Current Topics in Microbiology and Immunology

122

The BALB/c Mouse

Genetics and Immunology

Edited by M. Potter

With 85 Figures

Springer-Verlag
Berlin Heidelberg NewYork Tokyo

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ISBN-13:978-3-642-70742-1 e-ISBN-13:978-3-642-707-7
DOI: 10.1007/978-3-642-70740-7

Library of Congress Catalog Card Number 15-12910

2123/3130-543210

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 PRl repetitive sequences that is unique to the BALB/c family [KOMINAMI]. Variations in PRl 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.

May, 1985

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