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The mouse as a model for understanding chronic diseases of aging: the histopathologic basis of aging in inbred mice

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Inbred mice provide a unique tool to study aging populations because of the genetic homogeneity within an inbred strain, their short life span, and the tools for analysis which are available. A large-scale longitudinal and cross-sectional aging study was conducted on 30 inbred strains to determine, using histopathology, the type and diversity of diseases mice develop as they age. These data provide tools that when linked with modern *in silico* genetic mapping tools, can begin to unravel the complex genetics of many of the common chronic diseases associated with aging in humans and other mammals. In addition, novel disease models were discovered in some strains, such as rhabdomyosarcoma in old A/J mice, to diseases affecting many but not all strains including *pseudoxanthoma elasticum*, pulmonary adenoma, alopecia areata, and many others. This extensive data set is now available online and provides a useful tool to help better understand strain-specific background diseases that can complicate interpretation of genetically engineered mice and other manipulatable mouse studies that utilize these strains.

Keywords: *pseudoxanthoma elasticum*; *rhabdomyosarcoma*; *MoDIS*; *The Jackson Aging Center*; *pulmonary adenoma*

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Mutant and inbred strains of mice are critically important tools necessary to study complex genetics and disease mechanisms for almost all human diseases (1). With the combination of high resolution genetic variation data plus the ability to manipulate the genome, the current level of technology for working with inbred strains and spontaneous and genetically-engineered mutants (especially for analyses of complex genetic traits) makes the mouse the tool of choice for these types of studies. Most of the common causes of human morbidity and mortality are associated with age-related degenerative or neoplastic disease, such as atherosclerosis or cancer, and with an increasingly long-lived population, the economic and social impacts of these diseases are increasing (2). Because of the relatively short lifespan of mice, many studies have utilized both inbred strains and hybrid stocks to investigate aging (3–5). However, these types of studies often focus on the genetics of lifespan itself while disregarding the underlying diseases commonly associated with aging, which usually have a direct impact on lifespan.

Historically, much work was done on aging lesions in strains of mice that were commonly used in biomedical research at the time. This provided background data to aid in interpreting other experimental procedures but also insight into the aging process itself and how inbred strains differed from each other. This historical work focused on a few inbred and hybrid strains (BALB/cStCrlfC3H/Nctr and B6C3F1 [C57BL/6N X C3H/HeN]F1) used by the National Center for Toxicologic Research, also diet restriction studies (C57BL/6NNIA, DBA/2NNia, B6D2F1 [C57BL/6NNia X DBA/2NNia], or B6C3F1 [C57BL/6NNia X C3H/NNia]), and a variety of other strains and stocks (3, 6–8). More recently studies

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focused on general types of lesions in aging mice used in genetic engineering experiments, both inbred and those on segregating backgrounds (9). Husbandry, pathogen status, and genetic quality control have all improved since these earlier data sets were generated. For example, *Helicobacter hepaticus* is now recognized as a pathogen and is eliminated in most research and vendor colonies (10, 11). The same is true for *Klebsiella oxytoca*, especially in strains that have mutations in the toll-like receptor 4 (*Tlr4*) gene (12). Another example is elimination of exogenous mouse mammary tumor virus, and therefore the high frequency of mammary cancer, from C3H substrains that are distributed by commercial vendors (13).

Understanding the complex genetics of chronic diseases of aging in humans will ultimately provide markers to identify genetic susceptibility that identify lifestyle changes or pharmacologic intervention which, if done early, will greatly prolong life and health and reduce health care costs. The best examples practiced currently are screens and prevention for myocardial infarction. While large-scale human population studies are ongoing, many failed to anticipate the need for collection of specific types of specimens to take advantage of modern molecular biotechnology (RNA, DNA, tissue and cell-specific gene expression, etc.). Studies are now being redesigned on a large-scale in the United States, United Kingdom, and elsewhere but it will be decades before data can be analyzed for many diseases, especially at the molecular level (14). Use of the laboratory mouse circumvents these problems as mice get many of the same diseases for the same reasons as humans do, mice have a short lifespan, and many reagents, new technologies, and extensive databases are available for studying mice.

We report here an overview of the extensive histopathology investigations of 30 inbred strains of mice at various ages in both cross-sectional and longitudinal studies. Not all strains of mice (28/30) survived to the planned age for cross-sectional testing; 20 months of age. Testing and utilization of a database, the Mouse Disease Information System (MoDIS) (15, 16), using the Mouse Anatomy (17) and Mouse Pathology Ontologies for data capture (18–20) provided a computable system for compiling and analyzing the subsequent massive data sets. Summaries of these data with representative photomicrographs can now be accessed on several public databases (Mouse Tumor Biology Database, http://tumor.informatics.jax.org/; Mouse Phenome Database, http://phenome.jax.org/; and Pathbase, http://www.pathbase.net) (16, 21–24). These data provide a unique resource and background information on lesions that inbred strains of mice commonly or rarely develop. This information can be an aid to correctly interpret lesions seen in old mice or the data can be utilized in genome-wide single nucleotide polymorphism (SNP) association studies, a method similar to human genome-wide association studies (GWAS), to define the underlying genetics and gene networks that regulate chronic diseases.

Materials and methods

Mice

Mice were obtained from the Jackson Laboratory (Bar Harbor, ME). Thirty inbred strains were selected (Table 1) as those commonly used in biomedical research and for their genetic diversity, as estimated by SNP genotyping of 102 strains in 7 genetically related groups (25). Included among these strains was the sequenced strain C57BL/6J and 15 strains 'resequenced' by Perlegen Sciences (http://www.perlegen.com) and later by the Wellcome Trust Sanger Institute (http://www.sanger.ac.uk/cgi-bin/modelorgs/mousegenomes/snps.pl). Additional strains were added for diversity so that 3–7 strains were represented in each of the 7 genetic groups (25). Two wild-derived strains were included in this group (WSB/

Table 1. Thirty inbred strains used for detailed aging analyses. The JR# indicates The Jackson Laboratory stock number for each strain.

Strain	JR#	Strain	JR#	Strain	JR#
129/SvImJ	2448	C57BR/cdJ	667	NZO/HILtJ	2105
A/J	646	C57L/J	668	NZW/LacJ	1058
AKR/J	648	CAST/EiJ	928	P/J	679
BALB/cByJ	1026	CBA/J	656	PL/J	680
BTBR-T^{+}tf/J	2282	DBA/2J	671	PWD/PhJ	4660
BUB/BnJ	653	FVB/NJ	1800	RIIIS/J	683
C3H/HeJ	659	KK/HIJ	2106	SJL/J	686
C57BL/6J	664	LP/J	676	SM/J	687
C57BL/10J	665	MRL/MpJ	3896	SWR/J	689
C57BLKS/J	662	NON/ShiLtJ	2423	WSB/EiJ	1145

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EiJ for *Mus musculus domesticus* and PWD/PhJ for *Mus musculus musculus*).

Mice were maintained in a humidity-, temperature-, and light cycle (12:12 hrs) controlled vivarium under specific pathogen-free conditions (http://jaxmice.jax.org/html/health/quality_control.shtml#Animalhealth). Mice were housed in double-pen polycarbonate cages (330 cm^2 floor area) at a maximum capacity of four mice per pen. Mice were allowed free access to autoclaved food (NIH 31, 6% fat; Lab Diet 5K52, Purina Mills, St. Louis, MO) and acidified water (pH 2.8–3.2).

Aging colonies

The study was divided into a longitudinal or life span investigation and a cross-sectional study, to evaluate onset and diversity of diseases at 6, 12, and 20 months of age. Mice in the longitudinal study were allowed to become moribund at which point they were euthanized by CO_2 asphyxiation. Criteria for euthanasia approved by our Institutional Animal Care and Use Committee were as follows: not responsive to stimuli, slow respiration, cold to the touch, hunched with matted fur, sudden weight loss, failure to eat and drink, prominent appearing ribs and spine, and/or sunken hips.

Mice in the cross-sectional study were euthanized in cohorts during a 4 month period for mice at 12 months + 28 days and 20 months ± 28 days of age. At the time of necropsy blood was collected via the submandibular vein for hematology (Siemens Advia 2120 Hematology Analyzer, Siemans Healthcare Diagnostics, Newark, DE) and blood chemistry (Beckman Coulter 600 Pro Chemistry Analyzer, Beckman Coulter Corp., Brea, CA). Mice were euthanized and had their body mass evaluated using a PIXImus machine (Lunar PIXImus, GE Medical Systems, Hermosa Beach, CA), and were subjected to a complete necropsy (26).

The longitudinal lifespan study

The first cohort of mice included 32 males and 32 females for each of the 30 strains being studied. A second cohort of 32 females was later added. The total number of 96 mice/strain was calculated to provide enough statistical power to detect a 10% difference in lifespan (5). We also assessed aging-related physiological phenotypes (27) of 15 males and 15 females from each strain every 6 months in addition to lifespan. Complete necropsies (26) were done on moribund mice but not on mice found dead, as autolysis precludes a meaningful interpretation.

The cross-sectional study

To characterize important age-related phenotypes that can only be assessed using invasive methods, a separate cohort of 45 males and 45 females/strain was set up. Fifteen females and 15 males were aged and those that survived to 12- and 20-months of age were euthanized by CO_2 asphyxiation and a complete necropsy performed (26). An additional cohort was aged to 6 months for physiological phenotyping only.

Physiological phenotyping

We assessed neuromuscular function by forelimb grip strength and automated gait analysis (28), kidney function by blood urea nitrogen and urinary albumin and creatinine levels (29), liver function by alanine aminotransferase, albumin and total bilirubin levels, and immunological function by fluorescent-activated cell sorting (FACS), and routine hematological parameters (30). Each six-month evaluation included a complete hematological screen and routine clinical chemistries. In a three-day test, we used comprehensive laboratory animal monitoring cages to assess food and water consumption, respiratory exchange ratios, metabolic heat production, rest/activity patterns, and sleep behavior. We also measured levels of hormones that were thought to be involved in the basic mechanisms of aging: insulin-like growth factor 1 (IGF1), insulin (5), leptin (31), and thyroxin.

Tissue collection

Tissues were collected in a systematic manner and fixed by immersion in Fekete's acid alcohol formalin solution (26). This is an optimal fixative for histology and especially for antigen preservation for immunohistochemistry of mouse tissues (32). After overnight fixation, tissues were transferred to 70% ethanol and later trimmed, processed routinely, embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin (H&E). Pancreata were fixed attached to the intestines but additional samples were removed without any attached tissues other than mesentery, fixed in Bouin's solution, washed in running water overnight, processed as above, but stained with aldehyde fuschin to evaluate pancreatic islets for insulin production. Skulls and the vertebral column were also fixed in Bouin's solution, allowed to fix and decalcify for a week, and then processed as above to generate H&E stained slides. Additional special stains (such as toluidine blue for mast cell tumors or phosphotungstic acid hematoxylin for rhabdomyosarcomas) were used as needed to aid in reaching a definitive diagnosis. More extensive workups were done, including immunohistochemistry, gene arrays, and other state-of-the-art techniques on specific diseases which are being reported separately. On average, 24 slides were generated per mouse averaging about three tissues per slide. These included 'Swiss Rolls' of the entire intestine, stomach, and cecum (5 slides).

Data management

The majority of slides were reviewed by one board certified veterinary pathologist (JPS) with the exception of the central nervous system, which was reviewed by a board certified veterinary neuropathologist (RB). Diagnoses were entered into a relational database, the Mouse Disease Information System (MoDIS) (15, 33), using the mouse anatomy ontology (MA) to code for the organ (17) and the mouse pathology ontology (MPATH) (16) to code for the disease process (diagnosis). A severity score was recorded (0, normal; 1, mild; 2, moderate; 3, severe; or 4, extreme) to account for differences in the size, severity, and biological behavior of lesions, based on standard criteria used by pathologists. Data were downloaded into Excel spread sheets for large-scale editing, especially to standardize the use of terms over time. This was needed in order to disaggregate overall diagnoses used in the initial phase of the study into their constituent MPATH terms when MoDIS was adopted, and subsequently updated.

Information distribution

Data from MoDIS was edited (to standardize terms) and made available to the Mouse Phenome Database (MPD; http://jax.org/phenome) (23, 34). In addition, physiological data collected at the various time points and total lifespan (Kaplan Meier plots) were also provided to MPD (5, 9). As the histologic sections were reviewed by the pathologists, representative lesions were photographed, images filed using a limited access image database (Extensis Portfolio, Celartem Inc., Portland, OR), and curators from the Mouse Tumor Biology Database (MTB, http://tumor.informatics.jax.org) (22, 35–38) or Pathbase (http://www.pathbase.net) (16, 18, 39) obtained images that were key-worded for their respective websites. Curators downloaded the images, key words, and descriptions associated for each image and then uploaded the edited files onto their respective databases on a regular basis, thereby making these images freely available to users worldwide.

Results

Numbers of mice examined

In most cases, no six-month-old mice were examined histologically as relatively few lesions were anticipated based on large-scale disease surveillance done on our production colonies (40). However, complete necropsies were done on six-month-old KK/HIJ mice because evaluation of older mice revealed widespread mineralization, especially of the vibrissa wall, a lesion restricted to null mutations in the *Abcc6* gene which is mutated in human *pseudoxanthoma elasticum* (41, 42). Major skeletal muscles were collected (one front and rear leg and the muscles around the vertebrae) from A/J, SJL/J, and BALB/cByJ mice, because A/J and to a lesser extent BALB/cByJ mice were found to develop a high frequency of rhabdomyosarcoma as they aged and both A/J and SJL/J are known to have spontaneous null mutations in the dysferlin (*Dysf*) gene causing a form of muscular dystrophy (R. Sher and J.P. Sundberg, manuscript in preparation). Almost all of the strains studied reached 12 months of age but many died before reaching 24 months of age, the original planned endpoint for the cross-sectional studies. For this reason, 20 months of age became the age at which mice were collected for the older endpoint. All AKR/J mice died prior to reaching this age and thus were necropsied at 12 months of age or in the longitudinal study. In the latter, AKR/J mice developed lymphomas, a known strain-specific lesion due to an endogenous retrovirus (43, 44). All AKR/J mice had structural abnormalities of their hair shafts, which were due to a mutation and unrelated to age (45, 46). Other strains, especially SJL/J fought extensively, especially but not exclusively the males, requiring many to be euthanized. As a result, no SJL/J mice were available for necropsy at 20 months of age. There were wide variations in numbers of mice euthanized at the later time points (Fig. 1). Other diseases, such as alopecia areata, were found in old mice in strains previously identified to develop the disease (47, 48).

Cause of death

One of the key questions often asked is the cause of death of mice in the cross-sectional study. This reflects a frequent misconception in the aging field; that *the* cause of death can be attributed to a single disease and more precisely that the actual cause of death is actually informative. To an extent this is the consequence of the epidemiological paradigm in which clinical aging science is still largely founded. Morbidity is much more informative about the aging process than mortality. The mice selected at 12 and 20 months of age were, for the most part, in reasonably good health and were euthanized by CO_2 asphyxiation, which was the actual cause of death. However, detailed histologic analyses of all organ systems revealed chronic changes that when limited to a few strains, could be analyzed using haplotype association mapping tools using SNP databases to define the underlying genetic predisposition. The types, frequency, and severity of lesions found are summarized in Figure 2 (see Supplementary files under Reading Tools online). More detailed summaries for cancer are reported elsewhere (49). By contrast, moribund mice, by definition, were near death so a definitive diagnosis could be made.

Diseases were either restricted to only a few strains, such as rhabdomyosarcomas (R. Sher and J.P. Sundberg, manuscript in preparation) or mineralization (similar to

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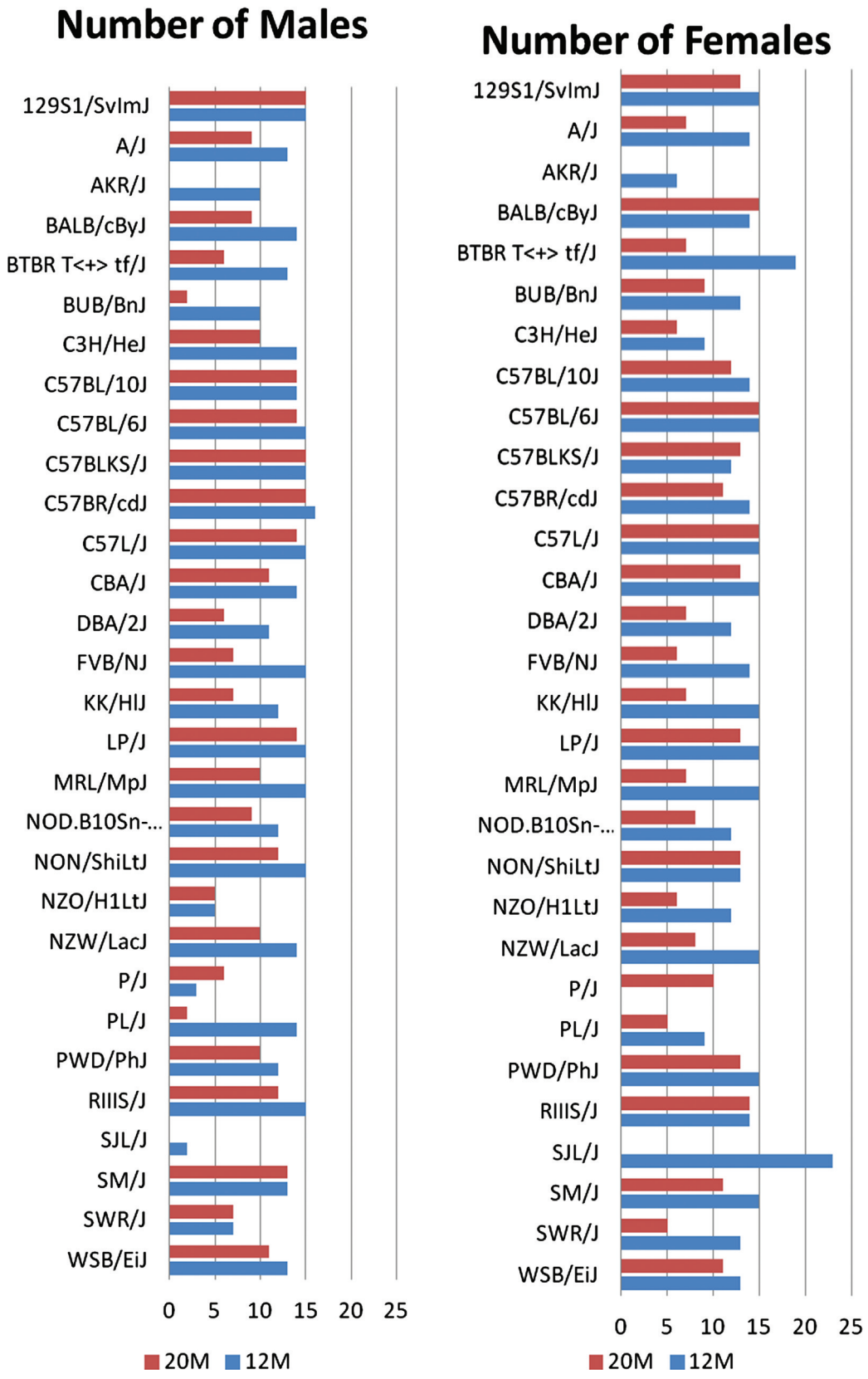

Fig. 1. Numbers of females and males in the cross-sectional study that lived until 12 (blue) or 20 (red) months of age.

that found in human *pseudoxanthoma elasticum*) (42); diseases found in about half the strains consistently, such as pulmonary adenomas (A. Berndt and J.P. Sundberg, manuscript in preparation); or diseases found in almost all the animals regardless of strain (foreign body periodontitis due to hair shaft impaction around teeth (50) or a combination of ductal ectasia, sebaceous gland atrophy, or acute to chronic inflammation, sometime with abscess formation of the clitoral and preputial glands) (51). Few strains showed evidence of frank neoplasia or degenerative conditions.

Physiological phenotyping methods, ranging from hematology and serum chemistry to behavioral or body mass studies, yielded data that supported and helped to confirm diagnoses, but were not diagnostic on their own.

Due to the large amount of data collected it is not possible to include detailed analyses in an overview of this kind and therefore as individual workups integrating haplotype mapping, gene expression data, and physiological phenotyping are completed these will be reported as a series of discrete publications.

Discussion

Whilst the data gathered here are enormously valuable for understanding the types and diversity of diseases these commonly used strains develop, one of the most valuable outcomes was an understanding of how to set up these types of aging, histopathology based, studies. We initially had numerous discussions as a group about whether to focus on moribund mice to establish a mean life span with detailed histopathology near the time of death or to collect samples from mice at specific ages/time points. Based on our experience doing large-scale disease surveillance, while lesions, and more specifically, disease trends, can be found in young mice up to 8 months of age (40), massive numbers of mice are needed. For very detailed, multi-organ, histologic studies, only small numbers of old mice are practical due to the work volume and animal maintenance costs. Diseases were identified in 12-month-old mice that were found in the 20 month group but less frequently. Even for the 20-month-old group, some diseases, such as rhabdomyosarcoma in A/J, were just barely starting to show up. Rhabdomyosarcomas changed from a rare to a common disease in A/J mice over 20 months of age (R. Sher and J.P. Sundberg, manuscript in preparation). Others, such as AKR/J mice, are highly prone to lymphomas and rarely survive to 20 months of age (43, 44). Therefore, while evaluating mice at standardized ages provides a cross-sectional profile of all strains at a particular age, it is not the best way to determine what diseases are serious and common in any particular strain. Aging mice until they become moribund provides a higher chance of discovering strain-specific disease predisposition and correlating these diseases to mean lifespan. Regardless, both approaches yield valuable information.

A second concern, which is a major discussion in the design of high throughput phenotyping studies, is whether or not histopathology is a useful or cost-effective tool for evaluating phenotypes or if physiological (*in vivo*) phenotyping (27), panels of diagnostic tests, provide an adequate and more cost-effective means of evaluating mouse health. Histopathology, when done by experienced personnel, has for over 150 years been the stand-alone standard for arriving at a diagnosis. By contrast, physiological phenotyping approaches reflect human clinical practice and, in the context of model organisms, are often applied later in hypothesis driven approaches to understanding phenotypes as confirmatory assays selected on the basis of histopathology findings. A problem with *in vivo* assays is that they often provide data out of context. For example, high neutrophil counts in peripheral blood of C3H/HeJ mice may well be considered a strain characteristic, but consistently finding severe suppurative otitis media in these toll-like receptor 4 ($Tlr4^{Lps\text{-}d}$) mutant mice (52) due to infection with *Klebsiella oxytoca* (12) would suggest that this is a response due to susceptibility to infection by Gram-negative bacteria, not an inherent neutrophilia. Finding otitis media by histopathology and understanding well-established strain-specific mutations, provides context to these findings. Another example is high red blood cell counts in some members of a cohort of a strain. While statistical analyses would suggest that there was an error in the hematological assay, finding that some but not all of these mice had an erythropoeitic neoplasm puts this diagnostic data into proper context. Our conclusion is that while manipulations can be made with the physiological data to study genetics of 'baseline' data differences between strains, it is not in and of itself definitive or diagnostic. By contrast, histopathology in most cases is and can be used independently and is diagnostic for arriving at a definitive answer. For example, histologic lesions of multiorgan mineralization in several strains, especially the KK/H1J, with mineralization of the vibrissa fibrous capsule permitted a differential diagnosis of *pseudoxanthoma elasticum* (PXE) and several other diseases associated with mineralization. Gene association studies, in which non-synonymous SNPs were screened in genes known to cause PXE or calcium metabolic diseases provided the definitive answer (42). While serum electrolytes might suggest a propensity for this type of disease (41), there is no context to suggest that these were markers for PXE.

Physiological phenotyping will not pick up many diseases such as lung cancer and most serological screens

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are not of diagnostic value until a large mass of the organ is abnormal. In mice, pulmonary adenomas are relatively common and increase in frequency as mice age, as we show here. Pulmonary function tests may not detect effects due to small tumors so these lesions will only be identified at the time of necropsy and more often as incidental findings when the pathologist reviews the slides. Even in the current study where at least four sections of lung were routinely examined histologically, it is likely that not all pulmonary adenomas were found. However, enough were found consistently to enable haplotype association mapping to identify the major genes involved in this disease (A. Berndt and J.P. Sundberg, manuscript in preparation).

Histopathology, when done correctly, covers more tissues more completely than physiological data thereby increasing the likelihood of finding a definitive phenotype that can be used successfully to obtain genetic linkages. More importantly, direct correlation can be made to homologous human diseases in most cases even without any physiological data.

Although large volumes of data have been published on age-associated lesions in mice with or without correlation to humans, some are incorrect due to the lack of pathology expertise of the investigators. For example, teratomas (53, 54) and sebaceous gland tumors (55) were reported in aging genetically engineered mice supposedly due to the induced mutation. These, however, were actually common normal 'aging changes' of the the preputial and clitoral glands, organs found in mice but not humans, affecting all strains in the current study (51). Foreign body periodontitis due to hair shaft impaction around the incisors and especially the molars has been associated with ulcerative dermatitis in C57BL/6 strains and hybrids (56). This actually is found in almost all mice regardless of their hair coat (50, 57) and was found commonly in the B6 and related strains in this aging study in mice with no evidence of alopecia. Many other examples are depressingly abundant in the literature (58).

The data obtained from this study provide a broad overview of the types and variety of lesions seen in mice at various ages and identify many new disease models that will be useful for understanding the pathophysiology of disease in humans and other mammals, especially as they age. The raw data (physiological phenotyping measurements, photomicrographs, etc.) are now available and searchable online from MTB, MPD, and Pathbase. More detailed datasets and tissue samples (paraffin blocks and glass slides) are available through collaboration. Further studies are planned for the future which makes strain comparisons for histopathology of aging a work in progress.

Conflict of interest and funding

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