The crucial role of mutant and immunodeficient mouse strains selection in biomedical research: a systematic review of main strains.

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ABSTRACT

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| **Abstract**  The selection of appropriate mutant and immunodeficient mouse strains is paramount in biomedical research, significantly impacting the validity and translatability of experimental findings. This systematic review examines key mouse strains frequently employed in immunological and biochemical studies, highlighting the critical role of strain-specific characteristics in experimental design. We explore the genetic and phenotypic diversity among strains, emphasizing how variations in immune response, metabolism, behavior, and disease susceptibility influence research outcomes. Focusing on prominent examples like SCID, Nude, and NOD mice, we discuss their unique strengths and limitations in various research contexts, including transplantation, tumor xenografts, and type 1 diabetes models. The review underscores the necessity of aligning strain selection with specific research objectives, considering factors such as target phenotype, gene-environment interactions, compatibility with experimental techniques, and ethical implications. Furthermore, we address the inherent limitations of murine models and emphasize the importance of rigorous phenotypic characterization to ensure the relevance and reproducibility of preclinical studies. This review provides a comprehensive overview of major mouse strains, offering researchers a valuable resource for informed decision-making in animal model selection and ultimately contributing to the advancement of biomedical knowledge. |

*Keywords: Keywords: [Murine models*(NOD, SCID, RAG1/2-/-, Nude *knockout}*

1. INTRODUCTION

The use of animal models, particularly the mouse (Mus musculus), is a cornerstone of biomedical research, especially in immunology and biochemistry [Fink, 2014; Miller et al., 2017]. The mouse, with its small size, short reproductive cycle, well-characterized genome, and the availability of a wide range of strains, has become the quintessential mammalian model organism [Nguyen & Xu, 2008; Bryda, 2013]. However, the plethora of available murine strains, each exhibiting distinct genetic and phenotypic characteristics, underscores the crucial importance of rigorous selection to ensure the relevance and validity of experiments [Crawley, 2008]. This often-overlooked choice can have a considerable impact on the results obtained and their interpretation [Zur & Witzgall, 2010].

The choice of mouse strain is critical because genetic variations between murine strains can influence many biological aspects [Dumont, 2011]. Immune response varies across different strains [Abbas et al., 2014], with some exhibiting distinct innate and adaptive immune response profiles, including variations in cytokine production, immune cell activity, and susceptibility to autoimmune or infectious diseases. The metabolism of murine models, including carbohydrate, lipid, and protein metabolism, can affect the results of biochemical studies [Speakman & Westerterp, 2010]. Behavior differs according to the murine model chosen and can lead to behavioral variations that may influence studies on the nervous system or models of psychiatric illnesses [Schwartzer et al., 2013]. Susceptibility to diseases is linked to the genetic heritage of the strain considered. Certain strains are predisposed to developing specific diseases (e.g., diabetes in NOD mice, cancer in some transgenic strains), while others are resistant.

The advent of mutant and immunodeficient mouse strains has revolutionized biomedical research [Bryda, 2013]., providing invaluable tools for studying pathophysiological mechanisms and developing novel therapies. These animal models, harboring specific genetic modifications, enable the recapitulation of complex human pathologies, paving the way for a deeper understanding of diseases and the preclinical evaluation of innovative therapeutic strategies [Schwartzer et al., 2013].

However, the diversity of available strains, each exhibiting distinct phenotypic and immunological characteristics, underscores the critical importance of rigorous and informed selection [Dumont, 2011]. The choice of mouse strain must be perfectly aligned with the specific objectives of the study. For instance, NOD (Non-Obese Diabetic) mice are a model of choice for studying type 1 diabetes [Anderson et al.; 2012], whereas SCID (Severe Combined Immunodeficiency) mice are indispensable for transplantation studies and the generation of humanized mice [Abbas et al., 2014]. Similarly, RAG1/2 deficient mice and Nude (nu/nu) mice, respectively lacking mature B and T lymphocytes and T lymphocytes due to a mutation in the FOXN1 gene, are widely used in immunology and tumor xenograft studies [6].

Thus, a thorough understanding of the characteristics of each strain is essential to ensure the relevance and reproducibility of the results obtained [Dumont, 2011]. A judicious choice of mouse strain, in accordance with the study objectives, is therefore a determining factor in achieving the goals of biomedical research.

This review aims to highlight the importance of appropriate mutant and immunodeficient mouse strains selection in biomedical research. We will explore the characteristics of the main strains used, emphasizing their strengths and weaknesses in different experimental contexts. Understanding the genetic basis and physiological particularities of each strain is essential to design relevant studies, correctly interpret results, and avoid erroneous conclusions.

2. material and methods

This review was conducted using an exhaustive literature search across the PubMed, Web of Science, and Google Scholar databases. Search terms included, but were not limited to: "mouse strains," "mouse models," "murine immunology," "murine biochemistry," "murine genetics," "murine phenotyping," " "NOD," "SCID," "RAG," "nude," "animal models in immunology," "animal models in biochemistry," and "murine models in biomedical sciences."

**Article selection criteria**

Articles and books were selected based on the following criteria:

* Relevance: The material explicitly addressed the characteristics of mouse strains and/or their applications in immunology, biochemistry, or biomedical research in general.
* Scientific quality: Emphasis was placed on the methodological rigor of the cited studies, prioritizing articles published in reputable peer-reviewed journals.
* Publication date: While older articles were included for historical or conceptual context, preference was given to recent publications (within the past 20 years) to reflect the current state of knowledge.
* Publication type: Reviews, original research articles, book chapters, and reference manuals were all considered.

**Review organization**

The review is structured as follows: Each mouse strain is accompanied by a literature synthesis covering its origins and history, genetic and phenotypic characteristics, strengths and weaknesses, and typical applications. Strains of both species are grouped into classical inbred strains, mutant and immunodeficient strains, and transgenic and knockout strains. A conclusion summarizes key points and future directions.

**Data analysis and synthesis**

Information extracted from the articles was synthesized and compared to highlight the distinct characteristics of each strain and their relevance to different types of experiments. Particular attention was paid to comparative studies between different strains, illustrating the impact of strain selection on experimental outcomes.

**Limitations of the review**

This review is not exhaustive, and some less commonly used strains may not be covered in detail. Additionally, the search focused on the mentioned databases, and other sources of information may exist.

3. results and discussion

Among the numerous strains used in biomedical studies, the following strains have garnered our attention due to their higher frequency of use and relevance.

**SCID Mice**

Severe Combined Immunodeficiency (SCID) mice are indispensable animal models in immunology. They carry a genetic defect that prevents the development of a functional adaptive immune system, specifically the absence of T and B lymphocytes. This profound immunodeficiency renders them highly susceptible to opportunistic infections.

**Origin and genetics**

* The SCID mutation was first identified in the 1980s [Bosma et al., 1983].
* It is an autosomal recessive mutation affecting the Prkdc gene (Protein kinase, DNA-activated, catalytic polypeptide) [Hartley et al., 1995]. This gene encodes the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs).
* DNA-PKcs is a crucial enzyme involved in the repair of DNA double-strand breaks, particularly those occurring during V(D)J recombination [Schatz et al., 1989]. This process is essential for the maturation of B and T lymphocytes and the generation of diverse immunoglobulin and T-cell receptor (TCR) repertoires.
* The absence of functional DNA-PKcs impairs V(D)J recombination, halting the production of mature, functional B and T cells [Weaver et al., 1995].

**Key characteristics**

* Absence of functional T and B lymphocytes: The hallmark of SCID mice is the lack of functional T and B cells [Serra et al., 2002]. This results in lymphopenia (reduced lymphocyte count) and hypogammaglobulinemia (low immunoglobulin levels).
* Thymic hypoplasia: The thymus, the site of T-cell maturation, is underdeveloped in SCID mice [Vosshenrich et al., 2003].
* Extreme susceptibility to infections: Due to their severe immunodeficiency, SCID mice are highly vulnerable to infections by bacteria, viruses, fungi, and parasites, even those considered non-pathogenic in immunocompetent animals [Aluri et al., 2023]. Strict sterile housing conditions are essential.
* Acceptance of grafts: The absence of a functional adaptive immune system allows SCID mice to accept foreign cells and tissues without rejection. This is a critical feature for various research applications [Pearson et al., 2008].

**Experimental applications in immunology**

SCID mice are widely used in various areas of immunological research:

* Immune system development: SCID mice allow researchers to investigate the early stages of B and T lymphocyte development in the absence of V(D)J recombination [Schorle et al., 1991].
* Transplantation models: Their ability to accept grafts without rejection makes them ideal for studying mechanisms of immune tolerance and testing novel transplantation strategies [Bluestone, 2011].
* Humanized mouse models: SCID mice are frequently used to create humanized mouse models by engrafting them with human immune system cells or tissues [Akkina, 2014]. These models enable the study of human immune responses in vivo, particularly against human pathogens, and the testing of therapies targeting the human immune system. Different humanization approaches exist:
  + Engraftment with human hematopoietic stem cells (CD34+): Allows reconstitution of a human hematopoietic system, including T and B lymphocytes [Nolta et al., 1994].
  + Engraftment with human peripheral blood mononuclear cells (PBMCs): Enables the study of pre-existing human immune responses [Holguin et al., 2022].
  + Engraftment with human thymic tissue: Allows for more physiological maturation of human T lymphocytes [Lan et al., 2006].
* Cancer research: SCID mice are used to study tumor growth and dissemination, as well as to test novel cancer therapies, including immunotherapies [Tian et al., 2020].

**Advantages**

* Severe and reproducible immunodeficiency: Allows for controlled studies of the effects of T and B lymphocyte absence.
* Graft acceptance: Facilitates transplantation studies and the creation of humanized models.

**Limitations**

* Susceptibility to infections: requires strict housing conditions.
* Incomplete innate immunity: While innate immunity is generally functional, some functions may be impaired.
* Possible immune escape: In some cases, "leakiness" can occur, with the development of a few functional T or B lymphocytes, potentially complicating results.

**Variants and related models**

* NOD-SCID mice: Combining the SCID mutation with the NOD genetic background, which predisposes to type 1 diabetes, results in even more severe immunodeficiency. These mice are widely used for creating humanized models [Chen et al., 2018].
* NSG (NOD-SCID Gamma) mice: Combining the SCID mutation with inactivation of the Il2rg gene (interleukin-2 receptor gamma), which encodes a common subunit of several cytokine receptors, leads to even deeper immunodeficiency. NSG mice exhibit impaired NK cell function in addition to the absence of T and B lymphocytes, making them even more receptive to human cell engraftment [Ito et al., 2002].

**Specific application examples**

* HIV infection studies in humanized mice: Allows for studying HIV infection mechanisms and testing antiretroviral therapies [Denton et al., 2011].
* CAR-T therapy development: Enables evaluation of CAR-T cell therapy efficacy and toxicity in vivo [Jogalekar et al., 2022].
* Study of human immune response against human tumors: Allows for investigating interactions between the human immune system and human tumor cells [Chen et al., 2012].

**Nude mice (nu/nu)**

Nude mice (nu/nu) are a widely used animal model in biomedical research, particularly in immunology, oncology, and infectious disease studies. Their primary characteristic is the absence of functional mature T lymphocytes, which results from a specific genetic mutation.

**Origin and genetics**

The "nude" phenotype was first observed in the 1960s in a laboratory in Glasgow, Scotland [Pantelouris, 1968]. It is caused by a recessive mutation in the FOXN1 gene (Forkhead box protein N1), also known as Hfh11 or winged helix nude (whn) [Nehls et al., 1994]. This gene encodes a transcription factor crucial for the development of the thymic epithelium, hair follicles, and other epithelial tissues [Balciunaite et al., 2002]. Mice homozygous for this mutation (nu/nu) exhibit the nude phenotype, while heterozygous mice (nu/+) have a normal phenotype.

**Key characteristics**

* Hairlessness (Athymia): This is the most visible characteristic of nude mice. They lack hair due to the role of FOXN1 in hair follicle development [Porter, 2003].
* Severe T-lymphocyte deficiency: The FOXN1 mutation disrupts thymus development, leading to a near-absence of functional mature T lymphocytes. The thymus is hypoplastic or absent [Wortis et al., 1971].
* Immunodeficiency: The absence of functional T lymphocytes compromises cell-mediated immunity, making nude mice highly susceptible to opportunistic infections from bacteria, viruses, fungi, and parasites [Dickerson et al., 1983].
* Function of other immune components: Innate immunity (macrophages, NK cells, etc.) and humoral immunity (antibody production by B lymphocytes) are generally functional, although some alterations have been reported [Reynolds et al., 1982].
* Graft Acceptance: Due to their T-lymphocyte deficiency, nude mice accept grafts of foreign tissues and tumors (xenografts) without rejection. This is an essential characteristic for certain research applications [Hudd et al., 1991].

**Experimental applications**

Nude mice are widely used in the following areas:

* Oncology:
  + Study of human tumor growth and metastasis: Nude mice are used to engraft human tumor cells (tumor xenografts) and study their growth, angiogenesis, and metastasis in vivo. This allows for modeling human cancer and testing novel anticancer therapies [Giovanella and Fogh, 1985].
  + Development of new anticancer therapies: They are used to evaluate the efficacy of new anticancer molecules, immunotherapies, and targeted therapies [Sharkey and Fogh, 1984].
* Immunology:
  + Study of T-lymphocyte function: They allow for studying the functions of T lymphocytes by transferring them to nude mice and observing the effects on the immune response [Bishop and Hinrichs, 1987].
  + Study of interactions between tumor cells and the immune system: They allow for studying how tumor cells evade immune surveillance [Dunn et al., 2002].
* Developmental biology:
  + Study of thymus and hair follicle development: They are used to study the role of the FOXN1 gene in the development of these organs [Vaidya et al., 2016].
* Infectious disease research:
  + Study of opportunistic infections: They allow for studying infections caused by pathogens that do not typically cause disease in immunocompetent individuals [Marincola et al., 1989].

**Advantages**

* Xenograft acceptance: This is their primary advantage, allowing the study of human tumors and tissues in vivo.
* Well-established model: They are widely used and well-characterized.

**Limitations**

* Susceptibility to infections: Requires very strict breeding conditions (sterile or controlled atmosphere environment).
* Incomplete immune function: Although the T-lymphocyte deficiency is significant, other components of the immune system may influence results.
* Hairlessness: Can influence certain studies, particularly those involving the study of skin or interactions with the environment.

**Variants and related models**

* RNU (Rowett Nude) Mice: Another strain of nude mice with a different mutation in the FOXN1 gene [Smeds et al., 1981].
* SCID Mice: Although genetically different (mutation in Prkdc), they share severe immunodeficiency and are also used for xenografts [Bosma et al., 1983].
* NSG (NOD-SCID Gamma) Mice: A combination of SCID mutations and inactivation of the Il2rg gene, resulting in even more profound immunodeficiency and better acceptance of human cell grafts [Fujiwara, 2018].

**Examples of specific applications**

* Xenografts of human tumors to test new anticancer therapies: Allows for evaluating the efficacy of chemotherapies, immunotherapies, and targeted therapies on human tumors in vivo [Harrison et al., 2011].
* Study of metastasis development: Allows for studying the mechanisms of tumor cell dissemination and the formation of metastases [Mallya et al. 2021].
* Study of interactions between tumor cells and the tumor microenvironment: Allows for studying how tumor cells interact with cells in the surrounding tissue [Chen et al., 2022].

**NOD (Non-Obese Diabetic) mice**

NOD (Non-Obese Diabetic) mice serve as a crucial animal model in type 1 diabetes (T1D) research. T1D is an autoimmune disease characterized by the destruction of insulin-producing pancreatic β-cells. The NOD mouse model is particularly valuable because, unlike chemically or genetically induced diabetes models, NOD mice develop spontaneous diabetes, closely resembling the human disease.

**Origin and genetics**

The NOD strain originated in Japan in the 1970s through crosses between ICR and NCS (non-obese cataract) mice [Harada et al., 1984]. T1D development in NOD mice is a complex process involving multiple susceptibility genes, some located within the mouse major histocompatibility complex (MHC) region (H2g7) [Leiter et al., 1987]. The H2g7 gene, present in NOD mice, is a major risk factor for T1D [Thomson, 1984].

Several non-MHC genes also contribute to T1D susceptibility in NOD mice, including Ins1 (insulin gene), Ctla4 (Cytotoxic T-lymphocyte-associated protein 4), Il2 (Interleukin 2), and Ildr2 (Interleukin 1 receptor like 2) [Al-Balushi et al., 2023]. These genes play roles in immune system regulation and autoimmune response.

Diabetes incidence varies with sex (females are more susceptible) and environmental conditions [Cho et al., 1991]. Environmental factors, such as diet, infections, and gut microbiota, can also influence disease development [Like et al., 1983].

**Key characteristics**

* Spontaneous T1D development: The hallmark of NOD mice. They develop progressive insulitis (immune cell infiltration of pancreatic islets of Langerhans), followed by β-cell destruction and hyperglycemia [Buschard, 2022].
* Insulitis: Infiltration of islets by CD4+ and CD8+ T lymphocytes is a key step in NOD mouse diabetes development [Atkinson, 2012]. These immune cells attack β-cells, leading to their demise.
* Autoantibodies: NOD mice produce autoantibodies against β-cell antigens like insulin, glutamic acid decarboxylase (GAD65), and IA-2 (Insulinoma-associated protein 2) [Nikolic et al., 2005]. These autoantibodies are considered disease markers and may contribute to β-cell destruction.
* Environmental dependence: Diabetes incidence in NOD mice is influenced by environmental factors like diet, infections, and gut microbiota [Regnell & Lernmark, 2017]. These factors can modulate immune response and affect disease development.
* Non-Obesity: Unlike some other diabetes models, NOD mice are not obese.

**Experimental uses in immunology and diabetology**

NOD mice are widely used to study:

* Mechanisms of autoimmunity in T1D: They allow investigation of CD4+ and CD8+ T cells, dendritic cells, cytokines, and autoantibodies in β-cell destruction [Knip et al., 2010].
* Genetic and environmental factors in T1D: They enable study of interactions between susceptibility genes and environmental factors in diabetes development [Luo et al., 2010].
* New T1D therapies: They are used to test novel therapeutic approaches, such as immunotherapies, cell therapies, and preventive strategies [Atkinson & Eisenbarth, 2001].
* Gut Microbiota's Impact on T1D: They allow study of the gut microbiota's role in modulating autoimmune response and diabetes development [Herold et al., 2019].

**Advantages**

* Spontaneous diabetes model: Faithfully reproduces several aspects of human T1D, including insulitis and autoantibody production.
* Well-established model: Widely used and characterized, with extensive research and data available.

**Limitations**

* Differences from human T1D: While relevant, differences exist between mouse and human T1D, notably in disease onset age and environmental factors involved.
* Incomplete penetrance: Not all NOD mice develop diabetes, and onset age can vary.
* Influence of Housing Conditions: Diabetes incidence is affected by housing conditions, potentially complicating comparisons between studies.

**Variants and related models**

* NOD-SCID Mice: Combine the NOD genetic background with the SCID mutation, making them immunodeficient and allowing human cell transplantation [Dunne et al., 2014].
* NOD.CB17-Prkdc scid J Mice: Another version of NOD-SCID mice.

**Specific applications**

* Immunotherapy studies: Evaluating the effect of different immunotherapies on preventing or slowing diabetes development.
* Regulatory T Cell Studies: Investigating how regulatory T cells can suppress autoimmune response against β-cells.
* Diet and microbiota studies: Examining how diet and gut microbiota composition influence diabetes susceptibility.

This review underscores the critical importance of judiciously selecting murine strains for immunological and biochemical study design [Abbas et al., 2018]. Strain selection is not merely a methodological detail; it profoundly influences experimental outcomes and their interpretation [Murphy et al., 2017]. The intrinsic genetic variations among different strains—whether inbred, mutant, transgenic, or knockout—manifest as significant phenotypic differences affecting diverse biological parameters [Klein & Horejsi, 2000]. Thus, genetic variations exert a major impact on phenotypes [Flurkey et al., 2001].

Mutant and immunodeficient strains, such as NOD mice (a type 1 diabetes model) or SCID mice (deficient in T and B lymphocytes), provide valuable tools for studying specific aspects of the immune system [Abbas & Lichtman, 2017]. However, it is crucial to acknowledge the inherent limitations of each model. For example, the absence of T and B lymphocytes in SCID mice precludes the study of classical adaptive immune responses but renders them indispensable for xenograft or human immunology studies [Janeway et al., 2001].

The advent of transgenesis and knockout technologies has vastly expanded the range of available murine models, enabling the modeling of complex human diseases [Nagy et al., 2007]. Nevertheless, interpreting results obtained with these models requires caution, considering potential off-target effects of genetic manipulation and physiological differences between mice and humans [Yang et al., 2014].

**Considerations for choosing a mouse strain**

Several factors are critical when selecting an appropriate mouse strain for research:

* Target Phenotype: The strain must exhibit the specific physiological or pathological characteristics relevant to the study [Reynolds et al., 1982].
* Gene-environment interactions: Housing conditions (diet, environment, health status) can significantly influence an animal's phenotype. These factors must be standardized to minimize experimental variability [Yang et al., 2014].
* Compatibility with experimental techniques: Certain strains are better suited for specific techniques (e.g., manipulation of embryonic stem cells for knockout models) [Muqbil et al., 2016].
* Ethical considerations: The principles of the 3Rs (Replacement, Reduction, Refinement) should guide all animal research [Muqbil et al., 2016].

Of these, thorough phenotypic characterization of the chosen strain is of paramount importance [Reynolds et al., 1982]. This includes assessing relevant physiological, immunological, and biochemical parameters to confirm that the animals accurately represent the expected phenotype and to detect any potential intra-strain variations.

4. Conclusion

This review emphasizes the crucial role of judicious mouse strain selection in biomedical research, particularly immunology and biochemistry. Appropriate animal model selection is not a mere technicality but a key determinant of experimental validity and reproducibility. Genetic diversity among mouse strains, including mutant, immunodeficient, and knockout strains, leads to significant phenotypic variations impacting immune response, metabolism, behavior, and disease susceptibility. Mismatched strain and research objective can lead to flawed conclusions. Therefore, understanding strain-specific genetic and phenotypic profiles, aligning strain with research question, controlling environmental factors, and performing thorough phenotypic characterization are essential. Advances in genetic manipulation offer promising avenues for developing even more precise models for human disease study.

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