic airway disease (BALB/c mice).	365,366,501–503
Halogenated aromatic hydrocarbons (PCDFs;PCDDs)	Contaminated food and bedding: inhibited innate and adaptive immune responses; atrophy of lymphoid organs; TCDD targets thymic lymphoblasts.	364,504,505
Metals (As, Cd, Pb, Hg, Se)	Complex immune-modulating effects (immunosuppression and immunostimulation). As: decreased DCs in mediastinal lymph nodes of influenza A-infected C57BL/6 mice.	504,506
Microbial status, pathogens, and biosecurity		
MHV	MHV-3-infected C57BL/6: impairment of pre-B cells maturation and B cells functions. A59-infected BALB/c: transient lymphocyte apoptosis in the thymus. MHV-JHM-infected BALB/cByJ: functionally altered CD4+ and CD8+ T cells, and APCs.	507–509
Sendai virus	Interference with macrophage and their phagocytic activity, NK cells, and T and B cell function; increased isograft rejection.	507,510–513
MNV	Lethal infection in mice deficient for STAT1 and IFN receptors; alteration of immune/inflammatory parameters in diverse mouse models including *Mdr1a* deficient animals infected with *Helicobacter bilis* interfering with dendritic cell function and cytokine responses; infection of wild-type mice associated with mild intestinal inflammation, splenic red pulp expansion, and white pulp activation.	514–516
MuHV-1	Loss of splenic T and B cells; interference with key coordinating role of DCs; functional impairment of macrophages and loss of response to cytokines; altered responses to mitogens, antigens, increased allograft rejection, delayed type hypersensitivity responses, and clearance of other pathogens; formation of anti-cardiac autoantibodies.	440,517–520
MuHV-3	Thymic necrosis (specific targeting of CD4+ T cells in newborn mice); autoimmune gastritis in BALB/c and A strain; autoimmune oophoritis and production of antibodies to thyroglobulin.	413,440,521
MPV	Suppressed proliferation (spleen, popliteal lymph node), increased proliferation (mesenteric lymph node) in ovalbumin-primed mice; altered alloreactive T cells	522,523

Continued

Table 5 Continued

Immunomodulators	Possible Effects on the Immune and Other Systems	References
	and abnormal CD8+ T cell rejection of tumors and skin allografts (BALB/c); rejection of syngeneic grafts.	
MVM	MVM: oncolytic, cytotoxic, replicative cancer inhibitor; deregulation of the Raf signaling cascade. MVMi: depressed myelopoeisis in neonatal BALB/c; depletion of hemopoietic precursors, leukopenia, and compensatory erythropoiesis in adult and neonate SCID mice.	415,524
Murine retroviruses	Insertional mutagenesis (with reintegration of endogenous retroviruses or transposition of retroelements): immune relevant mutation such as *Foxn1*^{nu}, *Lep*^{ob}, *Fas*^{lpr}. Endogenous retroviruses in pancreatic islets: contribution to immune-mediated insulitis NOD mice. LP-BM5-infected C57BL/6 mice: lymphadenopathy, splenomegaly; hypergammaglobulinemia; T and B cell dysfunctions; late appearance of B cell lymphomas; opportunistic infections.	439–443,448,525–529
LCMV	LCMV disease: all pathological alterations following infection are immune-mediated; prototype for virus-induced T-lymphocyte-mediated immune injury and for immune complex disease; protection from LCMV-induced disease conferred through immunesuppression; noncanonical type I IFN signaling responsible for lethality in LCMV-infected *Stat1* deficient mice.	530–532
MHV-68	Experimental infections of laboratory mice to study the pathogenesis of human lymphoproliferative disorders associated with EBV.	422,426–430
Bacteria	Mortality/morbidity (sepsis) in immune deficient mice: *Pseudomonas aeruginosa*, *Klebsiella spp*., *E coli*; potentially any bacteria in severely immunocompromised mice. Abscesses: *Staphylococci*, *Pasteurella pneumotropica*. Skin disease/morbidity: *Corynebacterium bovis*, *Staphylococci*. *Mycoplasma arginini*: suppurative arthritis in *Prkdc*^{scid} mice inoculated with contaminated cell lines.	375,378,381,440,451,533
Fungi	*Pneumocystis murina*: respiratory disease and mortality in immunodeficient mice. *Candida* spp.: recent reports associated with immune deficiency/suppression and or use of antimicrobials.	378,381,534–536
Biosecurity in immunodeficient mice	High risk of *Pneumocystis carinii* infection in T cell-deficient mice including *Foxn1*^{nu}, *Prkdc*^{scid} mice and immune impaired GEMs; immunodeficient traits in mutant mice masked by the immune/inflammatory response associated with chronic γ-herpesvirus infection; MNV infection in *Atg16l1*-deficient mice associated with Paneth cell abnormalities; murine papillomavirus associated with proliferative lesions at the mucocutaneous junctions of *Foxn1*^{nu} mice; mousepox recrudescence following immunosuppression and transmission to naïve mice.	375,400,537–540
Biosecurity: contaminated biologicals	Rodent pathogens (latent infections): contaminated serum with mousepox. Human pathogens: contaminated human cell lines (humanized mice and patient derived xenografts mice). *Mycoplasma arginini*: suppurative arthritis in *Prkdc*^{scid} mice (contaminated cell lines).	378,410,434,451,452,541
Modulation of the microbiome	SFB associated with the development of IL17 and IL22-producing CD4+ T cells (TH17 cells) in the intestinal lamina propria of germ-free mice. *Tritrichomonas muris*: associated with elevated TH1 response in the cecum of naive WT mice and accelerated colitis in *Rag1*-deficient mice after T cell transfer.	386,387,405,406
Drugs administered for clinical or experimental purposes		
Tamoxifen-inducible *Cre/loxP* system (Cre-ERT2)	Estrogen-dependent and -independent tamoxifen immunomodulatory effect; shift from a TH1- to a TH2-mediated immune response.	458,459
Tetracycline/doxycycline-inducible Tet-Off/Tet-On system	Doxycycline-dependent modulation of immune and inflammatory functions including allotransplant rejection, response to LPS, neutrophil chemotaxis; tetracycline/doxycycline-induced dysbiosis.	461,462,472
Nitrosamines, nitrates, nitrites (mutagens, carcinogens)	DMN: suppression of both humoral and cell-mediated immunity. ENU: lymphoma (AKR/J, C58/J, C57BL/6J, NOD/LtJ); myeloid malignancies (SWR/J, DBA/2J); thymic lymphoma with/without K-ras mutations.	542–544
TMP-SMX	TMP-SMX alone: no effect on hematopoiesis or immune cell functions.	545

Continued

Table 5 Continued

Immunomodulators	Possible Effects on the Immune and Other Systems	References
Ivermectin	TMP-SMX synergized with zidovudine: anemia, thrombocytopenia, lymphopenia, and neutropenia, decreased splenic macrophages, suppressed AC-dependent T cell responses. Immunomodulation of T-helper cells; decreased recruitment of immune cells and cytokines in a model of asthma; unintended activation of tamoxifen-regulated Cre fusion protein in T cells.	460,546,547
Estrogens (for engraftment of estrogen-dependent tumors)	Increased splenic neutrophils (estrogen-treated C57BL/6 mice); enhanced IFNγ expression; thymic atrophy (DERKO mice); myelosuppression (decreased pluripotent hematopoietic stem cells). Synthetic estrogens (DES): altered thymic T cell differentiation through interference with positive and negative selection processes in prenatally exposed mice; functionally defective NK cells and increased tumor susceptibility in neonatally exposed female mice. Other: increased trabecular bone mineral density, fat reduction and increased uterine weight (DERKO mice); fibro-osseous lesions (bone marrow replacement by fibrovascular stroma (KK/HlJ and NZW/LacJ female mice).	501,548–552
Androgens (for engraftment of androgen-dependent tumors)	Androgen stimulation: thymic involution resulting from decreased colonization of bone-marrow-derived stem cells; loss of thymic epithelial cells; thymocyte apoptosis; inhibition of CD4+ T cell differentiation through upregulation of phosphate Ptpn1; erythroid hyperplasia. Castration: enhanced CD8+ T cell vaccine response to prostate-specific antigens.	553–556
Streptozotocin	Early lymphopenia in both blood and spleen; relative increased Tregs in spleen, peripheral blood, and lymph nodes; delayed islet and skin allograft rejection.	557
NPs	Suppression of systemic humoral immunity (multi wall carbon nanotubes); inhibition of T cell-mediated immunity (iron oxide NPs, fuellerene 60); myelosuppression (Sb2O3, Co, ZnO, TiO2 NPs); allergic reactions (Ag NPs); anti-inflammatory activity and inhibition of cellular responses induced by IL1B (citrate-coated gold NPs).	558–563
Other experimental interventions		
Cre/loxP	Activation of STING antiviral response by endonuclease activity of Cre recombinase.	457
CRISPR-Cas9	Adaptive immune response against Cas9.	458,459
Tetracycline/doxycycline-inducible Tet-Off/Tet-On system	Apoptotic response in activated lymphocytes resulting from DNA binding by tTA/rtTA.	464
Classical reporter molecules	Increase in the CTL response against transplanted eGFP-expressing leukemia cells in BALB/c mice; IFNγ response to the dominant CTL epitope of Luc, with consequent restricted growth and metastatic activity of the reporter-labelled tumor cells in a mouse model of mammary adenocarcinoma; antigen specific activation of T cells to the reporter gene β-galactosidase, with loss of transgene expression.	465–470,564,565

AA, arachidonic acid; AC, accessory cell; BPA, Bisphenol A; CTL, cytotoxic T lymphocyte; CYP, cyclophospharmide; DCs, dendritic cells; DERKO, double ER knockout mice; DES, diethylstilbestrol; DP, double positive; DHA, docosahexaenoic acid; DMN, dimethylnitrosamine; EBV, Epstein-Barr virus; eGFP, enhanced green fluorescent protein; ENU, N-ethyl-N-nitrosourea; GVHD, graft-versus-host disease; IBD, inflammatory bowel disease; IELs, intra-epithelial lymphocytes; ILC3, type 3 innate lymphoid cells; ILC2, type 2 innate lymphoid cells; LCMV, lymphocytic choriomeningitis virus; Luc, luciferase; MHV, mouse hepatitis virus; MHV-68, murine gammaherpesvirus 68; MNV, murine norovirus; MNM, minute virus of mice; MPV, mouse parvovirus; MuHV-1, murid herpesvirus 1 (mouse cytomegalovirus); MuHV-3, murid herpesvirus 3 (mouse thymic virus); NKs, natural killer cells; NPs, nanoparticles; PPE, personal protective equipment; rtTA, reverse tetracycline-controlled transactivator protein; SFB, segmented filamentous bacteria; TCDD, 2,3,7,8-tetrachlorodibenzodioxin; TMP-SMZ, trimethoprim/sulfamethoxazole; Tregs, regulatory T cells; tTA, tetracycline-controlled transactivator protein; VDR, vitamin D receptor.

and microbial burden (discussed further below) are among the variables with expected immune effects.[322–325]

Housing density

Co-housing or group housing of mice is practical and economical with compatible animals that do not fight and kill each other before study endpoints. Single housing can be required, especially for male mice to survive to study endpoints. Co-housing vs single housing effects on stress and immunity vary with strain, sex, and other conditions.[326–329]

Enrichment

Enrichment for shelter, nesting, and gnawing have variable effects that are often associated with strain, sex, and other conditions. In general, provision of nesting material helps to reduce the level of stress and influences positively several immune parameters including NK cell antitumor functions.[331–336]

Temperature humidity

Current temperature recommendations for mouse housing of 22–26°C are below the mouse thermoneutral zone of 30–32°C.

The "mild" cold stress caused by standard sub-thermoneutral housing temperatures affects immune responses, tumor growth, and other experimental outcomes. Huddling and nest building are methods of behavioral thermoregulation used by mice under cold stress. Recommended relative humidity is 55% ± 10%. Humidity levels vary with type of caging, season, and geographic location. Higher humidity is associated with increased levels of ammonia and bioburden with severe impairment of respiratory mucosal immune response and increased risk of opportunistic infections, respectively.[327,328,337–342]

Illumination (Light)

Circadian and light effects on immunity are recognized in many species, including humans and mice. Albino animals have higher light sensitivity, and a number of common mouse strains are blind with retinal degeneration but still exhibit responses to light and light cycles.[343–345] Dysregulation of circadian rhythmicity in mice induces a generalized proinflammatory macrophage activation and exacerbates diet-induced systemic insulin resistance and glucose intolerance. A balanced circadian rhythm is also critical to maintain immune homeostasis via the immunoregulatory activity of the neurohormone melatonin.[346,347]

Noise vibration

While a number of common mouse strains are deaf or become deaf with age, hearing mice perceive and respond to sounds outside of human ranges. Noise and vibration are shown to cause stress, induce corticosterone, and negatively affect reproduction.[348–351]

Bedding

While contemporary commercial contact bedding materials tend to be far more standardized with more quality control and freedom from contaminants than previously, contaminants with potential effects on research outcomes can still occur in bedding material. Dust, ammonia levels, fungal spores, phytoestrogens, and endotoxins in bedding also have implications for diverse research. Regional variation among bedding material has implications for various research areas, including immunology, with corncob bedding more available in the United States than in the European Union and other sites, and with hardwoods, cellulose, or paper being other common options. The relative palatability of or preference for a bedding over the intended diet may affect consumption of the diet.[323,352–357]

Diet

Contemporary commercial research diets also are far more standardized with more quality control than previously, and nutritional deficiencies are unlikely on contemporary commercial diets. Nutritional requirements for mice, including adequate levels of nutrients,[358] minerals,[359] and vitamins,[360] exist as do guidelines for contaminants in laboratory rodent diets.[361,362] Possible contaminants with immunomodulatory effects include industrial chemicals (e.g., PCBs, PCDDs, and PCDFs), pesticides (e.g., DDT), metals, nitrosamines, endocrine-disrupting compounds, and mycotoxins. However, contaminants are identified in contemporary diets and are a concern for biomedical research and regulatory toxicology.[363,364] Endocrine-disrupting phytoestrogen-rich ingredients, especially soy and alfalfa, as primary protein sources are expected in natural ingredient (aka grain-based or cereal-based) diets. Phytoestrogens are recognized to have influences on rodent reproduction, immunity, cardiovascular, neoplastic, and other conditions.[365,366] Animal byproducts, bone meal, and fish meal are used in many natural ingredient diets and are a source of nitrites and nitrosamines.[363,367]

Poor reporting of research-relevant diet factors such as differences between purified and natural ingredient diets have attracted attention and concern recently.[10,358,368] Research diets are frequently provided ad libitum to rodents on shorter term studies. Diet restriction in long-term studies usually improves survival and reduces neoplastic, kidney, inflammatory, and other lesions.[369–371]

Water

Contemporary water sources and delivery methods frequently include reverse osmosis, filtration, hyperchlorination, acidification, or some combination of these, delivered by water bottles, glass, or various plastics, tinted or untinted, and/or automated watering systems.

Acidification became a common practice for research rodents to control opportunistic bacteria (especially *P. aeuroginosa*) causing morbidity mortality in immune-deficient rodents that were further immunosuppressed by irradiation that further compromised or eliminated their innate immunity. Water treatments including administered drugs can affect water consumption and have immune or other effects that warrant reporting in publications.[343,372–374]

Husbandry and Biosecurity

Special husbandry needs of immunodeficient mice are largely related to protection from agents that may cause morbidity and mortality. Such agents may be harbored by clinically "healthy" immune sufficient mice, or possibly by human handlers, and may be transferred by common equipment and other fomites. Proximity to immune sufficient mice or to any mouse cohort with different microbial status warrants special procedures and policies for sanitation and sterilization of caging, feed, water and other materials, sequence of animal handling, and microbial surveillance. GEM models may also manifest unexpected immunodeficiencies.[375] Immunomodulatory effects by common agents (Table 5) demand that immune relevant research must pay greater attention to microbial exclusion lists and definition of the specific pathogen free (SPF) status in the vivarium as well as in reporting. Use of the term SPF requires specification of the excluded agents.[316,376–378]

Some of the most concerning opportunistic agents in contemporary immunodeficient mice, such as *Staphylococcus xylosus*, *Corynebacterium bovis*, and *Pneumocystis murina*, are fairly common and usually subclinical in immune sufficient mice.[379–384] (see also Table 5)

Microbiota and Microbiome

Autochthonous (commensal and symbiotic) microbiota

Systemic and mucosal immunity in mice are influenced by the intestinal flora (microbiota).[27,375,385] The intestinal microbiota are important to effective mucosal immunity and to immune responses beyond the gut. As an example, segmented filamentous bacteria (SFB) have been identified as an important antigenic stimulus in inducing Th17 responses, and murine Th17 responses are blunted in mice that lack SFB.[395] Also SFB are shown to influence neuroinflammation in EAE models, diabetes

susceptibility in NOD mice, and development of autoimmune arthritis in some models.[387–390] SFB normally colonize the distal small intestine of infant mice and decline with the maturation of the mucosal barrier and local IgA levels.[391] In mice with deficient adaptive immunity or Ig production, or mice specifically deficient in IgA, SFB persist with expanded distribution throughout the small intestine.[392,393] SFB are difficult to propagate *in vitro* and have not been included in the standardized communities of intestinal microbiota (e.g., Altered Schaedler flora) specifically maintained in some sources of laboratory mice to uniform the influence of microbiota on the experimental conditions. In this context, SFB are not expected in immune deficient mice from certain commercial vendors that maintain the mice in isolators with defined or highly restricted flora.[394,395]

Strain-associated and vendor-dependent differences in the gut microflora of laboratory mice have been identified and are implicated in variability in research results (see Table 5).[378,385,396–400] Flora with more *Bacteroides* spp. and *Parabacteroides* spp. such as *Parabacteroides distasonis* may mitigate DSS-induced colitis.[401] Mice of similar strains but from sources with more simplified or restricted microbiota, lacking SFB, have quite different dendritic cell profiles and Th17 responses.[402] In several immune relevant GEM including IL10, T cell receptor alpha, and IL2 knockout mice, intestinal inflammation also is substantially influenced by intestinal microbiome.[403,404] Enteric protists are common in mice (but usually excluded from commercial sources) and also have been shown to influence Th17 and Th1 responses as well.[405,406] The microbiota or autochthonous microflora of research animals are increasingly recognized as highly research relevant. The restricted microflora of naïve mice from reputable commercial sources have been presented as a research concern, but their well-characterized microbiota also represent an opportunity for this area of immune relevant research.[407–408]

Allochthonous (noncommensal) agents

Morbidity, mortality, and other adverse or confounding effects of infectious agents on research have led to great effort and expense toward microbial definition and exclusion by commercial sources of mice and for quarantine and surveillance by research programs to protect animals and research from infections.[410] Immune deficient mice are notoriously susceptible to disease and death from pathogens and opportunists. The same agents in immune sufficient mice may result in subclinical infections or a spectrum of disease phenotypes that are influenced by genetic background, age, sex, and other factors. But any agent detected by an immune system can be expected to elicit an immune response, or "immunomodulate." Table 5 summarizes examples of microbial effects on immunity and particular concerns for morbidity and mortality in immune deficient mice.[411,412]

Viruses with selective tropisms for immune cells include some of the murine parvoviruses, herpesviruses, and retroviruses. Many of the parvoviruses infecting mice are lymphocytotropic, altering both CD4+ and CD8+ T cell-mediated responses during acute infection.[378,413,414] Although long-term immune effects may not be identified with natural infections by some parvoviruses, significant immunomodulation is well documented with infection by others (Table 5).[378] Parvoviruses replicate in actively dividing cells and are studied as oncolytic agents in combined anti-cancer therapies.[415] Several mouse parvoviruses were identified originally as contaminants in biological materials such as tumor cell lines. They remain among the most common agents identified in research mice, pet store and feral mice, and biological materials. Despite the usual absence of clinical signs in parovirus-infected mice, these agents should be especially concerning in immune relevant and cancer studies.[409,416–420]

Although mouse herpesviruses are not expected in contemporary research colonies, mice are host to several lymphocytotropic herpesviruses that are reported in pet store and feral mice.[421,422] Mouse thymic virus infection in newborn mice causes thymic necrosis, with selective targeting of T cells, and transient immunosuppression.[413] This agent or a close relative was recently classified under the genus *Roseolovirus* similar to human roseoloviruses.[423,424] Murine cytomegalovirus is used to model human cytomegalovirus infection and targets hematolymphoid tissues and salivary glands. Disease manifestations vary with the genetic background.[425] Occult (seronegative) murine cytomegalovirus infection has been shown to affect responses to allografts.[426]

Murine gammaherpesvirus 68, a natural pathogen of bank voles, is related to human gamma herpesviruses Epstein-Barr virus (EBV) and Kaposi sarcoma-associated herpesvirus and is used to study the pathogenesis of gammaherpesviruses in experimentally infected mice. However, *Mus musculus* ssp. are not the natural host, and horizontal transmission between laboratory mice is not expected.[422,426–430] EBV is a human B-lymphotropic gamma herpesvirus that infects more than 90% of the human population. Human infections are subclinical (latent) when effectively controlled or can result in infectious mononucleosis or malignancies such as Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma, and post-transplant lymphoproliferative disorders. Immunodeficient and humanized mice have been informative preclinical tools for studying the pathogenesis of some of the conditions associated with EBV.[431–433] EBV-induced post-transplant lymphoproliferative disorders are also increasingly recognized to complicate research with human patient derived xenografts in severely immunodeficient mice[434–436] and may be amenable to suppression of human lymphocyte proliferation in the donor tissue.[437,438]

Exogenous retroviruses and active endogenous retroviruses have lymphocyte tropisms and roles in immune modulation and lymphoproliferative conditions as well as in mammary carcinogenesis, sarcoma development, and lymphomagenesis. Exogenous horizontally transmitted retroviruses have been eliminated from commercially available mice but are identified in wild mice. Insertional mutagenesis with reintegration of endogenous retroviruses or transposition of retroelements has resulted in spontaneous mutations including some immune relevant ones such as *Foxn1*^{nu}, *Lep*^{ob}, and *Fas*^{lpr}.[439–441] Mice infected with LP-BM5 (defective) murine leukemia virus develop murine acquired immunodeficiency syndrome and have been widely used as a preclinical model to study the pathogenesis of human retroviral infections (Table 5).[442,443] Lifelong expression of viral proteins encoded by endogenous retroviruses/retroelements may be responsible for most of the spontaneous immune-mediated conditions observed in some inbred strains during aging, including glomerulonephritis and polyarteritis.[440,444] Strain-specific variations in the composition and activity of endogenous retroviruses/retroelements and immune response against retroviral antigens also play a role in the susceptibility of specific mouse backgrounds to experimental autoimmune conditions including SLE and T1D.[445–448]

While the parvoviruses, herpesviruses, and exogenous retroviruses have been eliminated from commercial sources of contemporary laboratory mice because of disease or other confounding effects on research, recent interest in the "normal" immunity of wild or pet store mice may render these agents, as

well as historically important mouse disease problems and zoonotic concerns, more relevant.[449,450]

Biological Materials

Biological materials, including transplantable tumors, cell lines, serum, embryos, and gametes, can harbor a diversity of mouse viruses (parvoviruses, ectromelia virus, MHV, lactose dehydrogenase elevating virus, and retroviruses), human viruses, and bacteria, notoriously the Mycoplasmas.[420,451,452] They therefore represent a substantial concern as a source of pathogens and microbial confounders, especially in studies that involve immunodeficient rodents. Reporting recommendations plead for QA of cell lines: genetic QA (authentication to confirm the identity of the cell lines), and microbial QA (to assure freedom from pathogens).[453–456]

Unintended Consequences of Genetic Engineering Strategies

Genetic engineering strategies have immune effects that may have unintended or unexpected consequences for diverse research areas.

Cre/loxP-based DNA recombination technology is used for conditional (tissue-specific) gene targeting. The endonuclease activity of Cre recombinase, including the "illegitimate" targeting of the numerous pseudo-loxP sites across the mouse genome, results in the strong induction of an antiviral response. This is due to the recruitment of the specific cytosolic DNA sensor stimulator of interferon genes (STING), concurrent with Cre-dependent DNA damage and the accumulation of cytoplasmic DNA fragments. Given the primary role of STING in the activation of antiviral immune pathways (including type-I IFN), Cre expression can impact multiple immune parameters in Cre/loxP-based mouse models. Appropriate Cre-only controls may help in distinguishing signal from noise.[457]

The tamoxifen-inducible Cre/loxP system (Cre-ERT2) allows site- and time-specific gene targeting in the mouse. Tamoxifen has immune relevant effects, as well as toxic and genotoxic effects. The estrogen-dependent and -independent effects of tamoxifen have been demonstrated to promote a shift from a Th1- to a Th2-mediated immune responses. Such effects can especially impact allergy and autoimmune models involving activation of Th1-mediated immunity (e.g., EAE and some SLE models).[458,459] Recently, oral ivermectin treatment has been specifically linked to the unintended activation of Cre-ERT2 system in T cells.[460]

Tetracycline-controlled transcriptional activation (Tet-Off/Tet-On) systems allow site-specific, reversible, and dose-dependent control of gene expression in mice. Doxycycline (a tetracycline derivative) is administered or withdrawn to regulate target gene expression. Doxycycline in mice interferes with and modulates immune and inflammatory responses relevant to allotransplant rejection, response to LPS, and neutrophil chemotaxis, among others.[461–463] Recent works have also unveiled the effect of doxycycline on murine gut microbiota and how the resulting dysbiosis might affect the immune response in diverse experimental settings.[461–463] DNA binding by tetracycline/doxycycline-controlled Tet-transactivator (tTA) and its reverse is apparently sufficient to induce apoptosis in activated lymphocytes. These findings indicate that a major experimental bias exists in the use of the Tet-On/Off system for lymphocyte targeting as the approach may (1) limit the extent of the adaptive immune reaction and (2) favor the outgrowth of apoptosis-resistant subpopulations of lymphoid cells.[464]

Expression of fluorescent or enzymatic reporters driven by gene-specific regulatory elements is used to study *in vivo* or ex vivo activity and distribution of specific molecular targets or mutant alleles in GEM models. However, an increasing number of studies show that reporters can be highly immunogenic. Indeed, response of the mouse immune system against classical reporter molecules (including enhanced green fluorescent protein, luciferase, and β-galactosidase) has been demonstrated. The inherent immunogenicity of reporter gene's products depends on different factors including the mouse's background strain as well as level of expression and tissue distribution/accumulation. It is therefore extremely important to consider carefully any potential variable associated with the use of genetic reporter systems for immunological studies in mice.[465–470]

Even the most recent and sophisticated strategies for genome editing, including the revolutionary CRISPR-Cas9 system, have demonstrated experimental caveats influencing the immune system. In addition to the potential immunogenicity of viral vectors in viral delivery systems, human and mice have demonstrated preexisting adaptive immunity to Cas9 homologues expressed by common bacteria such as *Staphylococcus aureus* and *Streptococcus pyogenes*. The inherent immunogenicity of Cas9 is a concern not only for the preclinical application of the CRISPR-Cas9 system, but also for its potential clinical use as gene therapy strategy.[471,472]

Future Directions in Mouse Immunology

Human Surrogate/"Avatar" Approaches

Options to take advantage of humanized mice and other animals to study human derived immune elements in nonhuman surrogates are reviewed elsewhere. These present a diversity of opportunities for better understanding of human disease conditions as well as a number challenges that also may be informative if approached critically and scientifically.[431,566,567] For a comprehensive overview on this topic, readers are encouraged to consult the contribution from Simons et al. in the present issue of the *ILAR Journal*.

Genetic Approaches

Options to take advantage of the spectrum of mouse genetic and immune diversity include factorial study design and Collaborative Cross (CC)-derived RI strains and Diversity Outbred (DO) mice. In a factorial study design, significance can be achieved with relatively small "n" from several strains selected for informative differences in immune relevant genotypes and phenotypes.[568,569] Recognizing that an inbred strain represents an intentionally limited fraction of the spectrum of genetic variability of laboratory mice not designed or suited to model immunological endpoints at a population scale,[570,571] the CC-derived RI strains represent the genetic variability across the 7 major families of mice and offer fairly new options for dissecting genetic and molecular mechanisms of immunity and disease.[572,573] The CC is a mouse reference population with high allelic diversity constructed by a breeding strategy that systematically outcrosses 8 founder strains, followed by inbreeding to obtain new RI strains. Five of the 8 founder strains are "classical" laboratory strains including 129S1/SvImJ, A/J, C57BL/6J, NOD/ShiLtJ, and NZO/HlLtJ. Three founder strains are "wild-derived": CAST/EiJ, PWK/PhJ, and WSB/EiJ. Currently available CC RI lines are distributed through consortia (e.g., http://csbio.unc.edu/CCstatus/index.py) and public repositories

(e.g., https://www.jax.org/strain/027296). Since their inception, partially inbred CC mice have been characterized and compared for the identification of deviant immune traits or phenotypes. They have provided opportunities to study the evolution of complex genetic interactions.[573] The application of immunogenomics and immunonogenetics techniques on CC mice has identified QTLs, polymorphic regions, and candidate genes that control mouse immunodiversity[572] and have contributed to our understanding of susceptibilities to SARS coronavirus, West Nile virus, and *Aspergillus fumigatus*.[574–577] DO mice (https://www.jax.org/strain/009376) were developed by random outcross matings of 160 CC RI lines, and the breeding strategy of continued random matings is designed to maximize their genetic diversity.[578–581] The genetic heterogeneity of DO mice far exceeds that of genetically undefined mice, termed "outbred," that derive from the Swiss branch of the mouse family tree (e.g., CD-1, CFW, ICR, ND4, NMRI, SW) originating from Clara Lynch's original 9 albino mice brought to the United States from Switzerland in 1926. The genetic heterogeneity and heterozygosity among these mice is more limited and varies with their source.[582,583] While the literature is still fairly limited on CC RI strains and the derived DO mice, these represent translational research tools that take advantage of mouse genetic variability to identify disease mechanisms, select novel drug targets, and discover associated biomarkers.

Microbial Approaches

There is recent interest in the use of genetically and microbially "wild-like" mice as a more human like or human relevant strategy.[3,4,6,450,573,584] The studies make relevant and useful points about the naïve immune systems of "clean" C57BL/6 mice recently received from microbially restricted commercial sources. However, many mice bred in house in research institutions are not quite so naïve or microbially restricted.[378,585–587] Undefined or incompletely defined microbiota of pet store or feral mice raise concerns for infection related morbidity, mortality, and unpredictable experimental confounds as well as biosafety concerns related to zoonotic agents. Advances in gnotobiotics and microbiota characterization offer opportunities for defined and strategic approaches that will deliver important insights to immune modulation by autochthonous and allochthonous microflora.[385,409,449,450]

Conclusions

Mice have had important roles in advancing the field of immunology and fostering the development of new diagnostic and therapeutic avenues. Recognition of intrinsic and extrinsic contributors to immune phenotypes is crucial for the selection of more relevant and reproducible mouse models and generation of robust translational data. Known contributors can be intentionally used or intentionally avoided in the experimental system. Accurate reporting of animals and study conditions is mission critical to communicating biomedical research. Well-designed and reported research in mice has much to offer to our understanding of immunity and important diseases of humans and other species.

Supplementary Material

Supplementary material is available at *Institute for Laboratory Animal Research Journal* online.

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