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Critique: Genetically Modified Mice for the Study of Human Health and Disease

Genetically modified (GM), or transgenic, mouse models were thought to pave the way for understanding and treating human disease. Despite impressive technical accomplishments, these experiments have failed to deliver. Mice are not miniature humans and our efforts to use them as such is an impediment to gathering human-relevant data. Though humans and mice share a significant genetic homology, important discrepancies in genetic code are amplified by species-specific differences in regulation at the transcriptional and translational level, leading to broad functional differences among genes. Even genetic twins "who are members of the species of interest and share all their genes, nonetheless have different and changing patterns of gene regulation and thus different disease risks and drug responses."[1] Some scientists have pointed out that "although it may seem obvious that there are important differences between men and mice, this is often overlooked by those modeling human disease."[2]

Experimenters have attempted to employ transgenic mice to study many human diseases, often targeting a gene analogous to one implicated in the human disease, or by studying a murine gene in which mutations produce a seemingly human-like phenotype. Generally speaking, the larger body size and longer lifespan of humans means that we experience increased incidence of somatic mutations compared to mice.[3] Forcing mutations into the more fleeting life of a smaller species does not necessarily provide insight into how these mutations occur naturally in our own bodies. In addition, important factors such as an animals' genetic background, which has a dramatic impact on the observed phenotype of a mutation, are often ignored.[4] Different genetic backgrounds also produce "linkage problems," where "genes close to the locus of the mutation are inevitably conserved, irrespective of all efforts to breed the line into a pure background. Thus, the closer an accompanying gene is to the mutated gene, the lower the chances will be that both loci are separated by chromosomal crossover."[5] This means that mice from different backgrounds may have different accompanying genes that are conserved along with the gene of interest during breeding, widening the gap of comparison and potentially confounding the results generated from mice of varying backgrounds with seemingly identical mutations.

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Here we will discuss just a few of the many instances in which transgenic mice have failed to produce translatable data for human diseases, using examples from neurodegenerative disease, diabetes, and cancer research:

Neurodegenerative GM models

GM mouse models of neurodegenerative disease, including amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease, exhibit an inconsistent range of pathological and behavioral phenotypes, due in part to the transgenes used, inconsistencies in transgene insertion and expression, and mouse background strains.[6] The most commonly used genetic mouse model of amyotrophic lateral sclerosis (ALS), the SOD1 model, is based on a gene that accounts for only three percent of ALS cases in the human population.[7] Systematic reviews have shown that findings from this model have not translated into any effective human therapy for ALS, that "a biased estimation of treatment efficacy in animals may lead to unnecessary (and possibly harmful) clinical trials in humans,"[8] and that "animal models are not an ideal system for studying ALS or for developing drug therapies."[9]

In Alzheimer's disease (AD) research, numerous transgenic mouse lines have been developed that mimic hallmark AD pathologies, including expression of mutated human beta-amyloid precursor protein, altered tau pathology, and neurofibrillary tangles; however, no one model has been able to replicate the wide array of neuropathological and behavioral abnormalities seen in human patients.[10] Mice also display AD symptoms differently, such as early as opposed to late brain atrophy, inconsistent regional specificity of plaques and tangles, soluble as opposed to insoluble plaques, and an immune response that does not mimic the one observed in human brains.[11] Comparing the chemical structure and morphology of beta-amyloid between transgenic mice and humans, Kuo and colleagues note "It is possible that the processing required to create authentic AD plaques cannot occur in transgenic animals because either the necessary enzyme homologs are not present or the elevated pace of amyloid deposition simply precludes the prerequisite maturational reactions."[12] Most importantly, close to 100 percent of the thousands of clinical trials based on so-called promising preclinical studies have failed in humans.[13]

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Diabetes GM models

Diet- and genetically-induced obese animal models are being used in an effort to understand obesity and its related comorbidities such as type II diabetes mellitus (T2DM). Between 2004 and 2014, approximately 75 papers were published *every month* examining rodent models of T2DM.[14] Considering these numbers, we learned a great deal about metabolic conditions in rodents, but many details of human T2DM pathogenesis remained unclear.[15] GM animal models of obesity lack construct validity: The observed phenotypes in these animals are only "secondary to genetic mutations that do not reflect disease etiology in humans."[16] For example, most genetic models of T2DM are based on leptin- or leptin receptor-deficiency when neither of these represent an important contributor to T2DM in humans.[17] Due to compensatory mechanisms and co-occurring developmental defects in GM mice, it is often difficult to distinguish what aspects of a phenotype are actually based on the genetic manipulation. As such, "genetically manipulated models offer limited value when combined with HFD [high-fat diet] feeding, where all of these issues are further exacerbated by HFD-dependent sex, age and strain variability."[18]

Cancer GM models

Publications describing GM mouse models for human cancer research are common in the scientific literature. The creation of these mice involves modifying the animals' genetic profile to express genes implicated in carcinogenesis or deactivating tumor-suppressing genes. In these models, the random nature of the insertion of oncogenes can alter the coding sequence of a given protein, resulting in off-targets, altered expression of neighbor genes, and can cause lethality.[19,20,21] It is often difficult to control gene expression precisely, meaning these models fail to replicate the sporadic and multi-step nature of the growth observed when humans develop tumors naturally. GM mouse models for cancer research also lack the genetic complexity observed in the clinic,[22] are unable to accurately recapitulate the human tumor microenvironment, and do not accurately predict the immune response nor the therapeutic effects of antineoplastic drugs in humans. Despite many efforts to improve the predictivity of these models, the failure rate for cancer drugs in clinical trials is 96.6 percent.[23]

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In addition to "modeling" human disease, GM mice have been used for screening purposes, such as for assessing carcinogenicity in safety evaluations of chemicals. Following a comparison of results from GM mouse bioassays and conventional chronic mouse bioassays used by the National Toxicology Program, Eastmond and colleagues found that GM mouse models were inappropriate for detecting carcinogenic agents and that "none of the GM models can be used as a stand-alone model for risk assessment due to their limitations."[24] The authors warn that caution should be exercised when interpreting carcinogenicity data from GM mice due to the variance in genetic background of the strains, uncertainty as to the mechanistic basis of carcinogenicity in these models, and ambiguous interpretations of outcomes resulting from accelerated cancer pathogenesis, and lack of reproducibility seen with GM models in general.[25]

The examples presented here only scratch the surface of experimental data showing that experiments using GM animals often fail to provide meaningful findings for human disease. Importantly, GM animals also commonly experience reduced welfare as a result of their condition. Genetic modifications can result in a number of unexpected side effects, such as lameness, susceptibility to other diseases, stress, reduced fertility, abnormally high or low body weight, immune impairment, loss of limbs, craniofacial and visceral malformations, morphological and functional brain defects, deafness, and death.[26] Resources should not be allocated to continuing experiments to use and create more GM animal models, but instead it should be diverted to more human-relevant, non-animal methods, such as studies using patient-derived induced pluripotent stem cells (iPSCs) which allow for direct analysis of genetic anomalies at their human source.

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