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Mouse mutagenesis and phenotyping to generate models of development and disease

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Abstract

For many years, the laboratory mouse has been the favored model organism to study mammalian development, biology and disease. Among its advantages for these studies are its close concordance with human biology, the syntenic relationship between the mouse and other mammalian genomes, the existence of many inbred strains, its short gestation period, its relatively low cost for housing and husbandry, and the wide array of tools for genome modification, mutagenesis, and for cryopreserving embryos, sperm and eggs. The advent of CRISPR genome modification techniques has considerably broadened the landscape of model organisms available for study, including other mammalian species. However, the mouse remains the most popular and utilized system to model human development, biology, and disease processes. In this review, we will briefly summarize the long history of mice as a preferred mammalian genetic and model system, and review current large-scale mutagenesis efforts using genome modification to produce improved models for mammalian development and disease.

Keywords

chemical mutagenesis; CRISPR/Cas9; gene knockout; high throughput; International Mouse Phenotyping Consortium; Knockout Mouse Project

1. The mouse fancy and the early days of mouse genetics

Mutant mice have been collected, kept as pets, and studied for many years. In the 19th century, the collection and trading of pet mice with unusual coat colors or oddities of behavior, referred to as the ‘mouse fancy’, provided many of the mutants analyzed by early mouse geneticists. Mice carrying these mutations were among the first mammals to be tested for conformation with Mendel’s laws of heredity, after their rediscovery in 1900. For example, in 1902 Lucien Cuénot in France demonstrated Mendelian ratios for the inheritance of coat color in mice (Cuénot, 1902; Silver, 1995). In the US, William Castle at the Bussey Institute at Harvard University demonstrated segregation and independent

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assortment of a number of different coat color markers, including albino versus colored, spotted versus solid colored, black versus brown, and yellow versus non-yellow (Paigen, 2003a; Russell, 1985). One of Castle's students at Harvard was Clarence Cook Little, who would later go on to found the Jackson Laboratory in Maine in 1929. Little also created the first inbred mouse line, the DBA strain, in 1909 when he was still in Castle's laboratory at the Bussey Institute. Castle was a major figure in the development of mammalian genetics. He directed the Bussey Institute at Harvard until its closure in 1936. Among the geneticists who trained with Castle were L.C. Dunn, Clarence Cook Little, Sewall Wright, and George Snell (Silver, 1995).

Cuénot, in 1905, described what ultimately proved to be the first embryonic lethal mouse mutation, the A^{y} allele of the agouti locus (Cuénot, 1905). However, Cuénot's non-Mendelian genotype segregation ratios were not fully explained until 1910, when Castle and Little demonstrated that crosses involving an embryonic lethal gene gave predictably aberrant Mendelian ratios in which the missing mice were accounted for by dead embryos (Castle and Little, 1910; Paigen, 2003a). These studies set the foundation for utilization of the mouse for the next century as a model for genetic insights into mammalian, and therefore human, development and biology.

2. Mutagenesis in mice

A variety of agents have been used to create heritable mutations in mice. These include various types of radiation, including X rays and gamma rays, and chemical mutagens such as the DNA alkylating agent N-ethyl-N-nitrosourea (ENU) (Gondo, 2008). Integration of exogenous DNA into the mouse genome (insertional mutagenesis) can also cause heritable mutations, either by inserting directly into gene exons, or by creating concomitant insertions or deletions around the integration site. This exogenous DNA is delivered by injection of DNA constructs into the pronuclei of fertilized eggs, or by integration of retroviruses or engineered retroviral constructs (Gridley et al., 1990). One type of engineered retroviral construct that has been widely utilized is the gene trap vector, which usually contains a strong splice acceptor site that disrupts normal transcription and splicing of the interrupted gene (Brown and Nolan, 1998; Joyner, 1991; Zambrowicz and Friedrich, 1998).

One of the most important advances in the field of mouse genetics was the development of embryonic stem (ES) cell technology, enabling germline transmission of cellular genomes maintained in culture, coupled with using gene targeting by homologous recombination to make mutations in these cells of a gene of interest. The 2007 Nobel Prize in Physiology or Medicine was awarded to Mario Capecchi, Oliver Smithies and Martin Evans for the development of this technology (Capecchi, 1989; Koller and Smithies, 1993). The earliest targeted mutant alleles in the Mouse Genome Informatics (MGI) database date from 1989, when eight novel mutant alleles were created using homologous recombination in ES cells, coupled with transfer of the mutant allele into the mouse germline (Bello et al., 2021). Initially, these mutant alleles were constructed and analyzed by individual research laboratories. This technology spurred decades of productive work by many labs generating basic, translational and preclinical mouse models for development and disease. However, it

was realized that economies of scale made it possible to use this technology to great effect in high throughput mutagenesis screens.

Initially gene targeting mostly involved generating a null allele of the gene of interest. However, the technology improved markedly over the years. It became routine to generate missense mutations, alleles tagged with reporter genes (e.g., lacZ or fluorescent proteins), and protein fusions or replacements with Cre or Flp recombinases, among other modifications. Genome modification got a further boost through the development of CRISPR technology (Clark et al., 2020). CRISPR technology made it possible to no longer be dependent on ES cells (which had become routine only for mice and, to a much lesser extent, rats) for generation of modified genomes. Now modified genomes can be constructed directly in zygotes. This has both greatly opened up the range of organisms whose genomes can be experimentally modified, as well as increased the efficiency and speeded up the timeline for mutant allele generation.

3. High throughput mutagenesis and phenotyping

There is a long history of large-scale mutagenesis screens using the laboratory mouse (Brown and Nolan, 1998; Gondo, 2008; Justice, 2000). Initially, these screens used the strategy of forward genetics (i.e., phenotype-driven screens): mice are exposed to a mutagenic agent, such as X-rays or other types of radiation, or a chemical mutagen such as the DNA alkylating agent N-ethyl-N-nitrosourea (ENU), which usually generates point mutations. The mutagenized mice are then bred, using various breeding schemes to detect dominant and recessive mutations, and the progeny are phenotyped to detect deviants (the putative mutants). Heritability of the observed mutant phenotype is established through breeding tests, and the gene mutated to cause the mutant phenotype is determined through positional cloning (Paigen, 2003b). An alternative screening strategy, reverse genetics (i.e., genotype-driven screens), is utilized when using techniques such as gene traps and gene targeting (see below).

In the late 1990s through 2000s, a number of these large-scale screens using ENU as the mutagenic agent took place at research centers around the world. Two large scale ENU mutagenesis screens were launched in 1997 in Europe (Gondo, 2008; Justice, 2000). One took place at the Helmholtz Zentrum München German Research Center for Environment and Health in Germany, and a second at the Medical Research Council (MRC) in the UK. Shortly thereafter, similar screens were opened at RIKEN in Japan and at the Australian National University, followed by NIH-funded programs at several sites in the US. Other mouse ENU screens were directed at more defined phenotypic endpoints, such as developmental mutants, including embryonic lethal mutations (Anderson, 2000; Caspary and Anderson, 2006), and models of congenital cardiovascular anomalies (Li et al., 2015; Yu et al., 2004). Bruce Beutler shared the 2011 Nobel Prize in Physiology or Medicine for his discoveries concerning the role of Toll-like Receptors in the activation of innate immunity. A key element in Dr. Beutler's work was the analysis of mutant mice generated in an ENU mutagenesis screen that he carried out for many years (Beutler and Moresco, 2008). Ultimately, around twenty such screens were organized in institutions around the world (Gondo, 2008). These efforts were incredibly productive, and the Mouse Genome

Informatics database has entries for 4,340 alleles created using ENU mutagenesis (Bello et al., 2021).

With the development of efficient methods for creating null mutations by homologous recombination in ES cells, and transferring these mutant alleles into the mouse germline, it became clear that this technology could be utilized in a similar fashion to large scale chemical mutagenesis screens to perform high throughput mutagenesis of designed null alleles into the mouse germline. Moreover, the phenotyping pipelines developed for the ENU screens, particularly the broad-based screens deployed by MRC Harwell and the German Mouse Clinic, provided a framework for performing systematic phenotyping of targeted mutant lines. This strategy (i.e., mutating a selected gene, followed by thorough phenotypic screening) has been termed reverse genetics, and allows for prioritization of specific genes of interest, including novel human disease genes.

A Banbury Conference meeting at the Cold Spring Harbor Laboratory took place September 30 – October 1, 2003, to discuss the idea of an international effort to assess phenotypes of null alleles of all protein coding genes in the mouse genome. Two white paper/commentaries were published in Nature Genetics after this conference. One white paper, entitled “The Knockout Mouse Project” (KOMP), proposed a genome-wide knockout screen to create a null mutation in every protein coding gene (Austin et al., 2004). This screen would create a resource of mutated ES cells that would be freely distributed. A subset of the mutant ES cells would be used to create mutant mice for phenotyping and distribution. The second paper, entitled “The European Dimension for the Mouse Genome Mutagenesis Program”, proposed creation of a European Mouse Mutagenesis Consortium, with similar goals (Aurwerx et al., 2004). However, unlike the KOMP program, the European initiative had from its beginning a strong focus on utilizing Cre/loxP technology to generate conditional null alleles, a principle that was embraced by the European Conditional Mouse Mutagenesis Program (EUCOMM). A similar initiative was started in Canada with creation of the North American Conditional Mouse Mutagenesis Project (NorCOMM). Reflecting the common goal to build and disseminate this valuable resource to the research community, individual teams coordinated their efforts under the auspices of the International Knockout Mouse Consortium (IKMC) (International Mouse Knockout Consortium et al., 2007). This coordination was critical to assuring the uniform quality of the resource, such as the use of a single C57BL/6N genetic background, and the open availability of the materials through dedicated repositories, such as the Mutant Mouse Resource and Research Centers (MMRRC) and the European Mouse Mutant Cell Repository (EuMMCR).

As the IKMC closed in on a complete genome-wide collection of targeted ES cell resources, there was increasing interest in realizing the original goals of the Banbury meeting: Tier 1 phenotyping of knockout lines to expand our understanding of the function of poorly annotated genes. In 2011, the International Mouse Phenotyping Consortium (IMPC) was created to coordinate efforts among these and other large-scale mutagenesis programs that had been initiated around the world. The IMPC currently includes 21 research centers on five continents dedicated to the design, production, and description of the function of all human gene orthologs in the mouse genome. In addition, all data, resources and strains developed are freely distributed. Table 1 describes a number of web sites with useful

information related to these efforts. In the US, the NIH-funded targeted ES cell production effort, the Knockout Mouse Project (KOMP), was expanded as the Knockout Mouse Phenotyping Program (KOMP2), with the goal of generating and phenotyping mutant mouse strains from these targeted resources. KOMP2 integrated operations with other members of the IMPC, and the introduction in 2014 of CRISPR/Cas9 technology for mutant production greatly increased the efficiency of the KOMP2 program. To date, the KOMP2 program has produced over 5,500 mutant mouse strains. In November 2020, the National Institutes of Health accepted applications for a final five-year project period for the mutagenesis and phenotyping centers comprising the KOMP2 network, with the stated objectives for this final funding period to generate and phenotype at least 1,200 new mutant mouse lines using CRISPR/Cas9 technology, and as with the previous phases, to make both models and data available to the scientific community.

Peterson and Murray recently summarized the progress made to date by the IMPC to generate a comprehensive catalog of null mutations for all protein coding genes in the mouse genome, what remains to be done, and how to prioritize which remaining genes to target (Peterson and Murray, 2021). To date, the IMPC has generated knockout lines for nearly 10,000 genes (Birling et al., 2021), and phenotyped knockout lines for 7,824 genes, from 8,457 independent mouse lines, resulting in 90,010 phenotype calls (IMPC Data Release 15.1, October 11, 2021). When the IMPC knockout number is combined with ongoing efforts in the scientific community, approximately 80% of the 16,847 mouse genes with a high-confidence human ortholog have been targeted, leaving 3,381 genes left to complete the mutant mouse null resource. Given the 1,200 genes planned for the final phase of KOMP2 and the ongoing efforts of other IMPC members, the prospect of a complete functional annotation of the protein-coding portion of the mouse genome, a goal set forth at the Banbury conference almost two decades ago, appears to be within reach.

The members of the IMPC have made great progress with their mutagenesis and phenotyping pipeline, which has enabled the discovery of novel genes involved in specific disease or phenotypic domains (reviewed by Brown, 2021). Table 2 describes these domains, which include sensory domains such as deafness and eye development, circadian rhythms, bone biology, and metabolism, and the references for each study. Analysis of the IMPC datasets has also led to the identification genes involved in embryonic development and lethality, and in sexual dimorphism between male and female mice (Table 2). Critically, the identification of genes essential for embryonic development has proven useful for prioritization of novel human disease gene associations, complementing metrics such as constraint against loss of function mutations inferred from ongoing human sequencing efforts. Interestingly, this study showed that genes essential in mice, but not in cancer cell lines, are highly enriched for human disease genes (Cacheiro et al., 2020).

4. Looking forward

Despite the considerable progress that has been made in generating and phenotyping null alleles of protein coding genes in the mouse genome, the functions of the majority of genes in both the mouse and human genomes remain either poorly understood, or entirely unknown. This portion of the genome has been termed the ‘dark genome’ (Brown, 2021;

Oprea, 2019). Genes encoding proteins included in the dark genome have very few scientific references, and a paucity of molecular tools, such as antibody reagents, for their analysis. High throughput mutagenesis and comprehensive phenotyping, as practiced by the members of the IMPC, are one mechanism to shed "light" on the dark genome. As described by Peterson and Murray (2021) and Brown (2021), of the genes in the dark genome that still lack null mutations, the highest priority for the IMPC should be to mutate and phenotype those genes with human orthologs, thus also providing new information on the human dark genome.

4.1 The Deep Genome Project

With the prospect of a complete set of protein coding gene knockouts in sight, a question arises: what other genome features and/or alleles would benefit from a similar systematic approach to further our understanding of mammalian biology? In a recent commentary publication, 45 scientists, many of them IMPC investigators, proposed undertaking a Deep Genome Project, which they define as the functional biological annotation of all human orthologous genomic elements in mice (Lloyd et al., 2020). There is over 80% conserved synteny, and a high degree of gene orthology, between the mouse and human genomes. Lloyd et al. state that a comparative mouse/human functional analysis, accompanied by the generation and analysis of genetically engineered mice to understand the pathobiology of human disease, will be essential for implementation of effective precision medicine and the optimization of clinical practice. The Deep Genome Project would include analyses not only of the protein-coding orthologous elements of the mouse genome, but would also include conserved non-coding genomic elements, as well as generation and analysis in mice of Variants of Unknown Significance of human genes associated with disease. The Deep Genome Project also includes the goal of integrating functional testing of genomic variation in mouse models into the clinical decision-making process, so that they can inform diagnostic decision and targeted therapies. Patient-derived xenograft models, also called avatars, are currently being utilized, particularly in cancer research (Durinikova et al., 2021; Tucker et al., 2021). Patient-derived avatar models also include generating patient-derived organoids, and patient-derived xenografts in the zebrafish model. However, integrating mouse avatar models into routine clinical practice will be an ambitious undertaking. Most of the goals of the Deep Genome Project are included in the current ten-year strategic plan for the IMPC, described in the next section.

4.2 IMPC Strategy 2021 – 2030

The IMPC has recently released its strategic plan for the period 2021-2030, entitled *The Function of Human Genetic Variation* (https://www.mousephenotype.org/wp-content/uploads/2019/05/IMPC_Strategy_2021-30.pdf). Their key goal for this period is "to deliver broad-based genomic insights into the function of human genetic variation in both coding and non-coding sequences that underpins future developments in precision medicine, rare disease, clinical genetics, and healthy living." To accomplish this, they propose six goals for this ten-year period. These goals include: 1) completing the generation of a null mutant mouse resource for the coding genome; 2) designing and producing a genome-wide mouse strain resource of human disease-associated coding variants; 3) designing and generating mouse strains that model genetic variation in the non-coding genome; 4) phenotyping mouse

strains with null mutations, human-disease coding variants, and variants in the non-coding genome to provide a comprehensive catalog of baseline information on mammalian gene function; 5) exploring genetic context to realize the wider potential for mouse functional studies; and 6) developing data integration, analysis, and visualization approaches to translate mouse functional genomics studies to the human gene and disease knowledge base, and vice versa. Through accomplishment of these ambitious goals, the IMPC proposes to further its mission during this ten-year period: “to generate a comprehensive catalogue of mammalian function and provide the foundations for the functional analysis of human genetic variation.”

5. Concluding remarks

As detailed in this review, the mouse has a long history as the leading model system to provide mechanistic insight into human development, biology and disease. Beginning with the studies of Cuénot, Castle and others early in the twentieth century, and continuing through the present world-wide efforts of the IMPC to complete the generation and phenotyping of a null mutation of every protein coding gene in the mouse genome, the laboratory mouse remains the most practical, cost-effective and widely utilized model system for mammalian biology. The ambitious goals for the next ten years of the IMPC are to catalog mammalian genome function and provide the foundations for the functional analysis of human genetic variation, ultimately impacting at multiple levels the diagnosis, management and treatment of human disease.

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Table 1.

Web sites for mouse information and resources.

Web Site	Address
International Mouse Phenotyping Consortium	www.mousephenotype.org
International Mouse Strain Resource	www.findmice.org
Mouse Genome Informatics	www.informatics.jax.org
Mutant Mouse Resource and Research Centers	www.mmrrc.org

Table 2.

Analyses of IMPC mutants in phenotypic and disease domains.

Disease/Phenotypic Domain	Reference
Deafness	Bowl et al., 2017
Eye/retina	Moore et al., 2018 Albrecht et al., 2018
Circadian rhythms	Zhang et al., 2020
Bone biology	Swan et al., 2020
Metabolism	Rozman et al., 2018
Embryonic development	Dickinson et al., 2016
Sexual dimorphism	Karp et al., 2017