ENVIGO

Research Models and Services

Hybrid Mice

NZBNZWF1 (NZB x NZW)F1

Origin

NZBNZWF1/OlaHsd

This F1 hybrid is a cross between NZB/OlaHsd females and NZW/OlaHsd males.

Characteristics

The F1 hybrid of two inbred strains can be a useful animal for many purposes. It is genetically uniform and heterozygous for all the genes for which the two parental strains differ. F1 animals are easy to produce (hybrid vigor) and are less susceptible to environmental influences than the parent inbred strain.

Animal model

The NZBNZWF1 is a mouse model for systemic lupus erythematosus.

Anatomy

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 (De Vries and Hijmans, 1967).

Behavior

Autoimmunity is associated with increased anxiety and less exploratory behavior (Schrott and Crnic, 1996).

Genetics

Coat color genes - *a/A, b/B, c/C, p/P* : agouti.

Histocompatibility - $H\text{-}2^{d/z}$

The NZBNZWF1 will be heterozygous for all the loci where the NZB and NZW differ and homozygous for all the loci where both parental strains are the same.

NZBNZWF1 hybrids develop a systemic lupus erythematosus (SLE)-like syndrome. It has been proposed that the NZB parent contributes the dominant *Ads-1* and *Ads-2* genes controlling anti-dsDNA production, and the NZW parent contributes the dominant *Ads-3* and *Ads-4* genes, which are modifier genes. Similarly, the NZW parent contributes two dominant genes *Ass-3* and *Ass-4*, which enhance the effect of *Ass-1* and *Ass-2* in the production of anti-ssDNA antibodies. The *Agp-3* gene of NZW intensifies the effect of NZB *Agp-1* gene controlling anti-gp70 circulating immune complexes. However, the NZW *Aem-1* gene suppresses the activity of the NZB *Aia-1* gene responsible for anti-erythrocyte antibody production. Finally, a dominant trait for lupus nephritis, *Lpn-1*, is modified by two additional genes, *Lpn-2* and *Lpn-3*, both of which are donated by the NZW partner. The genes *Ass-3*, *Ads-3*, *Agp-3* and *Lpn-2* are linked to the $H\text{-}2^{z}$ haplotype of NZW (Shirai *et al*, 1984; 1987; Bearer *et al*, 1986). The net result is that NZBNZWF1 hybrids have an intensified production of anti-dsDNA antibodies, anti-ssDNA antibodies, and circulating immune complexes; an increased susceptibility to lupus nephritis; and a decreased production of anti-erythrocyte antibody when compared with NZB. Although evidence exists for each of the proposed loci listed above, there is still disagreement concerning the precise assignment of genetic loci to autoimmune phenotype (Kotzin and Palmer, 1987).

Kotzin *et al* (1985) demonstrated a large deletion (8.8-kilobase segment) in the DNA containing $C\beta_1$, $D\beta_2$ and $J\beta_2$ cluster encoding the T-cell ß chain; this has been confirmed by Theofilopoulos (1986). The functional significance of this deletion in the NZBNZWF1 hybrid is unknown.

Husbandry

While certain infectious agents have been shown to induce autoantibodies and immune complex disease in normal mice (Schulman *et al*, 1964; Barnes and Tuffrey, 1967; Dixon *et al*, 1969), other infectious agents have been shown to inhibit and ameliorate disease in NZB and NZBNZWF1 hybrid mice (Oldstone and Dixon, 1972). Engleman *et al* (1981) proposed that virus-induced type 1 interferon is responsible for the accelerated autoimmune

disease seen in some NZBNZWF1 hybrids. Therefore, it appears prudent to maintain this hybrid in a pathogen-free environment (ILAR, 1989).

Immunology

NZBxNZWF1 hybrid B cells apparently differ from normal murine B cells in their capacity to produce IgG antibodies upon T cell-dependent antigenic stimulation (Riley *et al*, 1991). Genetic analysis of a backcross to NZW shows that one set of loci regulate serum levels of IgG antibodies to double-stranded DNA, single-stranded DNA, total histones and chromatin, and these overlap with loci that control autoantibodies to the viral glycoprotein gp70. These latter loci are most strongly linked with renal disease. A locus on distil chromosome 4 was linked with nephritis but not with any of the autoantibodies measured (Vyse *et al*, 1996). Daily intraperitoneal injections of DNase from four-seven months of age resulted in reduced proteinuria and serum creatinine and strikingly less severe renal pathology (Macanovic *et al*, 1996).

Life-span and spontaneous disease

Hybrids from NZB and NZW develop an autoimmune disease resembling human systemic lupus erythematosus (SLE) (Talal *et al*, 1972), with high titres of natural thymocytotoxic autoantibody in many animals (Shirai and Mellors, 1972). Caloric restriction and supplementation with fish oil increases life span and diminishes histological evidence of glomerulonephritis. This is associated with decreased expression of platelet-derived growth factor-A (Troyer *et al*, 1997).

NZBNZWF1 mice develop a disease characterized by high levels of antibodies directed toward nucleic acid antigens, progressive immune complex glomerulonephritis, and a marked enhancement of the disease in females. As early as two months of age, Anti-Nuclear Antibodies (ANA) can be detected in some NZBNZWF1 mice. By 12 months of age all NZBNZWF1 hybrids have detectable levels of ANA (Andrews *et al*, 1978; Quimby and Schwartz, 1982). The anti-dsDNA antibodies have nephritogenic properties and appear to be principally responsible for the immune complexes deposited in the glomerulus (Lambert and Dixon, 1968). Histopathology of renal lesions has been described by Hicks and Burnet (1966). Unique subsets of T- and B-lymphocytes are found in NZBNZWF1 mice that are responsible for the production of pathogenic (cationic) IgG anti-DNA (Datta *et al*, 1987).

Rabin (1985) reported a significant difference in the survival of NZBNZWF1 hybrids associated with the cage type. Mice held in wire mesh cages lived considerable longer than F1 hybrids housed in solid-bottom cages.

Miscellaneous

Characteristics of the NZBNZWF1 hybrid have been described by Festing (1997) and ILAR (1989).

References

1. Andrews BS, Eisenberg RA, Theofilopoulos AN, Izui S, Wilson CB, McConahey PJ, Murphy ED, Roths JB. Dixon FJ (1978) Spontaneous murine lupus-like syndromes. Clinical and immunopathological manifestations in several strains. J. Exp. Med. 148, 1198-1215.
2. Barnes AD, Tuffrey M 1967) Serum antinuclear factor and the influence of environment on mice. Nature (London) 214, 1136-1138.
3. Bearer E, Gershwin ME, Castles JJ (1986) Lupus – Insights from experimental models. Clin. Exp. Rheumatol. 4, 161-168.
4. Datta SK, Patel H, Berry D (1987) Induction of a cationic shift in IgG anti-DNA autoantibodies. Role of T helper cells with classical and novel phenotypes in three murine models of lupus nephritis. J. Exp. Med. 165, 1252-1268.
5. De Vries MJ, Hijmans W (1967) Pathological changes of epithelial cells and auto-immune disease in NZB, NZW and (NZBxNZW)F1 mice. Immunology 12, 179-196.
6. Dixon FJ, Oldstone MBA, Tonietti G 1969) Virus-induced immune-complex-type glomerulonephritis. Transpl. Proc. 1, 945-948.
7. Engleman EG, Sonnenfeld G, Dauphimee M, Greenspan JS, Talal N, McDevitt HO, Merigan TC (1981) Treatment of NZB/NZW F1 mice with *Mycobacterium bovis* strain BCG or type II interferon preparations accelerates autoimmune disease. Arthritis Rheum. 24, 1396-1402.
8. Festing MFW (1997) Inbred Strains of mice. Mouse genome 95, 519-686.
9. Hicks JD, Burnet FM (1966) Renal lesions in the "auto-immune" mouse strains NZB and F1 NZBxNZW. J. Path. Bact. 91, 467-477.
10. ILAR (1989) Immunodeficient rodents. A guide to their immunobiology, husbandry, and use. National Academy Press, Washington DC.
11. Kotzin BL, Bar VL, Palmer E (1985) A large deletion within the T-cell receptor beta-chain complex in New Zealand white mice. Science 229, 167-171.
12. Kotzin BL, Palmer E (1987) The contribution of NZW genes to lupus-like disease in (NZB x NZW)F1 mice. J. Exp. Med. 165, 1237-1251.
13. Lyon MF, Rastan S, Brown SDM (1996) Genetic variants and strains of the laboratory mouse. 2 Volumes. Oxford, New York, Tokyo: Oxford University Press.
14. Macanovic M, Sinicropi D, Shak S, Baughman S, Thiru S, Lachmann PJ (1996) The treatment of systemic lupus erythematosus (SLE) in NZB/W F1 hybrid mice; studies with recombinant murine DNase and with dexamethasone. Clin. Exp. Immunol. 106, 243-252.
15. Oldstone MBA, Dixon FJ (1972) Inhibition of antibodies to nuclear antigen and to DNA in New Zealand Mice infected with Lactate dehydrogenase virus. Science 175, 784-786.
16. Quimby FW, Schwartz RS (1982) Systemic lupus erythematosus in mice and dogs. In: Clinical aspects of immunology (Lachmann PJ, Peters DK, eds). Oxford: Blackwell scientific, pp 1217-1230.
17. Rabin BS (1985) Influences on life-span of NZB/W mice. Immunol. Today. 6, 287 (letter).
18. Riley RL, Kruger MG, Landa B, Elia J, Ringel A (1991) B cells in autoimmune (NZB x NZW)F1 mice show altered IgG isotype switching upon T cell-dependent antigenic stimulation in vitro. Clin. Immunol. Immunopath. 58, 33-45.
19. Schrott LM, Crnic LC (1996) Anxiety behavior, exploratory behavior, and activity in NZB x NZW F1 hybrid mice: Role of genotype and autoimmune disease progression. Brain Behav. & Immunity 10, 260-274.
20. Schulman LE, Gumpel JM, D'Angelo WA, Souhami RL, Stevens MB, Townes AS, Masi AT (1964) Antinuclear factor in inbred strains of mice: The possible role of environmental influence. Arthritis Rheum. 7, 753.
21. Shirai T, Hirose S, Ohta K, Maruyama N (1984) H-2 linked genes and autoimmune disease in New Zealand mice. In: Immunogenetics, its application to clinical medicine. (Sasazuki T, Tada T, eds). Tokyo: Academic Press, pp 75-84.
22. Shirai T, Hirose S, Seligawa I, Okada T, Sato H (1987) Genetic and cellular basis of anti-DNA antibody synthesis in systemic lupus erythematosus of New Zealand mice. J. Rheumatol. 14, 11-20.
23. Shirai T, Mellors RC (1972) Natural cytotoxic autoantibodies against thymocytes in NZB mice. Clin. Exp. Immunol. 12, 133-152.
24. Talal N, Sternberg AD, Staples PL (1972) Immunological hyperactivity in New Zealand mice. In: Tolerance, Autoimmunity and Aging (Sigel MM, Good RA, eds) Thomas, Springfield, III, pp 127-131.
25. Theofilopoulos AN (1986) Molecular genetics of murine lupus. Agents Actions 19, 282-294.
26. Troyer DA, Chandrasekar B, Barnes JL, Fernandes G (1997) Calorie restriction decreases platelet-derived growth factor (PDGF)-A and thrombin receptor mRNA expression in autoimmune murine lupus nephritis. Clin. Exp. Immunol. 108, 58-62.
27. Vyse TJ, Drake CG, Rozzo SJ, Roper E, Izui S, Kotzin BL (1996) Genetic linkage of IgG autoantibody production in relation to lupus nephritis in New Zealand hybrid mice. J. Clin. Invest. 98, 1762-1772.

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