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The effects of genetic background of mouse models of cancer: friend or foe?

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Abstract

Over the past century, mice have been selectively bred to give rise to the strains used in biomedical research today. Mouse models of cancer allow researchers to control variables of diet, environment, and genetic heterogeneity found in the human population to better dissect the role of these factors in cancer. Because of the important role of genetic background in cancer, the strain of the mouse can give confounding results in studies of mouse models if not properly controlled or can provide important new insights into cancer mechanisms. In this chapter the sources of genetic heterogeneity in mouse models and how it modifies cancer phenotypes is reviewed.

Origin of inbred mouse strains used in cancer research:

Classical inbred strains are a genetic mixture of the *Mus musculus* subspecies: *M. m. domesticus, M. m. musculus, M. m. castaneus, and M. m. molossinus* (which is itself a hybrid between *M. m. musculus and M. m. casteneus*) (Figure 1A) (Silver 1995). East Asian "fancy" mice were selectively bred from *M. m. molossinus* and *M. m. musculus* as pets in the eighteenth century and brought to England during the Victorian era. They were further selectively bred with *M. m. domesticus*, resulting in European "fancy" mice. A limited number of founders from the European "fancy" mice were brought to the US in the twentieth century and inbred to establish the current classical inbred mouse strains. Genetic analysis of these inbred strains show that they are 94% *M. m. domesticus*, 5% *M. m. musculus*, and <1% *M. m. castaneus* (Yang et al. 2011). In addition, many pure subspecies have been inbred to give rise to the "wild-derived" inbred strains, such as WSB/EiJ (*domesticus*), PWK/PhJ (*musculus*), MSM/Ms (*molossinus*), and CAST/EiJ (*castaneus*), which are more genetically diverse that the classical inbred strains.

Different inbred strains have been favored in different research fields and are differentially represented in the background of mouse cancer models. Most genetically engineered mouse models are generated in embryonic stem cells, involving the 129/Sv and/or C57BL/6 strain backgrounds, or in mouse zygotes, involving the FVB/N, C57BL/6 and/or SJL strain backgrounds. In addition, BALB/cJ and A/J are commonly used in studies of autoimmunity and DBA/2J has been important in many fields. As biomedical fields interact and overlap, mouse models on different strain backgrounds have been combined. The resulting mixed strain backgrounds have the potential to confound the interpretation of mouse models, but

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also allow researchers to identify interacting polymorphisms to better understand cancer pathways.

Sources of variation across different mouse strains:

Natural variation occurs in many forms and can be difficult to integrate (Scherer et al. 2007). The DNA sequence varies between different strains by single nucleotide polymorphisms (SNPs), small (<1kb) insertions and deletions (INDELs) that can give rise to restriction fragment length polymorphisms (RFLPs) or simple sequence length polymorphisms (SSLPs), and by larger (> 1kb) copy number variations (CNVs). Autosomal variants undergo germline recombination to produce additional variation in progeny of mixed strain crosses. In addition, these natural variations in DNA sequence are found on the X and Y sex chromosomes and the mitochondrial DNA. Because the sex chromosomes and mitochondrial genome do not undergo the similar recombination and inheritance as the autosomes, they can introduce bias into the mouse populations being studied.

Chromosome X:

The X chromosome undergoes germline recombination in females, but not males. On mixed strain backgrounds the X chromosome contributed by the father is fixed, but the X chromosome contributed by the mother can recombine compared to the previous generation. In female cells, one of the X chromosomes becomes inactivated to maintain the gene dosage similar to males. Whether the maternal or paternal copy of the X chromosome is inactivated is theoretically random, but is influenced by polymorphisms at the *Xce* locus (Chadwick et al. 2006). Loci on the X chromosome have been shown to modify ovarian granulosa cell tumors (Beamer et al. 1998; Dorward et al. 2003), mammary tumors (Koch et al. 2007), and testicular tumors (Hammond et al. 2007), so on a mixed strain background the choice of which X chromosome remains active could influence tumor phenotypes.

Chromosome Y:

The Y chromosome does not recombine, but has developed polymorphisms spontaneously between different strain backgrounds. Because the Y chromosome is inherited through the paternal line, male progeny of reciprocal F1 hybrids (AXB vs BXA) are not identical. Although there is not yet strong evidence for a role of Y chromosome polymorphisms in modifying tumorigenesis, a study of cardiac growth (Llamas et al. 2009) found expression changes in p53 pathway genes, including *Pten, Cnnd1* (CyclinD1), and *Cdkn1a* (p21), in mice carrying the A/J Y chromosome vs the C57BL/6J Y chromosome. Therefore, it remains a formal possibility that Y chromosome polymorphisms can affect tumor phenotypes and should be controlled in genetic crosses.

The mitochondrial genome:

The mitochondrial genome is inherited through the maternal line and, like the Y chromosome, does not recombine, but accumulates polymorphisms spontaneously. Although the role of mitochondrial variation in tumorigenesis is only beginning to be appreciated, it clearly affects tumor related phenotypes of apoptosis, proliferation, and invasion (Jandova et al. 2012a; Jandova et al. 2012b). Mitochondrial polymorphisms also affect phenotypes

related to diabetes (Chen et al. 2011; Weiss et al. 2012), autoimmune disease (Jonsen et al. 2009; Yu et al. 2009a; Yu et al. 2009b), and cell metabolism (Moreno-Loshuertos et al. 2006).

Controlling variation in genetic crosses of mouse cancer models:

Given the effects of strain on mouse phenotypes, it is critical to control for genetic background in experiments testing hypotheses of how genes, carcinogens, or therapies affect tumorigenesis (see Protocol 1). This can be achieved using well-controlled inbred backgrounds or by using appropriate sibling controls in mixed backgrounds, so that the extent of variation in the control group matches the variation in the experimental group. In this case, it is important to consider how the crosses are set up to ensure that variations in sex chromosomes and the mitochondrial genome are equally represented in all groups.

Once mutant mouse models are generated they can be switched to a different strain background by 10 or more generations of backcrossing; however, it is very difficult to completely remove the original strain polymorphisms in the region of the gene mutation. This leads to a window of strain contamination around the gene of interest that can modify the phenotype of the gene of interest (Bolivar et al. 2001; Reilly et al. 2004). It is particularly difficult to control this type of variation, particularly in heterozygous mutant models where mutants are compared with wild-type siblings. The wild-type siblings will not inherit the window of strain contamination, whereas the mutants will, leading to bias between the groups that is independent of the gene mutation. It is important to consider this caveat when interpreting results from this type of model system.

Modification of cancer genes by genetic background:

Genes that play important roles in tumorigenesis can be modified by strain background and can themselves by be polymorphic between different strains (Table 1). A better understanding of how strain-specific polymorphisms modify the cancer phenotypes can improve the understanding of cancer pathways. The role of a mutant gene in cancer, i.e. whether it is an oncogene, a tumor suppressor gene, or has no apparent phenotype, can be dramatically affected by the genetic background. For example, *p53−/+* mice develop mammary tumors on the BALB/c background, but not the C57BL/6J background (Kuperwasser et al. 2000; Blackburn et al. 2007; Koch et al. 2007). In another example, the expression level of *Nf1* varies between the C57BL/6J and 129S4/SvJae strains to the same extent as knocking out one copy of the gene in C57BL/6J (Hawes et al. 2007). Both *Mtor* and *Cdkn2a* have been found to carry polymorphisms between the BALB/c and DBA/2 strains that modify tumorigenesis (Zhang et al. 1998; Bliskovsky et al. 2003). Studies of modifier effects on many cancer genes (Table 1) all contribute to the idea that any pathway relevant to cancer will likely be influenced by the genetic background of mouse models.

The Collaborative Cross Mouse Resource:

Although variation in genetic background can be a confounder in experiments with mouse models of cancer, understanding how this variation alters cancer phenotypes is critical for understanding cancer pathways and modeling the genetic heterogeneity found in human

populations. Comparisons of different inbred strains have yielded some results (Table 1), but are limited in scope. Over the past decade a new resource, the Collaborative Cross, has been developed to more robustly study genetic variation in mice (Threadgill et al. 2002; Churchill et al. 2004; Chesler et al. 2008; Iraqi et al. 2008; Morahan et al. 2008; Collaborative Cross Consortium 2012; Threadgill and Churchill 2012). Eight founder strains (Figure 1B) were chosen to represent the diversity of the *M. musculus* species and the most commonly used classical inbred strains in biomedical research. The eight strains were mated pairwise to combine the eight genomes and then inbred to homozygosity to generate approximately 350 recombinant inbred lines. Because the lines are inbred, they are genetically stable and reproducible. The lines capture 90% of the genetic variation found across *M. musculus* and, unlike the classical inbred strains, the variation is evenly distributed across the genome, such that there are no “blind spots” for understanding the role of genetic background in disease (Roberts et al. 2007; Yang et al. 2011; Collaborative Cross Consortium 2012). It has been estimated that the Collaborative Cross panel carries 4–5 times the number of variants found in the human population. The Collaborative Cross will be a powerful tool in future research to improve mouse cancer models to represent the heterogeneity of the human population (see Protocol 2).

Summary:

Different mouse strains carry variants in cancer genes or in modifiers of cancer genes. If not properly controlled, experimental or control groups in cancer studies can carry biased representation of these variants, which can affect the phenotype as much as the experimental variable being studied. It is therefore important to take genetic background effects into consideration in designing mouse crosses and control groups. A new mouse resource, the Collaborative Cross, is making it more feasible to identify the genes and pathways underlying these genetic effects.

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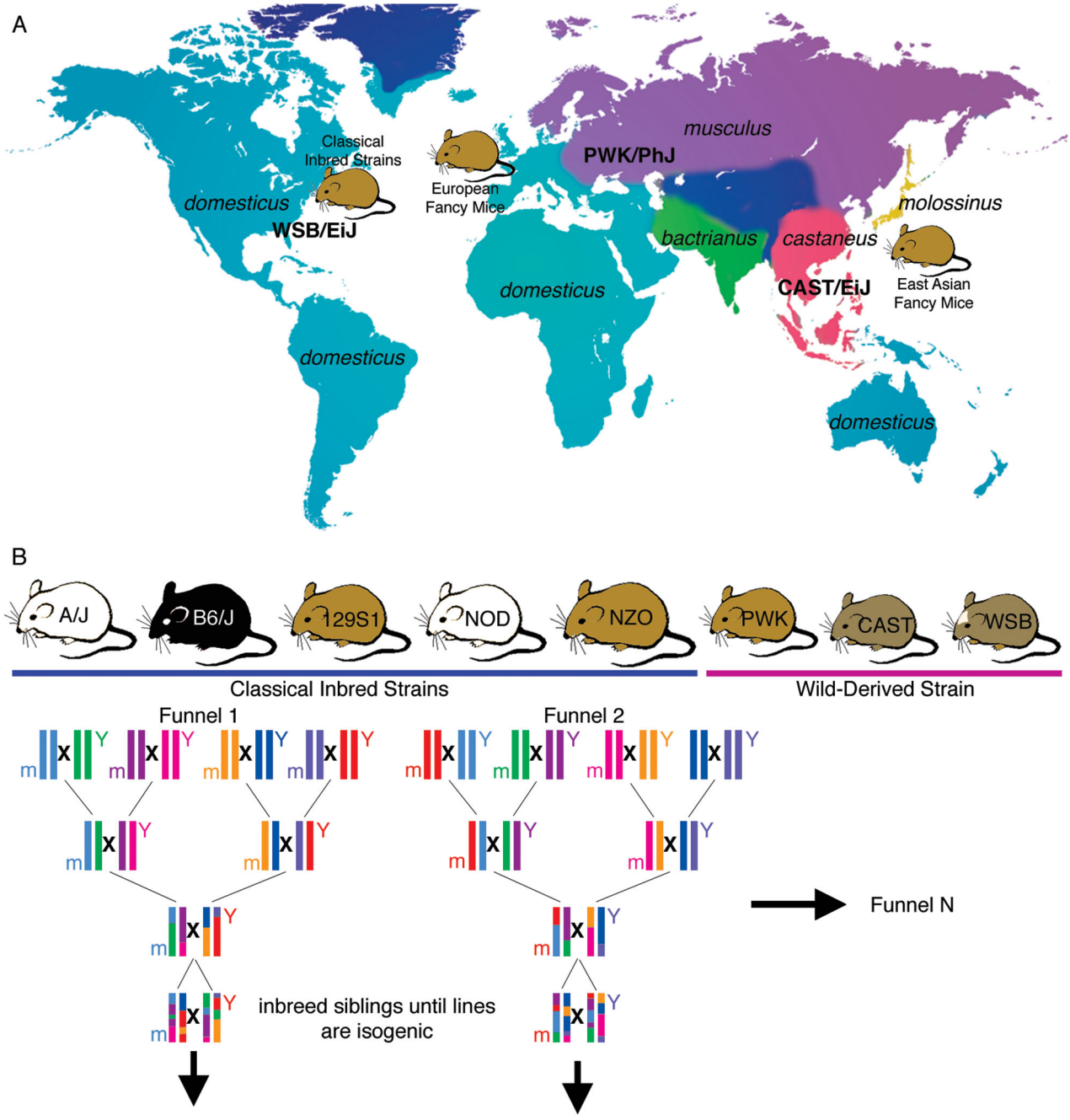

Figure 1:

(A) The distribution of *Mus musculus* subspecies and their contribution to modern day classical inbred strains. Classical inbred strains used in biomedical research were developed from European "fancy" mice that were descended from East Asian "fancy" mice. Classical inbred strains are mixtures of the *domesticus, musculus, castaneus,* and *molossinus* subspecies of *Mus musculus*. In addition, pure subspecies have been inbred to give rise to the "wild-derived" strains. WSB/EiJ is a *M. m. domesticus* strain originating in Maryland, USA. PWK/PhJ is a *M. m. musculus* strain originating near Prague, Czech Republic.

CAST/EiJ is a *M. m. castaneus* strain originating in Thonburi, Thailand. (B) The design of the Collaborative Cross to maximize genetic diversity across a panel of recombinant inbred strains. Eight founder strains include 5 classical inbred strains and 3 wild-derived strains. By varying the position of each founder in the different breeding funnels, polymorphisms in the mitochondria (m) and the Y chromosome (Y) can be equally represented across the resulting lines.

Table 1:

Genetic Effects on Cancer Genes in Mouse Models

Gene/Protein	Modifier Effect	Strains	References
Alk	modifier	C57BL/6J vs C3H	Chun et al. 2010
Apc	modified	C57BL/6J vs AKR/J,MA/MyJ, CAST, SWR/J, DBA/2J, BALB/cByJ; BTBR/Pas, A/J	Dietrich et al. 1993; Gould et al. 1996a; Gould et al. 1996b; Cormier et al. 1997; Shoemaker et al. 1998; Cormier et al. 2000; Kwong et al. 2007; Halberg et al. 2009
Aurka	modifier	NIH/Ola vs M. spretus, SEG/Pas, SPRET/EiJ	Ewart-Toland et al. 2003
Cdkn2a/p16INK4a	modifier	BALB/c vs DBA/2	Zhang et al. 1998
Egfr	modified	CF1 vs 129/Sv vs CD1; FVB/NJ, ICR/HaROS vs 129S6/SvEvTAC, BALC/cJ, NON/LtJ, NOD/LtJ, C57BL/6J, SJL/J, DBA2/J vs AKR/J, C3H/HeJ, SWR/J, ALR/LtJ, ALS/LtJ, APN, APS; C57BL/6J vs A/J	Threadgill et al. 1995; Strunk et al. 2004; Rinella and Threadgill 2012
Fbxw7	modifier	129/Sv, M. spretus vs C57BL/6J, FVB/N, NIH/Ola	Kwon et al. 2012; Perez-Losada et al. 2012
Hras	modified	NIH/Ola vs M. spretus; C57BL/6J, BALC/c vs C3H/HeJ, CBA, CF1; C57BL/6J vs FVB/N	Buchmann et al. 1991; Nagase et al. 2003; Wakabayashi et al. 2007
Kras	modifier	C57BL/6J vs A/J	Lin et al. 1998
Met	modified	C57BL/6J vs FVB/N	Graveel et al. 2010
Mtor (Frap)/mTOR	modifier	BALB/c vs DBA/2	Bliskovsky et al. 2003
Nf1	modified	129S4/SvJae vs C57BL/6J	Hawes et al. 2007
Nf1;Trp53 double mutant	modified	C57BL/6J vs 129/Sv, A/J, CAST/EiJ, SJL/J, CBA/J	Reilly et al. 2000; Reilly et al. 2004; Reilly et al. 2006; Hawes et al. 2007; Walrath et al. 2009; Amlin-Van Schaick et al. 2012a; Amlin-Van Schaick et al. 2012b
Ptch1	modified	C57BL/6J vs BALB/c	Hahn et al. 2004
Ptch1	modifier	C57BL/6J vs FVB/N	Wakabayashi et al. 2007
Tgfb1	modified	C57BL/6J/Ola vs NIH/Ola	Bonyadi et al. 1997
Tgfb1	modifier	NIH/Ola vs M. spretus, SEG/Pas, SPRET/EiJ	Mao et al. 2006
Trp53/p53	modified	BALB/c vs MSM; CE/J vs 129/Sv; BALB/c vs C57BL/6J; FVB/N vs MSM/Ms, 129/Sv vs C57BL/6J	Harvey et al. 1993; Donehower et al. 1995; Kuperwasser et al. 2000; Biggs et al. 2003; Ochiai et al. 2003; Evans et al. 2004; Blackburn et al. 2007; Koch et al. 2007; Liang et al. 2008; Okumura et al. 2012; Bohringer et al. 2013

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