

Could modern methods of genetics improve the disease resistance in farm animals?

(introductory lecture)

Content

Innate
immune
response

Adaptive
immune
response

Breeding
programs

Transgenesis

Innate and adaptive immune responses

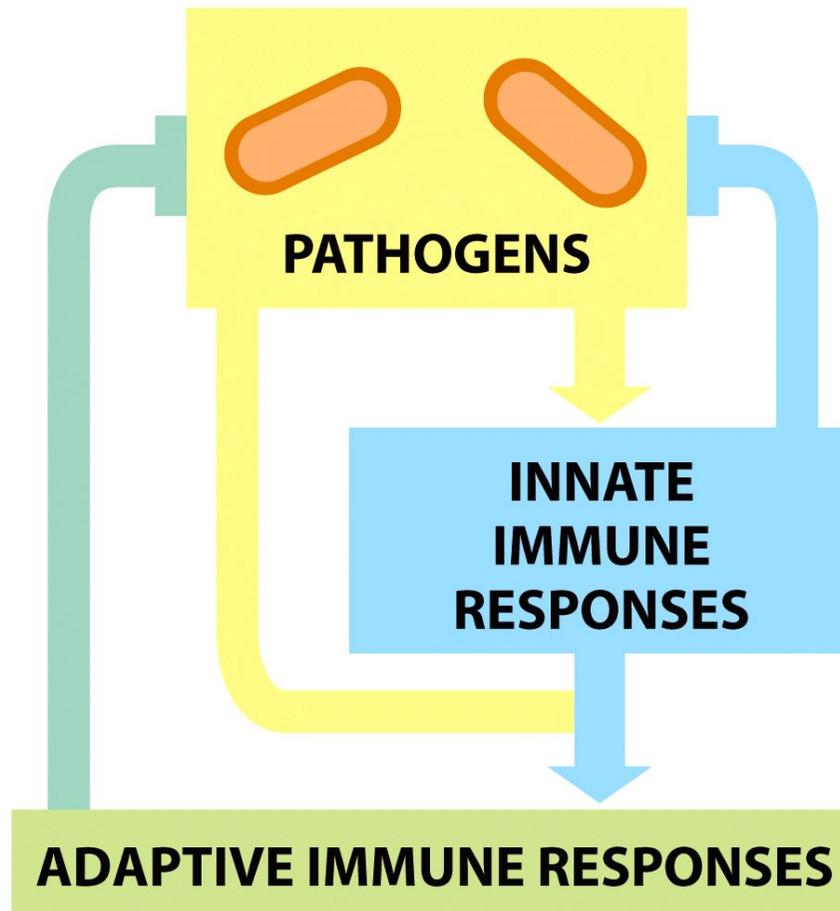


Figure 25-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

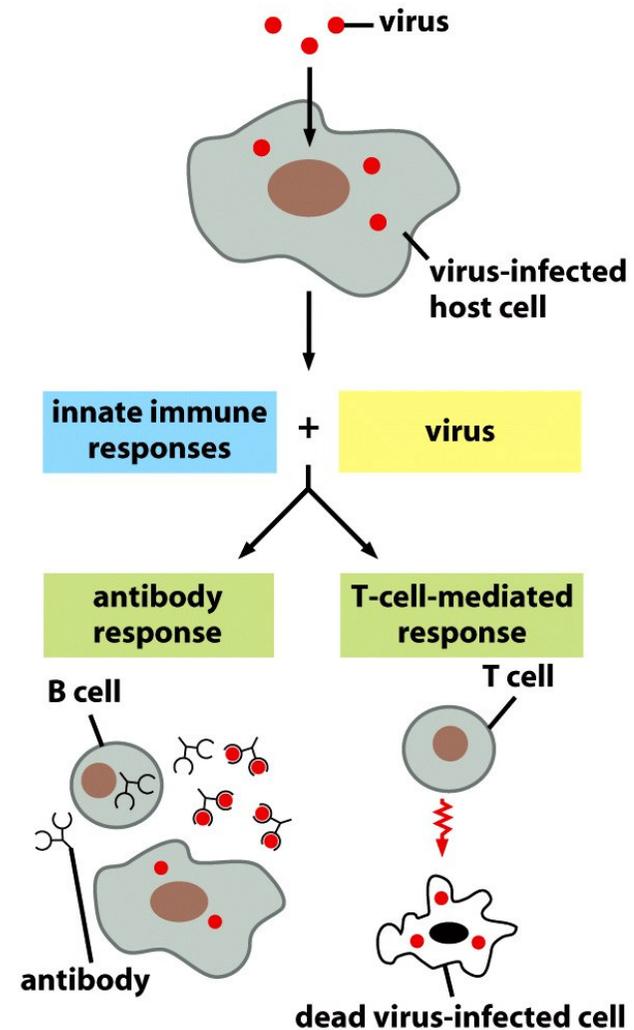


Figure 25-2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Definitions

Phenotype is the observed performance of an animal.

Genotype

Animal breeders use genotype to describe a particular strain of animal.

Molecular geneticists use genotype to describe the genetic variants (**alleles**) at a particular position in DNA (**locus**).

Genetic marker is a measurable variation in the DNA sequence of a population (SNPs, STRs, indels, CNVs).

Quantitative trait locus (QTL) is a segment of a chromosome that has been experimentally established to be correlated with variations in a quantitative trait.

Many-to-many data model: Phenotype \longleftrightarrow Genotype



Disease in farm animals

Resistance to Viruses

- African swine fever, foot-and-mouth disease, Marek's disease
- diseases caused by Maedi-Visna and other ovine lentiviruses
- transmissible spongiform encephalopathies

Resistance to Bacteria

- ovine footrot
- mastitis in dairy cattle
- *Escherichia coli* and *Salmonella* diarrhoea in pigs

Resistance to Parasites

- ticks and tick-borne diseases
- ovine cutaneous myiasis
- trypanosomes

Factors affecting resistance

- genetic variations at loci involved in the immune response
- environmental factors (infection pressure, stress)
- the age of an animal
- sexual maturity
- castration or hormone treatment...

Enabling technologies

Pacific Biosciences
PasBio RS



Illumina
HiSeq 2000

Roche Diagnostics
GS FLX



Applied Biosystems
3730xl DNA Analyzer



NATIONAL ANIMAL GENOME RESEARCH PROGRAM

NRSP-8 Bioinformatics Coordination Program



Highlights:

What's New ?

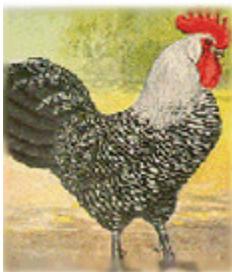
- **Newsletter:** NRSP-8 Bioinformatics Updates
- **Events:** Conferences, Meetings & Workshops
- **AnGenMap:** Animal Genomics Discussion Group
- **Directory:** Animal Genetics Community Members

- **Projects:**
 - Animal Trait Ontology (ATO) Project
 - Virtual Comparative Genomics
 - The Past, the Current, and the Potentials
 - Collaborative and Hosted Works

- **Resources & Tools:** **Animal QTLdb**
- **Resources & Tools:** **Animal GBrowse Tracks**
- **Resources & Tools:** **Biomart for livestock**
- **Resources & Tools:** **NAGRP Blast Server**
- **Resources & Tools:** **VCmap**
- **Resources & Tools:** **NAGRP Bioinformatics Tool Box**
- **Resources & Tools:** **Data/Software Repository**

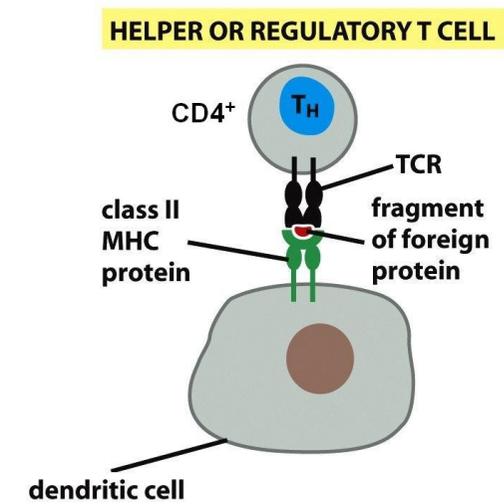
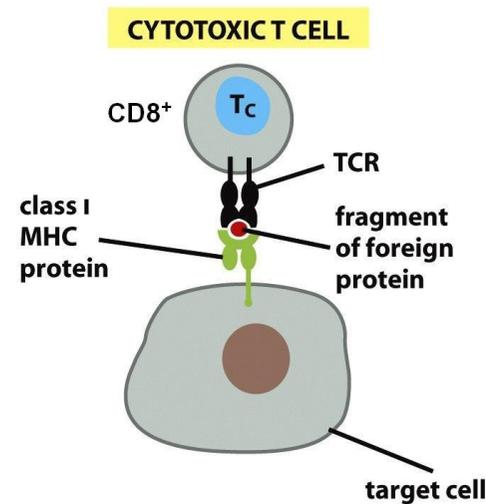
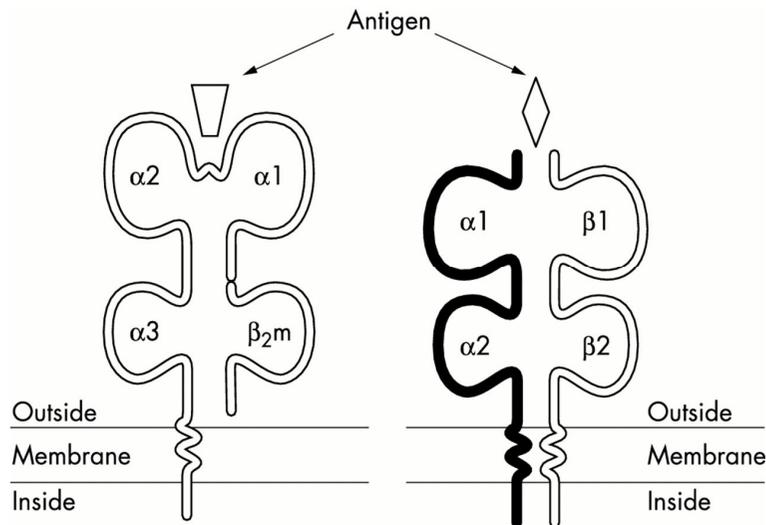
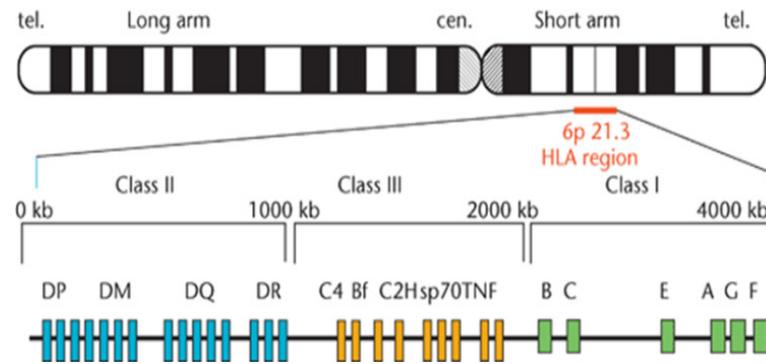
- **Services:**
 - Computing Resources
 - Bioinformatic Services at AnimalGenome.ORG

- **Team:** Members and responsibilities
- **Mission Statement:** Challenges and opportunities
- **Publications:** Abstracts and Papers

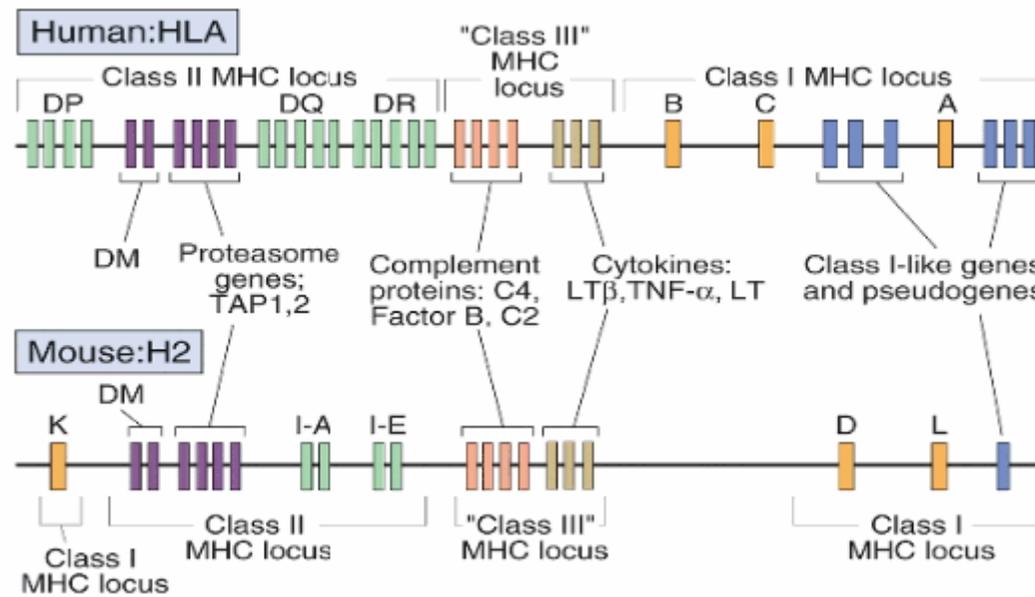


Loci involved in resistance and susceptibility to infectious diseases

Map of the human MHC



Comparative genomics

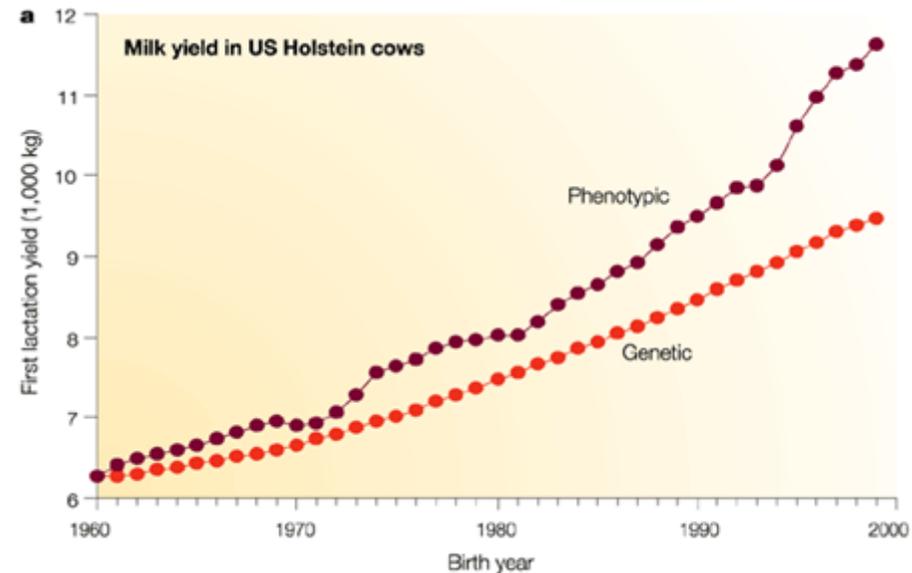


Marker-assisted selection (MAS), 'omics' breeding

MAS is indirect selection process where a trait of interest is selected, not on bases of the trait itself, but on a marker linked to it.

Genomic selection is a novel form of MAS where selection is using all marker data of whole genome.

Gene pyramiding has been proposed to enhance resistance to disease by selecting for two or more different genes at a time.



Genotype building is a 'building block' approach to create individuals with the right combination of alleles at each QTL.

Concerns about breeding for improved resistance

Continuous evolution of pathogens

- Pathogens will evolve faster than genetic gain in the host for resistance, thereby making any breeding programme unsustainable.

Impact of selection for a given trait on the genetic resistance to diseases

- Increased milk production in Holstein cattle is associated with increased susceptibility to bovine leukaemia virus infection.

Transgenesis vs. breeding

Breeding

- evaluation of genetic markers for selection against diseases
- the use of natural variation in species, rather than introduction of new genetic information

Transgenesis

- the direct transfer of 'resistance' genes into farm animals
- transgenic strategies to increase disease resistance in livestock include asRNA, knockdown, ribozymes, etc.
- resistant genes introduced into a population can persist for some generations

Modification of disease resistance

Possible candidates for gene transfer experiments

- MHC genes (?)
- T-cell receptor (TCR) genes (?)
- immunoglobulin genes
- genes encoding lymphokines
- specific disease resistance genes

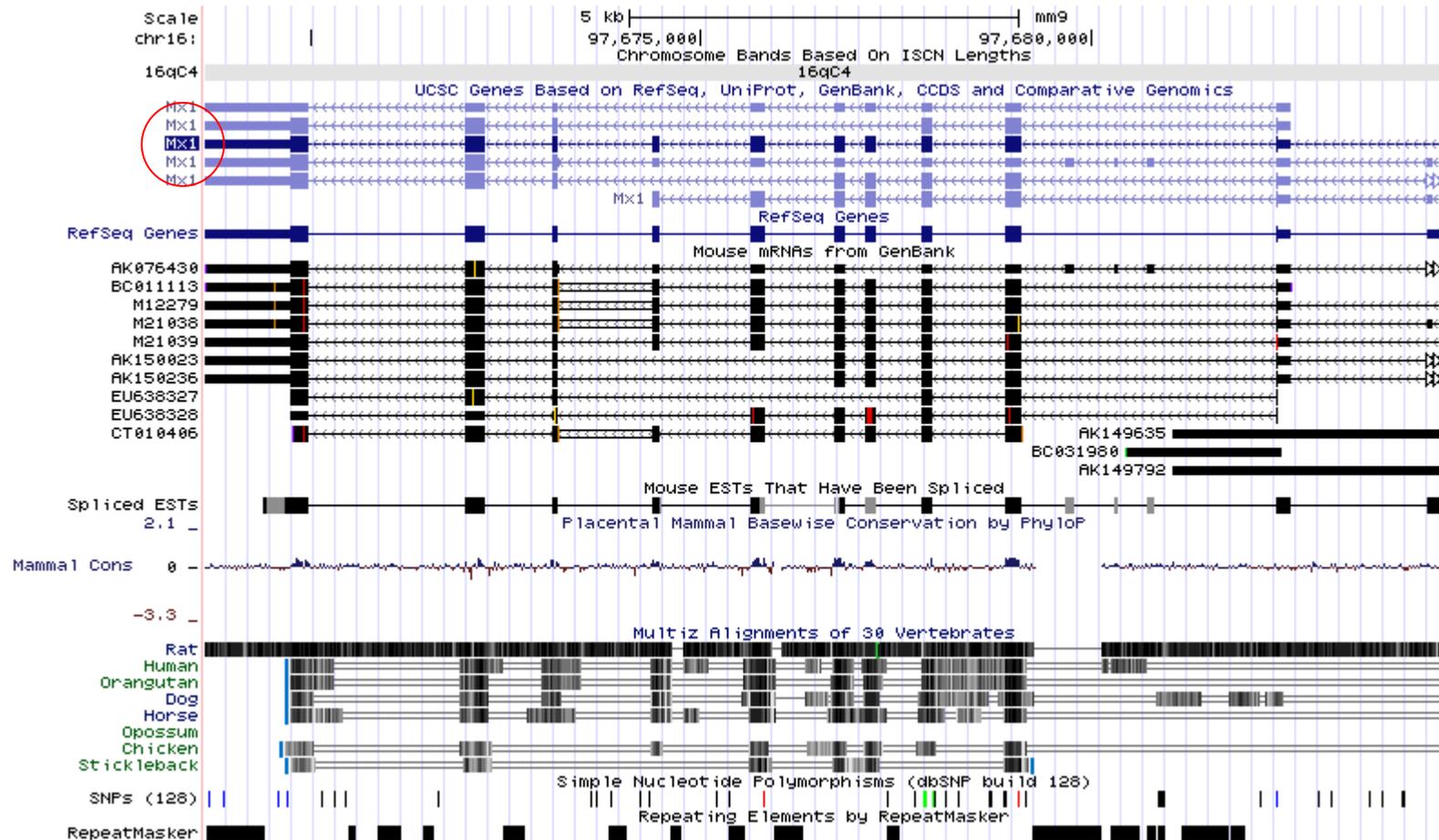
Obstacles

- The identification and characterisation of disease resistance genes is extremely laborious, and
- difficult to handle in conventional breeding programs.
- The final proof with a pathogen has not been reported.

Examples

- K88 antigen (Edfors-Lilia et al, 1986)
- *Ad5* RNA (Ernst et al, 1990)
- *MX1* (Muller et al, 1992)

Mx (myxovirus-resistant) system



Future research

State of the art

- QTLs that have a significant effect on phenotype are subsequently used for selection.

Prospects

- The location and function of all genes which affect quantitative traits are known. Although this is far from the case, the potential of MAS using computer simulation is promising.

Future research

- The whole genome of the host, coupled with the whole genome of the pathogen, will help in determining the mechanism of infection.

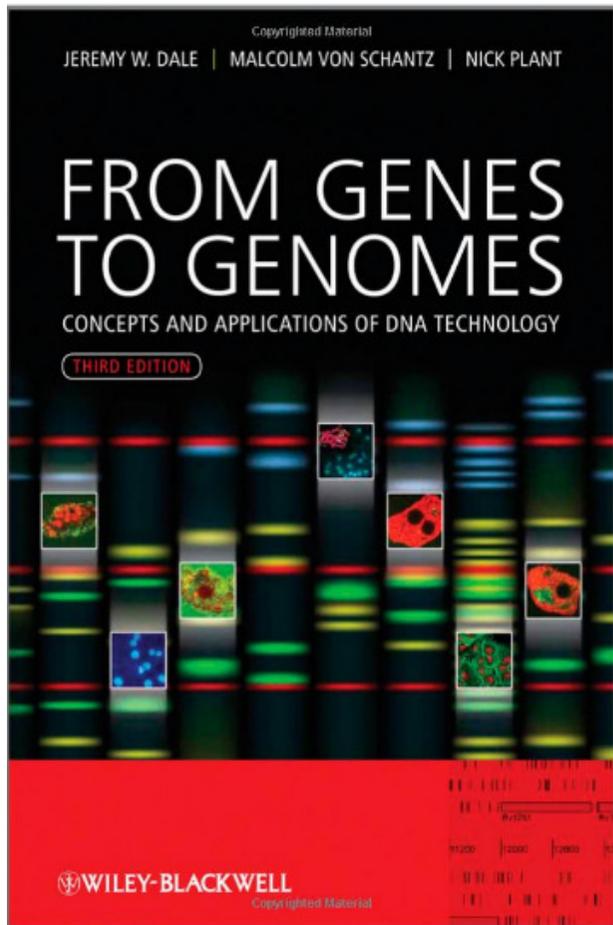
Challenges

- Rearrangements, aberrant expression of integrated genes, or harmful effects of transgenes could be avoided by the use of precisely defined regulatory elements and extensively tested gene constructs.

Conclusions

1. The immune responsiveness of individual animal is the product of interactions between host genes, pathogen and environment.
2. Resistance to most diseases is governed by a large number of genes.
3. 'Omics' technologies can be exploited to increase genetic gain in health.
4. High throughput genotyping will allow selection on the bases of marker information.
5. Development of gene mapping databases is desirable.
6. The use of the structural information will enhance genotype building and recurrent selection programmes.
7. However, observable phenotype will remain an important, because it takes account of the collective effect of all genes.

Literature



- Berry DP, Bermingham ML, Good M, More SJ. **Genetics of animal health and disease in cattle** // Ir Vet J. 2011 Mar 31;64(1):5. Review
- Dekkers JC, Hospital F. **The use of molecular genetics in the improvement of agricultural populations** // Nat Rev Genet. 2002 Jan;3(1):22-32. Review
- Haller O, Staeheli P, Kochs G. **Interferon-induced Mx proteins in antiviral host defense** // Biochimie. 2007 Jun-Jul;89(6-7):812-8. Review