ENVIGO

Research Models and Services

Inbred Mice

NZB (New Zealand Black)

Origin

Outbred mice from Imperial Cancer Research Fund, London, to University of Otago Medical School in 1930. Inbred by Bielschowsky in 1948. A number of other strains, including NZO, NZC, NZX and NZY, were developed from the same stock (Bielschowski and Goodall, 1970). Strain NZW was derived from the same outbred stock, but was inbred independently by Hall (Hall and Simpson, 1975).

NZB/OlaHsd

To Laboratory Animals Centre, Carshalton in 1964, to OLAC (now Envigo) in 1979.

Research applications

Autoimmunity, behavior, immunology, reproduction, lupus erythematosus, neurone ectopia, nephropathy, hippocampus.

Characteristics

Animal model

The NZB is a mouse model for autoimmune hemolytic anemia, immune complex glomerulonephritis and systemic lupus erythematosus.

Anatomy

About 30-40% develop neocortical ectopias due to a recessive gene with incomplete penetrance (Sherman *et al*, 1994). High bone density of femur (Beamer *et al*, 1996). The comparative study of the thymus in autoimmune and normal strains, revealed that important changes of the large medullary epithelial cells, involved in the formation of Hassall's corpuscles, occur in NZB, NZW and NZB x NZW)F1 mice. In the NZB mice the large epithelial cells are severely decreased in number in the first weeks following birth. The depletion of epithelial cells could be ascribed to a secondary degeneration of these cells soon after birth (De Vries and Hijmans, 1967).

Behavior

High balsa-wood gnawing activity (Fawdington and Festing, 1980).

Drugs

High coumarin hydroxylating ability (Lush and Arnold, 1975). Pentobarbital i.p. induces hepatic epoxide hydrase (Oesch *et al*, 1973). Sensitive to lethal effects of ozone (Goldstein *et al*, 1973). Resistant to the induction of atherosclerosis by an atherogenic diet (Paigen *et al*, 1990). The administration of synovial fluid of rheumatoid arthritis patients induced production of autoantibodies in NZB, NZW and (NZB x NZW)F1 mice but not in CBA mice (Abedi-Valugerdi *et al*, 1994).

Genetics

Coat color genes	- *a, B, C, D* : black.
Histocompatibility	- *H-2*^{d}.
Biochemical markers	- *Apoa-1*^{a}, *Car-2*^{a}, *Es-1*^{b}, *Es-2*^{b}, *Es-3*^{c}, *Gpd-1*^{b}, *Gpi-1*^{a}, *Hbb*^{d}, *Idh-1*^{a}, *Ldr-1*^{a}, *Mod-1*^{b}, *Pgm-1*^{b}, *Trf*^{b}.

There are differences between the several sublines at Pep-3 locus.

NZB/Hsd	= *Pep-3*^{b}
NZB/OlaHsd	= *Pep-3*^{c}

This strain carries the *Mus musculus musculus* Y-chromosome, while others have the *M. m. domesticus* type (Nishioka, 1987).

Husbandry

Spontaneous infections of NZB mice with certain murine viruses have been shown to modify the course of the autoimmunity disease (Tonietti *et al*, 1970). Therefore, this strain should be maintained in a pathogen free environment (ILAR, 1989).

Immunology

Pure-line mice have a high level of natural thymocytotoxic autoantibodies (Auer *et al*, 1974), a low immune response to Dextran (Blomberg *et al*, 1972), a low lymphocyte phytohemagglutinin response (Heiniger *et al*, 1975), a high 25% incidence of serum antinuclear factor (Barnes and Tuffrey, 1967) and a poor immune response to DNP-keyhole limpet hemo-cyanin (Borel and Kilham, 1974), and are discriminators between `H' and `L' sheep erythrocytes (McCarthy and Dutton, 1975). Mineral oil injected intra peritoneal induces plasmacytomas (Potter, 1972).

A primary B-cell defect has also been clearly demonstrated in NZB mice. This hyperactivity of B cells is manifested by high levels of IgG immunoglobulins by three months of age (Andrews *et al*, 1978), increased number and augmented secretion of IgM by B cells (Manny *et al*, 1979), and the production of numerous autoantibodies (Quimby and Schwartz, 1982). Defective clonal inactivation of autoreactive B cells has been proposed to account for the increased autoantibodies in NZB mice (Cowdery *et al*, 1987). However, Cantor *et al*, 1978) provided evidence that there was impaired feedback regulation of antibody synthesis because of an abnormally functioning Ly-123^{+} T-cell subset. At least one B-cell defect is known to reside in a Lyb-5^{+} subpopulation of B lymphocytes (Ly-1^{+} B cell) characterized by the normal allele of the *xid* gene (Steinberg *et al*, 1982). This Ly-1^{+} B cell is increased in young NZB mice, is responsible for much of the autoantibody produced, and has unusual oncogene and receptor gene expression (Steinberg *et al*, 1987; Wolfsy and Chiang, 1987).

Males resistant but females more susceptible to immunosuppression of contact hyper-sensitivity by ultraviolet B light (Noonan and Hoffman, 1994). In about a quarter of NZB mice, aged four months or older, cryoglobulins were found. The majority of the cryoglobulins were macroglobulins (Hijmans *et al*, 1969).

Infection

Susceptible to mouse hepatitis virus type 3 infection (Le Prevost *et al*, 1975). No transmission of murine leukemia virus (Scripps) to succeeding generations (Jenson *et al*, 1976). Carries no detectable endogenous ecotropic MuLV DNA sequences (Jenkins *et al*, 1982). In contrast to ten other strains, it does not carry type I and II endogenous type-c viruses (cf. SWR) (Stephenson *et al*, 1975).

Totally refractory to infection by *Leishmania tropica* parasite (Howard *et al*, 1980) and to *Leishmania major mexicana* (Lazama-Davila, 1997). Low immune response to ganglio-series gangliosides (Kawashima *et al*, 1992).

Life-span and spontaneous disease

Develops autoimmune hemolytic anemia of the Coombs-positive, warm antibody type (Simpson, 1976; Howie and Simpson, 1976) as well as a nephropathy, which is variable in expression and unpredictable in progress, but is probably an immune-complex-induced glomerulonephritis.

Hemolytic anemia usually develops five months following the appearance of autoantibodies and is not gender specific. Anemia is associated with reticulocytosis and reduced erythrocyte survival time. Splenomegaly is present as a result of erythrocyte sequestration, increased hematopoiesis, and lymphoid hyperplasia. Lymphoproliferative lesions resulting in hyperplasia of spleen, lymph nodes, bone marrow, thymus, lung, kidney, and salivary glands are consistent features of the disease progress in NZB mice. Between 3 and 11 months of age, the white pulp of the spleen and both cortical and medullary regions of the lymph nodes are characterized by enlarged lymphoid follicles containing multiple germinal centres. Later in life a second phase of lymphoproliferation occurs; this is characterised by extreme plasma cell hyperplasia in lymphoid tissue throughout the body (ILAR, 1989). An increased incidence of lymphoma has been reported (East, 1970). The thymus is characterized by hyperplasia with follicular aggregates of lymphocytes and mast cells in the medulla. There is premature thymic evolution in which degeneration and vacuolisation of epithelial cells are consistent features (Andrews *et al*, 1970). An impressive early decline in thymulin levels have been reported (Bach *et al*, 1973).

Burnet (1972a; 1972b) considered that at least two genes are involved, one of which is also present in NZC. Genetic linkage to chromosomes 1, 4, 7, 10, 13 and 19 imply that multiple genes in different combinations contribute to the severe renal disease (Drake *et al*, 1995). A virus may also be involved, although Simpson (1976) considered that: `...the case for a viral etiology is unproven, although the possibility exists that virus may be present in incomplete form'. According to Burnet, NZB mice have an abnormally high immunological vigour and resistance to induction of immunological tolerance or paralysis, which is manifested before the animals become Coombs-positive.

The condition may be transferred to young isogenic mice by cells from the spleen, but not from other lymphoid organs. Thus, the condition appears to depend on stem cells of immunocyte lines. Autoimmune plaque-forming cells, active against mouse erythrocytes, are present in old mice. Onset and severity of the condition can be influenced by diet (Fernandes *et al*, 1972). Theofilopoulos *et al* (1980) have compared immune function in this and other autoimmune strains. Only NZB splenic lymphocytes from autoimmune donors inoculated into pre-autoimmune NZB or in BALB/c mice could evoke a positive Coombs test (Jenkinson and East, 1980). Diethyldithiocarbamate (DTC), an immunomodulative agent, which may enhance T cells, prolongs life in autoimmune MRL-lpr/lpr mice, but not in autoimmune NZBxNZWF1 hybrids (Halpern and Yocum, 1991). Defect in the expression of the alloantigen, Ly6C, which is not detectable on spleen or lymph node cells (c.f. NOD and ST but contrast most other strains) and may be due to an interruption in the flanking region of the Ly6C gene at a point 475 bp upstream of the transcription initiation site, as found in NOD (Philbrick *et al*, 1990). Ultrastructural pathology of the thymic reticulum revealed several features in common with BXSB and MRL-*lpr* in varying

degrees according to sex and age of the mice. Main anomalies included vacuolized aspect of the thymic epithelium, an increased number of macrophages, interdigitating cells and cystic cavities, the presence of a great number of plasmocytes and mastocytes and extensive interstitial fibrosis and arteriosclerosis. The most intriguing finding was the presence of crystal-like inclusions in epithelial cells (Nabarra *et al*, 1990). Natural autoantibodies are involved in the hemolytic anemia (Hentati *et al*, 1994).

Median life-span 15.3 months in NZB males and 14.7 months in NZB females (Festing and Blackmore, 1971). Median life-span 9.3 months in NZB males and 9.0 months in NZB females (Stutman, 1974). Median life-span 16.6 months in both males and females (Eastcott *et al*, 1983). Andrews *et al* (1978) reported a mortality of 90% by 23 months.

Hypertrophy of the pituitary in 80% of survivors to 1 year and pituitary tumors in 25% of aged breeders (Russfield, 1966). Histopathology of renal lesions has been performed by Hicks and Burnet, 1966).

Three percent of the mice are showing degenerative arthristis at an oge of 12.9 months (Wigley *et al*, 1977). The NZB mouse spontaneously develops carditis as they age (Pansky and Freimer, 1974).

Miscellaneous

Characteristics of the NZB strain have been described by Festing (1997), ILAR (1989) and Lyon *et al*, (1996).

Physiology and biochemistry

High plasma triglyceride and cholesterol levels (Jiao *et al*, 1990).

Reproduction

Poor reproductive performance. Litter size 3.8 at weaning, colony output 0.5 young/ female/week (Festing, 1976). First litter size high but fourth litter low. Low proportion of females produce four or more litters and low percentage of fertile matings (Fernandes *et al*, 1973). Intermediate breeding performance (Hansen *et al*, 1973).

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