Inbred and Congenic Mice

A. MHC Haplotypes

- MHC loci are highly polymorphic, which means they have many alternative forms of the gene or alleles at each locus
- each set of alleles inherited from the parents is known as the haplotype
- one inherits one haplotype from the mother and one from the father

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- in outbred populations, offspring are usually heterozygous at many loci and will express both maternal and paternal MHC alleles
  - the alleles are codominantly expressed
- in inbred mice, however, each H-2 locus will be homozygous because the maternal and paternal haplotypes are identical, and all offspring therefore express identical haplotypes

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- designation of inbred mice:
  - some inbred mouse strains have been designated as prototype strains and the MHC haplotype expressed by these strains is designated by an arbitrary italic superscript
- if another inbred strain has inherited the same set of alleles as the prototype strain, its MHC haplotype is the same as the prototype strain

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- if two mice from inbred strains having different MHC haplotypes are bred to one another, the F1 generation inherits haplotypes from both parental strains and therefore expresses both parental alleles at each MHC locus
- next slide demonstrates mating of inbred mouse strains with different MHC haplotypes and shows how MHC haplotypes in inbred mouse strains are inherited

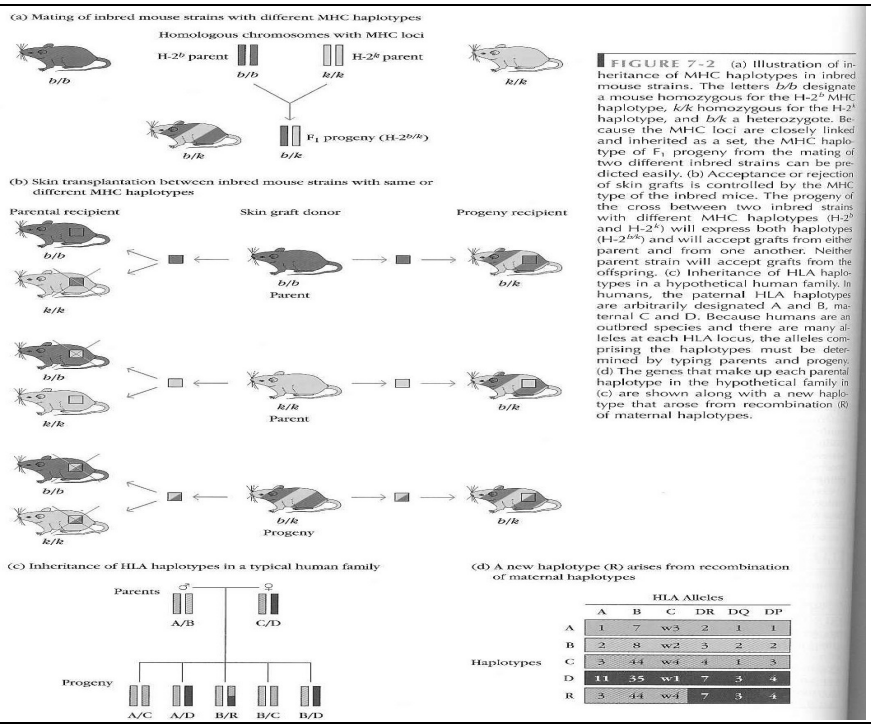

FIGURE 7-2 (a) Illustration of inheritance of MHC haplotypes in inbred mouse strains. The letters *b*/*b* designate a mouse homozygous for the H-2^b MHC haplotype, *k*/*k* homozygous for the H-2^k haplotype, and *b*/*k* a heterozygote. Because the MHC loci are closely linked and inherited as a set, the MHC haplotype of F_1 progeny from the mating of two different inbred strains can be predicted easily. (b) Acceptance or rejection of skin grafts is controlled by the MHC type of the inbred mice. The progeny of the cross between two inbred strains with different MHC haplotypes (H-2^b and H-2^k) will express both haplotypes (H-2$^{b/k}$) and will accept grafts from either parent and from one another. Neither parent strain will accept grafts from the offspring. (c) Inheritance of HLA haplotypes in a hypothetical human family. In humans, the paternal HLA haplotypes are arbitrarily designated A and B, maternal C and D. Because humans are an outbred species and there are many alleles at each HLA locus, the alleles comprising the haplotypes must be determined by typing parents and progeny. (d) The genes that make up each parental haplotype in the hypothetical family in (c) are shown along with a new haplotype that arose from recombination (R) of maternal haplotypes.

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- because inbred animals are syngeneic (genetically identical), their immune responses can be studied in the absence of variable introduced by individual genetic differences
- with inbred strains, lymphocytes subpopulations isolated from one animal can be injected into another animal of the same strain without eliciting a rejection reaction
- this type of experimental system allow immunologists to first demonstrate that lymphocytes from an Antigen-primed animal could transfer immunity to an unprimed syngeneic recipient

TABLE 23-2 SOME INBRED MOUSE STRAINS COMMONLY USED IN IMMUNOLOGY

Strain	Common substrains	Characteristics
A	A/He	High incidence of mammary tumors in some substrains
	A/J	
	A/WySn	
AKR	AKR/J	High incidence of leukemia
	AKR/N	
	AKR/Cum	*Thy 1.2* allele in AKR/Cum, and *Thy 1.1* allele in other substrains (*Thy* gene encodes a T-cell surface protein)
BALB/c	BALB/cj	Sensitivity to radiation
	BALB/c AnN	Used in hybridoma technology
	BALB/cBy	Many myeloma cell lines were generated in these mice
CBA	CBA/J	Gene *(rd)* causing retinal degeneration in CBA/J
	CBA/H	
	CBA/N	Gene *(xid)* causing X-linked immunodeficiency in CBA/N
C3H	C3H/He	Gene *(rd)* causing retinal degeneration
	C3H/HeJ	High incidence of mammary tumors in many substrains (these carry a mammary-tumor virus that is passed via maternal milk to offspring)
	C3H/HeN	
C57BL/6	C57BL/6J	High incidence of hepatomas after irradiation
	C57BL/6By	High complement activity
	C57BL/6N	
C57BL/10	C57BL/10J	Very close relationship to C57BL/6 but differences in at least two loci
	C57BL/10ScSn	
	C57BL/10N	Frequent partner in preparation of congenic mice
C57BR	C57BR/cdj	High frequency of pituitary and liver tumors Very resistant to x-irradiation
C57L	C57L/J	Susceptibility to experimental autoimmune encephalomyelitis (EAE)
	C57L/N	High frequency of pituitary and reticular cell tumors
C58	C58/J	High incidence of leukemia
	C58/LwN	
DBA/1	DBA/1J	High incidence of mammary tumors
	DBA/1N	
DBA/2	DBA/2J	Low immune response to some antigens
	DBA/2N	Low response to pneumococcal polysaccharide type III
HRS	HRS/J	Hairless *(hr)* gene, usually in heterozygous state
NZB	NZB/BINJ	High incidence of autoimmune hemolytic anemia and lupus-like nephritis
	NZB/N	Autoimmune disease similar to systemic lupus erythematosus (SLE) in F_1 progeny from crosses with NZW
NZW	NZW/N	SLE-type autoimmune disease in F_1 progeny from crosses with NZB
P	P/J	High incidence of leukemia
SJL	SJL/J	High level of aggression and severe fighting to the point of death, especially in males Tendency to develop certain autoimmune diseases, most susceptible to EAE
SWR	SWR/J	Tendency to develop several autoimmune diseases, especially EAE
129	129/J	High incidence of spontaneous teratocarcinoma
	129/SvJ	

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B. Congenic Mouse Strains

- inbred mouse strains are syngeneic or identical at all genetic loci
- two strains are considered congenic if they are genetically identical except at a single genetic locus or region
- congenic strains that are identical with each other except at the MHC can be produced by a series of crosses, backcrosses, and selections
- next slide demonstrates how the H-2 complex of homozygous strain B can be introduced into the background genes of homozygous strain A to generate a congenic strain, denoted A.B

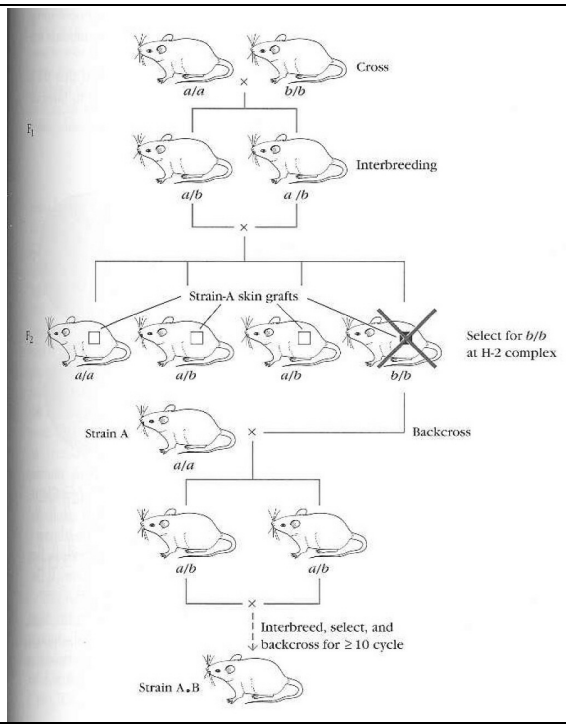

FIGURE 7-3 Production of congenic mouse strain A.B, which has the genetic background of parental strain A but the H-2 complex of strain B. Crossing inbred strain A (H-2^a) with strain B (H-2^b) generates F_1 progeny that are heterozygous (*a/b*) at all H-2 loci. The F_1 progeny are interbred to produce an F_2 generation, which includes *a/a*, *a/b*, and *b/b* individuals. The F_2 progeny homozygous for the B-strain H-2 complex are selected by their ability to reject a skin graft from strain A; any progeny that accept an A-strain graft are eliminated from future breeding. The selected *b/b* homozygous mice are then backcrossed to strain A; the resulting progeny are again interbred and their offspring are again selected for *b/b* homozygosity at the H-2 complex. This process of backcrossing to strain A, intercrossing, and selection for ability to reject an A-strain graft is repeated for at least 12 generations. In this way A-strain homozygosity is restored at all loci except the H-2 locus, which is homozygous for the B strain.

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- congenic strain A.B:

  - the first letter designation refers to the strain providing the genetic background and the second letter to the strain providing the genetically different MHC region

  - thus, strain A.B will be genetically identical to strain A except for the MHC locus or loci contributed by strain B

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- during congenic mouse strain production, a crossover event can occur within the H-2 complex, which yields a recombinant strain that differs from the parental strains or the congenic strain at one or a few loci within the H-2 complex
- the generation of new H-2 haplotypes under the experimental conditions of congenic strain development provides an illustration of how MHC continues to maintain heterogeneity even in populations with limited diversity

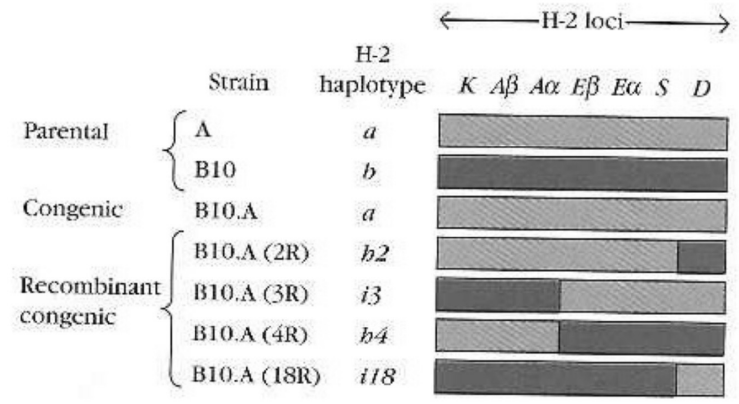

FIGURE 7-4 Examples of recombinant congenic mouse strains generated during production of the B10.A strain from parental strain B10 (H-2^b) and parental strain A (H-2^a). Crossover events within the H-2 complex produce recombinant strains, which have *a*-haplotype alleles (blue) at some H-2 loci and *b*-haplotype alleles (orange) at other loci.