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122

The BALB/c Mouse

Genetics and Immunology

Edited by M. Potter

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With 85 Figures

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Preface

The mouse was first used in immunological research by Paul Ehrlich in 1891 in an extraordinary series of experiments on the maternal transfer of antitoxic immunity. A short 22 years later in 1913 Halsey Bagg acquired a stock of albino mice from a commercial dealer and used them in a series of experiments on learning. Because he was interested in the genetics of intelligence, Halsey Bagg began breeding a pedigreed line of these mice that were subsequently named for him - Bagg Albino. Though Halsey Bagg is not credited with initiating the inbred strains of mice, his stock curiously has played an indisputably important role. Bagg Albinos were progenitors of the present day BALB/c family of sublines - the subject of this book. They were also used as one of the parents in the development of inbred strains A, CBA and C3H, three other very famous strains. Today the BALB/c mouse is among the five most widely used inbred strains in biomedical research and a particular favorite in immunology and infectious disease research. The hallmark of the BALB/c response to so many kinds of infections is susceptibility and sometimes an exaggerated susceptibility, but this paradoxically is not associated with immunodeficiency as BALB/c is an excellent responder to immunization. These characteristics have made the BALB/c mouse a model for identifying genes that determine susceptibility to infectious and neoplastic diseases.

In 1985 the laboratory BALB/c mouse became 72 years old. The current filial generations are somewhere around 350 generations [MURPHY]. Following its initial inbreeding in the 1920's and 1930's, principally by E.C. MacDowell at Cold Spring Harbor and George Snell at the Jackson Laboratory, branches of the BALB/c family were disseminated in the late 1930's and 1940's to many laboratories throughout the world. Today, extant colonies trace their lineage back to these original colonies. With the continued growth of mouse genetics and the identification of new polymorphic loci a characteristic profile of BALB/c genotypes is now well known [RODERICK; HILGERS]. Thomas Roderick at the Jackson Laboratory has a registry of these genes on a computer file, and a genetic profile can be used to determine the authenticity of a BALB/c mouse and detect contaminations. The remarkable feature of many of the current BALB/c sublines is the fact that they conform to this profile [RODERICK; HILGERS]. This indicates that many of the BALB/c sublines have not been contaminated during their long history - a matter always of considerable concern with an albino stock.

Genetic variations have been found in the BALB/c family. One of the first is the genes controlling the Qa2 lymphocyte alloantigen which was discovered by Lorraine Flaherty and her colleagues. These genes are a cluster of class I-like genes located to the right of H-2D in the mouse major histocompatibility (MHC) complex on chromosome 17. Although variation in Qa2 expression has been observed in other

inbred strains of mice, sublines within the Andervont branch of the BALB/c family vary in Qa2 expression. The loss of Qa2 expression appears to be associated with the loss restriction fragments that hybridize to MHC genes [ROGERS].

Another intriguing genetic variation among BALB/c sublines is embodied in a set of unusual phenotypes in the BALB/cJ subline: (1) high adult levels of serum alphafetoprotein (AFP), a trait that makes BALB/cJ unique among all inbred strains [PACHNIS; BLANKENHORN]; (2) aggressive fighting behavior in males; (3) high levels of enzymes determining catecholamine biosynthesis in the adrenal medulla; (4) high levels of inducible enzymes in other tissues, e.g., serine dehydratase in the liver of fasting mice, and L-glycerol 3-phosphate dehydrogenase in brown fat [KOZAK]; and (5) resistance to plasmacytoma induction in contrast to the striking susceptibility of other sublines [POTTER]. Other new phenotypes of BALB/cJ are described in this book [KOZAK; RODERICK; LEITER; BABU; TEUSCHER; ANDERSON].

The unusual nature of BALB/cJ within the BALB/c family has no easy explanation. Indeed, BALB/cJ has an interesting history, but its emergence as the most different BALB/c cannot be related to any specific breeding conditions or selective factors during its origin. Two hypotheses are now being tested in several laboratories to explain the BALB/cJ set of phenotypes: the single pleiotropic gene hypothesis of Leslie Kozak and the multiple gene hypothesis. The Kozak hypothesis suggests that many of the phenotypic differences in BALB/cJ vs. BALB/cAn are due to a mutation in a regulatory gene that affects the expression of multiple genes. The availability of DNA subtraction hybridization offers promise for resolving this question, and Huppi has succeeded in cloning DNA fragments that can be used to detect genetic differences among BALB/c sublines [HUPPI]. The complexity of such an analysis is exemplified by the interesting amplification of PR1 repetitive sequences that is unique to the BALB/c family [KOMINAMI]. Variations in PR1 bands have been found in BALB/c sublines [KOMINAMI; HILGERS].

Many of the infectious agents to which BALB/c is highly susceptible require intracellular habitats for propagation. The macrophage is the principal target cell. A variety of different kinds of these intracellular infections are discussed: Leishmania [BLACKWELL; MOCK; LIEW], Listeria [SKAMENE, KONGSHAVN], Nocardia [BEAMAN], and Chlamydia [WILLIAMS].

The most advanced model is Leismaniasis where at least four susceptibility resistance genes have been identified: LSH (chr 1), Scl-1 (chr 8), H-2 (chr 17), and Scl-2 (unlinked) [BLACKWELL]. The Leishmania system is complex because of variations of responsiveness to different species of Leishmania [BLACKWELL; MOCK], thus specific immune reactions play a critical role [BLACKWELL; LIEW; MOCK]. The complexity of the T-cell response to Leishmania infection and its dysregulation may well be at the root of the exaggerated responses in BALB/c [LIEW]. Other aspects of BALB/c immune regulation, isotype preference [SLACK] and T-suppressor cell activation [LYNCH] are provided by the respective authors.

The macrophage and the genes that regulate the special functions in this cell provide a fascinating aspect to the susceptibility-resistance problem - one in which much is to be learned. Tolerance induction in BALB/c [COWING; HOWARD], mechanisms of intracellular microbial killing [BEAMAN], and macrophage recruitment [KONGSHAVN] are relevant macrophage functions for which genetic variability has been observed.

BALB/c has had a long history as a low spontaneous tumor strain that is highly susceptible to tumor induction by tumorigenic retroviruses. Susceptibility genes controlling responses to mammary tumor viruses [HILGERS] and Moloney and Abelson leukemia viruses [RISSER] have been found.

Susceptibility to plasmacytomagenesis is one of the best known characteristics of BALB/c. The nature of genes that determine this susceptibility is not yet known. Since these tumors are induced by pristane (mineral oil), the comparative cellular response of BALB/c have been the subject of several investigations [LEAK; ANDERSON; POTTER]. Pristane also induces an unusual long latent period - arthritis in BALB/c [HOPKINS].

The authors of this monograph, after agreeing to complete this book, met in Bethesda, Maryland, on March 11 and 12, 1985, in Wilson Hall, Building 1, at the NIH. The meeting was sponsored by the National Cancer Institute although many of the participants used their own financial resources to travel to Bethesda. The chapters of the book are organized in three subjects. The first deals with general genetics of the BALB/c mouse, the second with the response to infections and immunizations, and the third to plasmacytoma susceptibility. We are very grateful to Springer-Verlag and Professor Dietrich Götze, Editor) for their help in publication of these papers. I thank Ms. Victoria Rogers for her editorial and administrative help in the preparation of this book.

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History of the BALB/c Family

M. Potter

The BALB/c sublines discussed in this book all originated from a stock of albino mice maintained by Halsey Bagg at Memorial Hospital in New York City. The origin of this stock is obscure. Bagg first acquired these mice from an Ohio dealer around 1913 (Strong 1936) and used them first in his master's thesis project at Columbia University carried out under the direction of Dr. J. McKeen Cattell. Halsey Bagg studied the abilities of mice and rats to learn a rather simple maze problem, he concluded that mice were much more active than rats and very suitable for behavioral studies. He used two stocks of mice, a yellow strain and the white strain - the latter were destined to be known as Bagg Albinos. Bagg found marked differences in the learning ability of the two kinds of mice to solve the maze problem. By 1916 Halsey Bagg had made filial matings of the albinos for 7 generations. He continued the work at New York University and maintained the albino mouse colony. Halsey Bagg must also have claimed that they were inbred, but after acquiring these mice in 1920 Leonell Strong found some kind of evidence to the contrary (Strong 1978). About this time many of the mouse geneticists in the U.S. were intent upon inbreeding mice. Mice were rapidly emerging as the premier species in experimental cancer research. The need for a reliable source spontaneous tumors and a means for propagating tumors by transplantation must have been acute. L.C. Strong stated that a mouse with a spontaneous tumor sold for $300.00 around 1919 (Strong 1978). As is well known many many of the first efforts of inbreeding began at Cold Spring Harbor, at the instigation of C.C. Little. Little's own dba was decimated about this time by an epidemic of "mouse typhoid" and he replenished his colony with mice from other sources. This must have been the motive for the importation of the Bagg Albinos from New York City. Strong obtained some of these mice and mated one of them called the "great white mother" to another albino male from Storrs, CT, to found strain A (Strong 1936, 1978). Subsequently, an emerging strain A prognitor was mated to one of Little's dilute brown (dba) survivors to found the beginnings of strains C3H and CBA (Strong 1935). Thus, genes from Halsey Bagg's stock are present in many of the 65 year old inbred families of today, e.g., A, C3H, CBA, and BALB/c.

At Cold Spring Harbor the Bagg Albino stock was inbred by E.C. MacDowell, and by 1927, they were at F12 (MacDowell et al. 1927). H.J. Muller, then at the University of Texas acquired some of these mice from MacDowell, and when George Snell came to work with him in 1931 Snell acquired the colony (personal communication from George Snell to H.C. Morse, III). In 1932 Snell moved to the Jackson

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Laboratory and took the Bagg Albinos with him. They were then at F26. Snell now called the strain by their present name, BALB/c. MacDowell continued the line at Cold Spring Harbor and one extant subline, BALB/wm, was derived directly from it in 1950 by J.T. Syverton. This line is maintained today at Ann Arbor by W.H. Murphy (Plata and Murphy 1972; Murphy, this volume).

The period between 1937 and 1939 was a critical one in the history of the Snell BALB/c mouse, because it was during this time that three major branches, the Andervont, Green and Scott, were separated. During this period the filial-mated strain was 17 years old and had attained approximately 36 generations. All three branches were derived from the main BALB/c Snell line at the Jackson Laboratory. Howard B. Andervont acquired BALB/c mice from this line from W.S. Murray and John Bittner in 1937 (personal communication from H. B. Andervont to the author circa 1964). Many sublines are derived from the Andervont line (see Fig. 1, also discussion by J. Hilgers about the derivation of European sublines of BALB/c, this volume) Andervont's BALB/c mice were extensively used at the National Cancer Institute. These mice had a low spontaneous incidence of leukemias, and therefore were frequently used to test the leukemogenic properties of viruses. John Moloney used BALB/c to isolate his famous leukemia virus (Moloney 1960). BALB/cAn also was a low spontaneous mammary tumor strain and was highly susceptible to developing mammary tumors when infected with the C3H derived mammary tumor virus (Andervont 1945). Andervont extensively used BALB/c for the induction of testicular tumors by implanting estrogen pellets (Andervont et al. 1957). BALB/c mice were used by Ruth Merwin and Glenn Algire as recipients in their experiments designed to test the long term survival of C3H H-2^K mammary tumor cells implanted in Millipore diffusion chambers (Merwin and Algire 1959). This led unexpectedly to the discovery of the inherent susceptibility of these mice to develop peritoneal plasmacytomas. When BALB/c mice became implicated in plasma cell tumor research. I, as others, went to H.B. Andervont for these mice. I can remember telling Andy that I was interested in BALB/c mice for plasmacytoma induction experiments. He groaned sympathetically and said that it was too bad as BALB/c mice were terrible to maintain, they were very prone to infections, such as infantile diarrhea and pneumonia. He bred these mice only in the late spring, summer and early fall. During the winter he separated the males and females as winter matings were very prone to produce progeny with infantile diarrhea.

The second branch of the BALB/c family was developed by Earl Green (Fig. 1). He acquired the mice in 1937-8 from Snell. Later he gave mice to W.L. Russell at the Oak Ridge Laboratory. These are the current ORNL mice. The Green stock has now become the Whitten subline.

The most unique BALB/c subline is paradoxically BALB/cJ, which is derived from the Scott branch of the family. I say unique because being at NIH this mouse is very different from BALB/cAn and in many ways from the derivatives of the Green branch. J.P. Scott as a summer investigator acquired these mice from the Jackson Laboratory in 1938 or 1939 for his studies on mouse behavior. Scott studied the fighting behavior of the mice (Scott 1942). He concluded they were "...moderately aggressive in comparison to C57BL/10's and C3H's" (letter from J.P. Scott to author, Jan. 13,

1983). He took these mice to Wabash College, and then brought them back to Bar Harbor in 1945. J.P. Scott's laboratory was downtown in Bar Harbor and his mouse colony survived the tragic fire that destroyed the Jackson Laboratory and the Snell BALB/c line. The progenitors of the current Jackson subline, BALB/cJ, were obtained from J.P. Scott in 1947. J.P. Scott did not select or purposely breed BALB/c mice for aggressive behavior, in fact he considered they had only a moderate amount of aggressiveness. In 1942 he notes that weanling BALB/c males could be housed 5 to a cage for rather extensive periods. Further BALB/c albinos became lethargic in warm weather. These observations put us at a loss to explain why BALB/cJ males are viciously aggressive when compared with their docile BALB/cAn counterparts. We have a colony of BALB/cJ in our conventional colony maintained at Litton Bionetics, Rockville, MD. In comparison to BALB/cAnPt, BALB/cJ is difficult to breed. The mothers often cannabilize the young, and domestic life between males and females is often strained. BALB/cJ females cannot maintain a nest in the presence of a male. In general appearance BALB/cJ often lacks a sleek coat, and frequently developes a dermatitis around the eyes and snout. We have a great variety of wild mice and different species of Mus in our colony that require supplemental feedings. Linda Byrd, a biologist at LBI began feeding BALB/cJ mice Wax Moth larvae (3 times a week) and a supplement of bird seed and found that the production of weanlings became vastly improved. The BALB/cJ mothers nested and became good nurses. Both the males and the females seemed less prone to cannabilizing the young. This was a dramatic change, for many times in the past our colony of BALB/cJ was threatened with extinction.

The first biochemical and genetic evidence of differences between BALB/cAn and BALB/cJ were reported by Ciaranello and Axelrod at the NIH (Ciaranello et al. 1974). These workers noted the striking differences in fighting behavior between the aggressive BALB/cJ and docile BALB/cAn and found that fighting behavior correlated with high levels of 3 enzymes (tyrosine hydroxylase, dopamine β-hydroxylase, and phenylethanolamine N-methyl transferase) in the adrenal gland. In BALB/cJ all three enzymes were greatly elevated as compared with BALB/cAn. Ciaranello and Axelrod postulated this could be due to a single gene that controlled the production of an enzyme that degraded the 3 enzymes, based on their breeding studies. The levels of the enzymes in F_1 hybrids of BALB/cJ x BALB/cAn were intermediate. As will be described in various papers in this workship other genetic differences of the BALB/c family have been found: Qa2 (a lymphocyte alloantigen controlled by a gene in the MHC complex on chromosome 17); Raf-1 (regulator of alpha fetoprotein); and genetic differences that are recognized by restriction enzyme cleaved DNA fragments.

The origin of the genetic differences in BALB/c sublines is a matter of some interest. The underlying assumption is that contamination is not the explanation. Two characteristics argue in favor of this: first, the phenotypes may be unusual and not found in other strains, e.g., the Raf-1 gene (Olsson et al. 1977). Second, the phenotype is not associated with other polymorphisms, an expected consequence of contamination. Thus, within the BALB/c family, genetic differences probably owe their origin to mutations, cryptic polymorphisms or other consequences of instability in complex genomes. In the latter case, it must be postulated that undetected polymorphisms were silently segregating for many generations. There are other explanations relating to the stability of complex genomes. Just