ENVIGO

Research Models and Services

Oncology - Mutant Mice

Athymic Nude Mice

Origin

In 1966 Flanagan described a spontaneous mutation resulting in 'nude' mice. This mutation was found in the animal colony of the Virus Laboratory, Ruchill Hospital, Glasgow, UK. These mice originated from an albino stock purchased in 1953 from Messrs Schofield in Oldham. In 1968 Pantelouris observed that these mice lacked a thymus.

Hsd:Athymic Nude-*Foxn1*^{nu}

In the early 1980's, Harlan Sprague Dawley, Inc., obtained NUDE mice, BALB/c-*nu/nu*, from the National Cancer Institute (NCI), National Institute of Health, Bethesda, Maryland, USA. Soon thereafter, NCI advised Harlan that genetic evaluation by NCI had produced evidence that these mice were not congenic to the BALB/c strain and that these mice should be designated as a heterogeneous or outbred stock. Since that time, Harlan maintained and produced these mice as an outbred stock and utilized the following nomenclature to be consistent with NCI: Hsd:Athymic Nude-*nu*. Harlan was renamed Envigo in 2015.

BALB/cOlaHsd-*Foxn1*^{nu}

Institute of Animal Genetics, Edinburgh to Laboratory Animals Centre, Carshalton, to GD Searle, High Wycombe, to OLAC (which became Harlan Laboratories) in 1978. Harlan was renamed Envigo in 2015.

HsdOla:MF1-*Foxn1*^{nu}

Institute of Animal Genetics, Edinburgh to Laboratory Animals Centre, Carshalton, to OLAC (which became Harlan Laboratories) in 1972 on mixed background. Backcrossed to Ola:MF1 mice. Harlan was renamed Envigo in 2015.

HsdCpb:NMRI-*Foxn1*^{nu}

Institute of Animal Genetics, Edinburgh to Laboratory Animals Centre, Carshalton, to CPB (which became Harlan Laboratories) in 1972. Backcrossing the nude gene into the Swiss mouse NMRI, resulted in an outbred NMRI-*nu* stock. Harlan was renamed Envigo in 2015.

Characteristics

Nude mice are hairless from birth throughout life and completely lack a thymus (Pantelouris, 1968), and therefore they have a T-cell deficiency. Because of its lack of thymus-dependent immune function, nude mice have been used as recipients of human tumours.

Lack of the thymus in homozygotes leads to many defects in the immune system, including depletion of lymphocytes from thymus-dependent areas of lymph nodes and spleen, a much reduced lymphocyte population composed almost entirely of B-cells, relatively normal IgM response to thymus-dependent antigens, very poor response to thymic-dependent antigens including failure to reject allogeneic and xenogeneic skin and tumour grafts, and greatly increased susceptibility to infection (Gershwin *et al*, 1975; Pantelouris, 1973; Rygaard, 1973; Rygaard and Povlsen, 1974). Heterozygotes (*nu/+*) are haired and have a thymus about 50 to 80 percent as large as that of *+/+* congenic controls.

Anatomy

Nude mice are hairless from birth throughout life and completely lack a thymus (Pantelouris, 1968). Abnormal hair growth in nude mice has been described by Eaton (1976). Absence of the thymus is due to a failure of the development of the thymus anlage, which arises from the ectoderm of the third pharyngeal pouch. The rudiments remain small and cystic (Cordier and Heremans, 1975). Development of thymus, parathyroids, and ultimo-branchial bodies in NMRI and nude mice have been described by Cordier and Haumont, (1980).

Genetics

Mutant stock gene - *nu* (autosomal recessive).

Coat colour
- ***Athymic Nude-Foxn1***^{nu}: albino;
- ***BALB/c-Foxn1***^{nu}: albino;
- ***MF1-Foxn1***^{nu}: albino;
- ***NMRI-Foxn1***^{nu}: albino

Husbandry

Homozygous *nu/nu* mice are highly susceptible to infection by a broad spectrum of bacterial and viral pathogens and they should be maintained in isolators, micro-isolators, laminar flow cabinets or pathogen free environment. Under these conditions their lifespan approaches that of normal littermates. Outbred nude mice are hardier than inbred nude mice and can be maintained under less stringent conditions if isolated from conventional housed mice. However, it should be recognized that any nude mouse housed in a conventional environment probably has a microbial infection and that this infection might influence experimental data considerably (ILAR, 1989). Husbandry of nude mice has also been described by Rygaard and Friis (1974).

Immunology

There is no intrinsic defect of T-cell precursors in nude mice; the T-cell defect can be corrected by transplanting mature T-cell(s), thymocytes, or normal thymic epithelium (Wortis *et al*, 1971). Cytotoxic T-cell activity can be induced in nude mice by the administration of IL-2 (Hunig and Bevan, 1980), and older mice, especially if they have a microbial infection, often have some functional T-cell(s). It has been suggested that failure of stromal thymic elements to interact with lymphocytic precursors to form T-cell(s) is due to an abnormal distribution of Ia antigens by epithelium components (Jenkinson *et al*, 1981). This is constant with the finding that Ia+ cells are absent from the thymic rudiment of nude mice (Van Vliet *et al*, 1985). The Thy-1 antigen is present on T-lymphocytes and neurons (Roitt, 1988). It seems that the number of Thy-1 expressing cells not only increases with age, but that the differentiation into Thy-1 bearing cells can be triggered by extreme environmental conditions such as infections and hormonal manipulations (Scheid *et al*, 1975).

Although the athymic nude mouse is grossly deficient in peripheral T-cell(s), the number of lymphocytes bearing T-cell markers (CD4, CD8) and the alpha beta or gamma delta T-cell receptor (TCR) increases steadily with age.

The anatomical site(s) where these cells arise are unknown. Splenocytes from 3-5-week-old C57BL/6-*nu* mice contain 2%-5% Pro-T-cell progenitors, but no mature T-cell(s). Studies by Palacios and Samaridis (1991) have shown that the spleen is one of the extrathymic sites where T-cell progenitors can rearrange TCRδ and TCRγ genes. However, there was no evidence for TCRß gene rearrangements in this organ. Furthermore, the extrathymic TCR gene rearrangements seem to be distinct and much less diverse than those found in the developing thymocytes (Palacios and Samaridis 1991, Kennedy *et al*, 1992).

T-cell maturation in an extrathymic environment has been studied using the congenitally athymic nude mouse as a model. The nude mice accumulate increasing numbers of lymphocytes bearing Thy-1, CD3, CD4, and CD8 with age characterized by a progression from heterogeneous dim to more homogeneous bright expression.

In contrast, the expression of heat-stable Ag (HSA), a marker of immature thymocytes, decreases with age. By analogy to intrathymic maturation, spleens and lymph nodes in nude mice contain T-cell(s) defined as immature, transitional, and mature based on the expression of these markers. Although the proportion of CD4+ and CD8+ T-cell(s) associated with bright CD3 expression increases with age, at no age are significant numbers of CD4+8+ cells observed, in contrast to intrathymic T-cell maturation. In addition to the frequently observed inversion in the ratio of CD4 to CD8, the CD8 T-cell subpopulation in older nude mice contains mainly mature cells (CD8+, CD3+, HSA-) whereas only 50% of CD4+ T cells express the mature (CD4+, CD3+, HSA-) phenotype. At any age, the spectrum of phenotypes observed indicates that lymph nodes contain more mature T-cells than spleen, suggesting a role for environmental antigens in driving extrathymic maturation, a process occurring most efficiently among CD8+ T-cell(s). A normal complement of B-lymphocytes is present.

The lymphocyte population is almost entirely composed of B-lymphocytes, and relatively normal IgM response to thymus-independent antigens is seen, however only a poor response to thymus-dependent antigens can be found. A B-cell defect has been reported, but it has not been demonstrated unequivocally (Mond *et al*, 1982; Wortis *et al*, 1982).

Lymphokine activated killer cells (LAK) and natural killer cells (NK) are more frequent in nude mice than in normal mice and their activity seems to be enhanced compared to euthymic mice (Hasui *et al*, 1989, Rygaard and Povlsen 1982, Møller Nielsen and Heron 1984). The activity of NK-cells is reduced in BALB/c-*nu* mice by transfer of T-cells (both CD4 and CD8) cells, indicating a regulative relationship between NK-cells and T-cells (Harada *et al*, 1989). Increased NK cell activity has been described (Minato *et al*, 1980; Clark *et al*, 1981).

Mononuclear cells are also present. Macrophage function seems to be enhanced (Cheers and Wallers 1975). Stimuli in the conventional environment are capable of activating the macrophages of thymic deficient mice. Therefore the macrophage function is not totally dependent upon functioning T lymphocytes (Rama Rao *et al*, 1977).

The number of mast-cells seems to be normal in the skin and lymphatic tissues of nude mice (Wlodarski *et al*, 1982). The function also seems to be normal indicating the thymus independence of this cell line.

Nude mice respond poorly to thymus-dependent antigens because of a defect in helper T-cell activity. When responses can be detected to such antigens, antibody is largely limited to IgM. Responses to thymus-independent antigens in nude mice are normal. Levels of serum IgG1, IgG2a, IgG2b, and IgA are reduced, while IgM levels tend to be slightly elevated and IgG3 is present in normal or slightly reduced amounts.

Spontaneous autoimmunity has been reported in nude mice by Monier *et al* (1974) and Morse *et al* (1974). Monier *et al* (1974), found that approximately one-third of nude homozygotes have circling ANAs as early as 6-8 weeks of age. ANAs were present in the eluates from kidneys containing immune responses.

Infection

Abnormal response of nude mice to endotoxin has been described by Moore *et al* (1976). Susceptibility and resistance to parasites in nude mice of various genotypes have been described by Mitchell (1984).

Life-span and Spontaneous Disease

Life-span and tumour incidence in SPF NMRI *nu/nu* mice has been described by Rehm *et al* (1980). Incidence and pathological features of spontaneous tumours in nude mice have been described by Sharkey and Fogh (1979).

Miscellaneous

Characteristics of the nu gene have been described by ILAR (1989) and Lyon *et al* (1996).

Physiology and Biochemistry

BALB/c nude mice maintained in the SPF environment have apparently intact adrenal, thyroidal and gonadal function; the function of these endocrine organs is the same as those of BALB/c control animals. Although the levels of pituitary growth hormone seem to be lower that those of the controls, the functions of the GH are apparently well maintained judging from the plasma GH and growth of the nude mice (Ohsawa *et al*, 1974). Later studies, however, revealed that the athymic nude mice had significantly reduced concentrations of serum gonadotropins and testosterone compared with normal littermates (Rebar *et al*, 1982). Brünner *et al* (1986) found the serum steroid genesis was normal in BALB/c nude mice, but the serum levels were decreased compared to those of the littermates.

Cytokine interleukin-2 (IL-2) influences expression of the genes encoding the neuropeptides vasopressin (VP) and oxytocin (OT) in the hypothalamus of the nude mouse. This effect is specific to the nude mouse. These observations stress the potential value of the nude mouse for studying interactions between the central nervous system (CNS) and the immune system (Pardy *et al*, 1993).

Reproduction

Nude females are no efficient breeders. The most effective breeding scheme uses homozygous nude males and heterozygous females.

The homozygous nude pups can be identified within 24 hours postpartum by their lack of vibrissae or poorly developed, crinkled vibrissae.

It might be advantageous to cull some normal littermates to optimise survival of the mutant mice (ILAR, 1989).

Xenotransplantation

Xenograft acceptance is the basis for the widespread use of nude mice as hosts for transplanted human tumours (Povlsen 1977, Spang-Thomsen and Visfeldt, 1977; Fogh and Giovanelli 1978; Fogh and Giovanelli, 1982; Spang-Thomsen, 1985; Engelholm, 1987), human tumour cell lines (Fogh *et al*, 1977), and for therapeutic studies on human tumours, transplanted to nude mice (Povlsen, 1978; Spang-Thomsen, 1985; Fogh and Giovanelli, 1978; Fogh and Giovanelli, 1982; Van Weerden *et al*, 1999; Van Weerden and Romijn, 2000).

Early studies revealed that the nude mouse was useful for serial transplantation of human solid tumours; the morphological and functional characteristics were maintained during the serial transplantation (Sordat *et al* 1974).

Compared to other nude mice or immune deficient mice, the BALB/c-*nu* has a relative high take rate for tumours (Dagnæs-Hansen *et al*, 1992). Maruo *et al* (1982) found that the tumour growth rate of human gastric cancers was lower in BALB/c nude mice compared to CBA/N, NSF/N and NIH nude mice.

Parameters

(Hsd:Athymic Nude- *Foxn1*^{nu}, Barrier 203I; Males 9-10 weeks old, Females 16-17 weeks old)

HAEMATOLOGY	MALE	FEMALE	UNIT		MALE	FEMALE	UNIT
WBC	2,60	2,60	x10^9/L	Platelets	1154,00	1101,00	x10^9/L
RBC	7,81	8,25	x10^{12}/L	Neutrophils	58	36	%
Hb	142,00	150,00	g/L	Lymphocytes	41	63	%
HCT	0,42	0,45	L/L	Monocytes	0	<2	%
MCV	54,00	54,10	fl	Eosinophils	<1	1	%
MCH	1,13	1,12	fl	Basophils	<1	<1	%
MCHC	21,02	20,83	mmol/L				

BIOCHEMISTRY	MALE	FEMALE	UNIT		MALE	FEMALE	UNIT
Glucose	12,88	11,04	mmol/L	Alk. Phosph.	124,0	88,0	mmol/L
Urea	5,66	5,00	mmol/L	LDH	464,0	263,0	U/l
Creatinine	17,68	26,52	µmol/L	AST	174,0	111,0	U/L
Uric acid	160,61	148,71	µmol/L	ALT	60,0	33,0	U/L
Cholesterol	116,0	90,0	meq/L	GGTP	0,0	0,0	U/L
Triglycerides	2,17	1,65	mmol/L	Calcium	2,53	2,38	mmol/L
Protein	61,0	60,0	g/L	Phosphorus	3,78	3,00	mmol/L
Albumin	31,0	33,0	g/L	Sodium	168,0	165,0	mmol/L
Globulin	20,0	21,6	g/L	Potassium	9,6	9,0	mmol/L
Bilirubin	<1,71	1,71	µmol/L	Chloride	124,0	122,0	mmol/L

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