ENVIGO

Research Models and Services

Inbred Mice

C3H

Origin

Developed in 1920 by Strong from a cross of Bagg albino female and DBA male. Strain CBA also originated from this cross. Strain CBA was selected for a low mammary tumor incidence and C3H for a high incidence. In 1930, to Andervont, National Cancer Institute, Bethesda, MD, USA and in 1941, to Heston and Law at the same institute.

C3H/HeNHsd

Derived from a nucleus colony obtained from the National Institutes of Health, Bethesda, Maryland.

Research applications

Behavior, aggression, mammary tumors, metabolism, immunology, infectious diseases, parasitology, etc.

Characteristics

Strain C3H was selected for a high mammary tumor incidence. Unfostered sub-lines have a very high incidence of mammary tumors caused by a virus (Bittner virus), which is transmitted, from mother to offspring through the milk. Fostering of the young to a mammary tumor virus-free strain eliminates the virus and therefore all Germfree or SPF (Specified Pathogen Free) C3H mice will be free of this virus. Fostered C3H mice are widely used as a general-purpose strain.

Anatomy

Low total leukocyte count, low erythrocyte count, low hematocrit, and low hemoglobin (Russell *et al*, 1951). Small thymus/body weight ratio (Belyaev *et al*, 1970), small thymus/body weight ratio (depending on age) (Albert *et al*, 1965). Large pituitary (Sinha *et al*, 1975). Adrenal gland X zone large, with high incidence of vacuolization (Delost and Chirvan-Nia, 1958). Low percentage of mice has accessory spleens (Hummel *et al*, 1966). Many Peyer's patches (Hummel *et al*, 1966). Plasma volume low at 5.97 ml/100 g and red cell volume low at 4.64 ml/100g body weight in He substrain (Kano and Mizuma, 1974). High bone density of femur (Beamer *et al*, 1996).

Behavior

C3H mice are easy to handle. Low intra-strain aggression (Southwick and Clark, 1966). Long latency to emerge from home-cage, low rearing, long latency to cross barrier in open-field, low hole-in-the-wall entries and low Y-maze exploration (McClearn *et al*, 1970). Low open-field activity (Bruell, 1964). Low open-field defecation (Bruell, 1969). High food drive (Thompson, 1953), but poor performance in food-seeking task (Henderson, 1970). Short time of immobility in a forced swimming test (Nikulina *et al*, 1991). Low shock-avoidance learning (Bovet *et al*, 1966; Bovet *et al*, 1969). Good short-term but poor long-term memory in contrast with DBA/2 (Bovet *et al*, 1969). Good T-maze learning (Stasik, 1970). Poor water-escape learning (Festing, 1973). Low radial-arm maze learning (Ammassari-Teule *et al*, 1993). High social grooming scores during aggressive encounters (Southwick and Clark, 1968). Carries the retinal degeneration gene and is capable of pattern discrimination up to 40 days, and brightness discrimination to at least 100 days (Nagy and Misanin, 1970).

Drugs

Susceptible to skin ulceration to DMBA (Thomas *et al*, 1973). Sensitive to the development of uterine tumors following treatment with DMBA at four weeks of age (Tsubura *et al*, 1993). Susceptible to induction of subcutaneous tumors by 3-methylcholanthrene, depending on substrain) (Kouri *et al*, 1973). Susceptible to tumor induction by 3-methylcholanthrene in fostered and unfostered substrains (Whitmire *et al*, 1971; Whitmire and Salerno, 1972). Susceptible to induction of liver but resistant to pulmonary tumors by neonatally administered DMBA (Flaks, 1968). High susceptibility to tumor induction by 3,4-benzopyrene (Liebelt *et al*,

1970). High susceptibility to induction of mammary tumors by urethane (Bentvelzen *et al*, 1970). High incidence of gastric tumors after administration of methylcholanthrene by gavage (Akamatsu and Barton, 1974). Susceptible to fibrosarcoma induction by methylcholanthrene (Strong, 1952). Highly susceptible to the induction of hepatocellular tumors by various carcinogens, with the volume of hepatic lesions being >100-fold greater than in more resistant strains. Susceptibility is linked to at least six chromosomal regions (Dragani *et al*, 1995). Phenobarbitone in the diet to give an intake of 85 mg/kg per day resulted in 70% of animals developing basophilic nodules by 91 weeks of age (contrast 4% in C57BL/6), but no increase in liver carcinomas (Evans *et al*, 1992). However, there was a two-fold greater level of DNA synthesis in C3H mice relative to C57BL/6 mice after partial hepatectomy, though partial hepatectomy is a tumor promoter in C57BL/6 but not in C3H mice (Bennett *et al*, 1995). Insensitive to histamine (Brown, 1965). Airways of C3H/HeJ hyporeactive to acetylcholine (Zhang *et al*, 1995). Resistant to teratogenic effect of acetazolamide (Green *et al*, 1973). Pentobarbital i.p. induces hepatic epoxide hydrase (Oesch *et al*, 1973). Sensitive to X-irradiation (Roderick, 1963). Long survival on Warfarin (Lush and Arnold, 1975). Sensitive to hyperbaric oxygen (Hill *et al*, 1968). Sensitive uterine response to estrogen's (Chai and Dickie, 1966). Short hexobarbital sleeping time (Vesell, 1968). Long survival in 90% oxygen and highly susceptible to pulmonary hyaline-membrane formation (Lieberman and Kellog, 1967). Resistant to the induction of pulmonary fibrosis by bleomycin (contrast C57BL/6) (Haston *et al*, 1996), and irradiation though the sensitivity of lung fibroblasts to irradiation in-vitro does not correlate with *in-vivo* sensitivity (Dileto and Travis, 1996). Sensitive to chloroform toxicity (Deringer *et al*, 1953). Susceptible to toxic effects of isoniazid (Taylor, 1976). High ED50 to behavioral effects of nicotine (Marks *et al*, 1989). Low self-selection of nicotine, which is inversely correlated with sensitivity to nicotine-induced seizures (Robinson *et al*, 1996). Low bronchial reactivity to methacholine and serotonin (Konno *et al*, 1993). No increase in renal lipid peroxidation following treatment with nickel (Misra *et al*, 1991). Susceptible to biliary tract injury following oral dosing with 500 micrograms of the fungal toxin sporidesmin (Bhathal *et al*, 1990).

Low histamine release from peritoneal mast cells induced by compound 48/80, a calcium dependent histamine releaser (Toda *et al*, 1989). High histamine release from peritoneal mast cells induced by Ca2+ ionophore A23187 (contrast C57BL/6) (Toda *et al*, 1989). Cadmium highly hepatotoxic (Shaikh *et al*, 1993). Resistant to ozone-induced decreases of tracheal potential (Takahashi *et al*, 1995, Kleeberger *et al*, 1993). Susceptible to weight loss induced by cocaine, but this is attenuated by anisomycin (Shimosato *et al*, 1994). Estrogen does not induce an increase in VLDL and LDL-cholesterol (like BALB/c, contrast C57BL/6 and C57L) (Srivastava, 1995).

Genetics

Coat colour genes - *A, B, C, D* : agouti (wild type).

Histocompatibility - *H-2^{k}, Thy-1^{b}*.

Biochemical markers - *Apoa-1^{b}, Car-2^{b}, Es-1^{b}, Es-2^{b}, Es-3^{c}, Gpd-1^{b}, Gpi-1^{b}, Hba^{c}, Hbb^{d}, Idh-1^{a}, Ldr-1^{a}, Mod-1^{a}, Mup-1^{a}, Pep-3^{b}, Pgm-1^{b}, Pgm-2^{a}, Trf^{b}*.

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

Immunology

Sensitive to amyloid induction but low level of spontaneous amyloid formation (Ram *et al*, 1969). Low lymphocyte phytohemagglutinin response (Heiniger *et al*, 1975). Good immune response to small doses of bovine gamma globulin (Levine and Vaz, 1970). Poor immune response to Cholera A and B antigens (Cerny *et al*, 1971). Good splenic PFC immune response to pneumococcal polysaccharide (Amsbaugh *et al*, 1972). Immune response of SJL mice to type-III pneumococcal polysaccharide declines by 42 weeks, in contrast to BALB/c and C3H (Smith, 1976). Females fail to reject male skin grafts after 100 days (contrast nine strains) (Gasser and Silvers, 1971). Poor immune response to ovomucoid and ovalbumin (Vaz *et al*, 1971). Poor primary immune response to bovine serum albumin (James and Milne, 1972). Good immune response to *Salmonella anatum, S. senftenberg* and *S. strasbourg* lipopolysaccharide (Di Pauli, 1972). Responder to synthetic polypeptide Glu^{57}, Lys^{38}, Ala^{5} (Pinchuk and Maurer, 1965). Good immune response to Vi antigen (Gaines *et al*, 1965). Precipitating and skin-sensitising antibodies have slow electrophoretic mobility (Fahey, 1965). High antibody affinity to HSA (Petty *et al*, 1972).

Erythrocytes have high agglutinability (Rubinstein *et al*, 1974). Low immune response to ferritin in He substrain (Young *et al*, 1976). Non- discriminator between `H' and `L' sheep erythrocytes (McCarthy and Dutton, 1975). High anti-DNP antibody concentration (Paul *et al*, 1970). Antibodies to lipoid A antigen do not cross-react with sheep red blood cells (contrast eight strains). Strain also resistant to toxic effect of *Salmonella* lipopolysaccharide (Rank *et al*, 1969). Refractory to sensitising effects of HSF from *Bordetella pertussis* to histamine (contrast sixteen strains) (Bergman and Munoz, 1968). Good immune response to Pro-Gly-Pro-ovalbumin and $(Pro\text{-}Gly\text{-}Pro)_n$ (Fuchs *et al*, 1974). High susceptibility to IgE-mediated passive cutaneous anaphylaxis (De Souza *et al*, 1974). He substrain resistant to induction of anaphylactic shock by ovalbumin (Tanioka and Esaki, 1971). He and HeN substrains are susceptible to experimental autoimmune orchitis induced by two or three sc injections with viable syngeneic testicular germ cells without any adjuvants, but C3H/BiKi is resistant (Tokunaga *et al*, 1993). High immune

response to ganglio-series gangliosides in C3H/HeN, but low response in C3H/HeJ (Kawashima *et al*, 1992). Anti-BPO IgE monoclonal antibody did not produce potent systemic sensitisation sufficient for provocation of lethal shock in most aged (six-ten months) mice (Harada *et al*, 1991). Carries a strain-specific allele at the alpha globin locus (Sato *et al*, 1996). High natural killer cell response to the immunostimulant 7-allyl-8-oxoguanosine (Pope *et al*, 1994).

Infection

Resistant to infection by *Salmonella typhimurium* strain C5 (Plant and Glynn, 1974), Susceptible to *Mycoplasma fermentens* (Gabridge *et al*, 1972). Experimental *Mycoplasma pulmonis* infection results in acute pneumonia with severe hemorrhage, edema and often death (Faulkner *et al*, 1995). Susceptible to mammary tumor virus, which is carried in an active form in unfostered substrains (Murray and Little, 1967). Susceptible to oncogenic effect of polyoma virus given at birth (Law, 1966). Susceptible to measles virus induced encephalitis, which correlates with a high cytotoxic T-lymphocyte response (like C57BL/6, contrast BALB/c) (Niewiesk *et al*, 1993). Susceptible to *Mycobacterium marinum* (Shepard and Habas, 1967). Susceptible to infection by *Mycobacterium marinum* (Yamamoto *et al*, 1991). Susceptible to infection by *Entamoeba histolytica* (Neal and Harris, 1975). Resistant to mouse hepatitis virus (Bang and Warwick, 1960). 100% transmission of murine leukemia virus (Scripps) through three successive generations (Jenson *et al*, 1976). Highly susceptible to measles virus (Rager-Zisman *et al*, 1976). Highly susceptible to tumor induction by polyoma virus (Freund *et al*, 1992). Following administration of murine cytomegalovirus, C3H mice exhibited minimal carditis after neonatal or adult infection. However neonatal infection appears to accelerate age-related cardiopathy, which is severe in retired breeders of this strain. (contrast BALB/c and C57BL/10) (Price *et al*, 1991). Highly susceptible to Lyme borreliosis (*Borrelia burgdorferi*) when inoculated at three weeks of age and as adults. Mice inoculated at age three weeks also developed polyarthritis, but severity was reduced when inoculated as adults. Carditis was also common (Barthold *et al*, 1990), and mice were susceptible to the development of arthritis (contrast BALB/c) (Matyniak and Reiner, 1995). Resistant to intra-vaginally inoculated *Neisseria gonorrhoea* (Johnson *et al*, 1989). Resistant to infection with *Ehrlichia risticii* (Williams and Timoney, 1994). Susceptible to infection by *Helicobacter felis* with moderate to severe chronic active gastritis in the body of the stomach, which increased over time (Sakagami *et al*, 1996).

Life-span and spontaneous disease

Almost 100% of mammary tumors in females of unfostered substrains (Heston, 1963). Mammary adenocarcinomas in unfostered substrains less than 1% in males, 95% in breeding and 88% in virgin females. Lymphatic leukemia zero incidence (Hoag, 1963). Mammary tumors 40% at 18.8 months in C3HfC57BL, but 99% at 7.2 months in unfostered C3H (Heston and Vlahakis, 1971). Mammary tumors 37% at two years in fostered substrain (Bentvelzen *et al*, 1970). Median latent period to develop mammary tumors in unfostered substrains ranged from 276 to 566 days, depending on breeding status and environmental stress (Riley, 1975). A high proportion of the mammary tumors are of the acinar type (Tengbergen, 1970). Incidence of mammary tumors reduced by bromocriptine and interferon Stravoravdi *et al*, 1991). Hepatomas 72-91% in males at 14 months, 59% in virgin females, 30-38% in breeding females (Heston, 1963). Hepatomas have eosinophilic cytoplasmic inclusion bodies (Liebelt *et al*, 1971). Good model of genetic predisposition to hepatocellular tumors, susceptibility being associated with six chromosomal regions (Dragani *et al*, 1995). Point mutations in H-ras do not generally play a major or initiating role in spontaneous hepatocarcinogenesis in this strain (Enomoto *et al*, 1993). Lung adenomas 2-10% in fostered A substrain, leukemia 6-30% (Muhlbock and Tengbergen, 1971). Occasional Harderian gland tumors (Heston, 1963). Rare "lipomatous" hamartomas or choristomas have been noted (Adkison and Sundberg, 1991). Life-span in SPF fostered conditions intermediate in both sexes (590 days in males, 676 days in females). Liver tumors 9-23%, lung tumors 2-10% and mammary tumors 21-36%. Heart defects 13-26% and cystic ovaries 13-26% (Festing and Blackmore, 1971). The relationship of genotype, sex, body weight, and growth parameters to lifespan in inbred and hybrid mice is described by Ingram *et al* (1982). The influence of MHC on aging is described by Smith and Walford (1977). Mean survival 98 ± 3.0 weeks. The influence of the H-2 and H-1 histocompatibility upon life-span and cancer incidence is described by Smith and Walford (1978). Tail lesions similar in appearance to bite wounds were found in grouped C3H/HeJ by Les (1972). Develop dystrophic cardiac calcification, which may be related to disturbed myocyte calcium metabolism (Brunnert, 1997). Can be made obese by a suitable diet (Fenton and Dowling, 1953).

Resistant to the development of aortic cartilaginous metaplasia (contrast C57BL/6) (Qiao *et al*, 1995). Resistant to diet-induced aortic fatty streak lesions which correlates with a high level of paroxinase mRNA (contrast C57BL/6) (Shih *et al*, 1996).

Miscellaneous

Recommended host for the following transplantable tumors: lymphosarcoma 6C3HED and mammary adenocarcinomas C3HBA and H2712 (Kaliss, 1972). Recommended host for sarcoma BP8 used as a model for screening potential anticancer drugs (EORTC Screening Group, 1972). High mortality after neonatal thymectomy (Law, 1966). High rate of spontaneous mutations and total deviants (Schlager and Dickie, 1967). Characteristics of the C3H strain have been described by Festing (1997) and Lyon *et al*, (1996).

Physiology and biochemistry

Low serum calcium in Fg substrain but He substrain has high level at 4 months (Barrett *et al*, 1975). High serum cholesterol (Bruell *et al*, 1962). High plasma cholesterol and triglycerides. High erythrocyte catalase (Hoffman and Rechcigl, 1971). Low serum haptoglobin level (Peacock *et al*, 1967). Low

peripheral nerve conduction velocity (Hegmann, 1972). Low percentage of time spent sleeping with low percentage of slow-wave sleep and small diurnal variation (Valatx and Bugat, 1974). Low metabolic rate (Pennycuik, 1967). High liver tyrosine aminotransferase level in fasted mice (Blake, 1970). Low adrenal corticosteroid production (Nandi *et al*, 1967). High peptidyl proline hydroxylase activity in tumor tissue and mammary gland fat pad (Cutroneo *et al*, 1973). Slow cell turnover as judged by rate of clearance of DNA-bound radioactivity (Heiniger *et al*, 1972). Harderian gland has a high porphyrin content (Margolis, 1971). Low hepatic ammonia-lyase activity in two substrains (Hanford *et al*, 1974). Low spermatozoal beta-glucuronidase activity (Erickson, 1976). Low basal level of renal glutathione S-transferase but high basal level of renal glutathione reductase (Misra *et al*, 1991). Low hepatic nicotinamide N-methyltransferase levels (Scheller *et al*, 1996). High level of alpha-fetoprotein in plasma at seven days (Adinolfi *et al*, 1990). Resistant to the development of atherosclerosis on a semi-synthetic high fat diet (Nishina *et al*, 1993). Loci on chromosomes 1, 3, 5 and 11 are associated with variation in high density lipoprotein levels with coordinate expression of cholesterol-7-alpha hydroxylase in a cross involving atherosclerosis susceptible C57BL/6 mice (Machleder *et al*, 1997). Hepatic iodothyonine deiodinase activity was only 18% of that found in C57BL/6 mice (Schoenmakers *et al*, 1993). Decreased levels of deiodinase mRNA and hyperthyroxinemia associated with a 21-base pair insert in the promoter region of the type 1 deiodinase gene (Maia *et al*, 1995). Resistant to severe hypercapnia with hypoxia assessed by elevated minute ventilation rate (Tankersley *et al*, 1994). Has a slow and deep breathing pattern phenotype (contrast C57BL/6) (Tankersley *et al*, 1997). High intra-ocular pressure (John *et al*, 1997).

Reproduction

Breeding performance intermediate/good. Good reproductive performance, litter size 6.4, sterility 10% (Nagasawa *et al*, 1973). Large litter size, high proportion of females produce four or more litters and high proportion of fertile matings (Fernandes *et al*, 1973). C3H/HeJ has shorter and less regular oestrus cycles than C57BL/6J (Nelson *et al*, 1992). Early opening of vagina and first cornification (compared with C57BL/6 and DBA/2), but late onset of cyclicity (Nelson *et al*, 1990).

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