Resolving the genetics of resistance to infectious diseases

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Summary

The genetics of resistance to disease is an area of great interest in agriculturally important plant and animal species. Selective breeding for resistance to pathogens in plants, animals and insects has demonstrated that resistance and susceptibility to pathogens are controlled by both genetic and environmental factors. The immune loci causally involved in susceptibility and resistance to disease are currently unknown. However, novel enabling molecular technologies promise to assist in unravelling the genetics of the host response to infectious diseases in new ways, and ultimately to improve seed stock genetics.

Keywords


Introduction

The breeding of domesticated animals for food production has traditionally focused on improving the genetic merit of performance traits related to growth, reproduction and carcass characteristics (63). In the past, intensive livestock production systems have employed extensive and expensive antibiotic, vaccine and chemoprophylactic methods to maintain herd health. New emerging diseases, issues related to biosecurity, food safety and the expansion of integrated production systems into diverse global management programmes have also contributed to a better understanding of disease and the impacts of disease, not only on animal mortality but more importantly on economic losses from sick, poorly performing animals. The increasing consumer pressure for antibiotic-free and ‘naturally’ produced foods is also of relevance.

When addressing the topic of genetic aspects to disease, a definition of resistance (efficient) versus susceptibility (deficient) to the infectious process is important (49). Figure 1 shows the stages in the interaction of pathogen and host which are relevant to this discussion. Thus, pathogen invasion, colonisation and the elimination of the pathogen can be defined in the context of resistance versus susceptibility. Many academic arguments have debated whether resistance and susceptibility are opposite sides of the same coin. Evidence presented in this paper argues that these are not opposites of the same coin, but rather form discrete, independent mechanisms.

Moreover, the immune responsiveness of any individual animal will be the product of multiple interactions between host genes, pathogens and the environment (31). Although plant breeders have identified and used disease resistance genes (R genes) to control plant diseases since the beginning of the 20th Century (70), tools for similar approaches in animal breeding are just emerging (58).
Dynamics of host resistance: lessons from plants and insects

Selective breeding in plants and insects has provided a vast amount of knowledge on the mechanisms involved in pathogen resistance. Studies investigating parasite resistance in plants have concluded that R genes may have evolved from common signal transduction mechanisms for the expression of resistance to a wide range of unrelated pathogens (70). Furthermore, susceptibility of the mosquito *Aedes aegypti* to the malarial parasite *Plasmodium gallinaceum* has demonstrated two putative quantitative trait loci (QTL) which affect susceptibility, thus accounting for a large part of the phenotypic variance observed in the two populations. Both QTL exhibit a partial dominance effect on susceptibility, with dominance inherited (67).

One consequence of modern agricultural practices has been the reduction of genetic diversity of the primary gene pool (e.g., sorghum crops use the F1 hybrid seed which is produced using cytoplasmic male sterility). Valuable and irreplaceable genes may be lost during this procedure. This problem assumes significance as crop-based agriculture becomes more vulnerable to climatic conditions (unseasonable weather/greenhouse effect) and other stress factors (38). Studies performed on both plants and insects indicate that genetics will be required to extend or replace extant management practices (e.g., chemical fertilisers, pesticides) (38).

Nurture (environmental) versus nature (genetics)

Resistance to infectious diseases is an endpoint of many genetically controlled processes which may be under the control of one or more gene(s) (41). However, resistance to infectious agents can also be influenced by various environmental factors. Management practices such as nutrition and housing (confinement versus free range) provide unique environmental stress factors (heat, air/water quality) which affect physiological parameters, including immune responses (51).

The age of an animal when exposed to the pathogen can also affect the immune response to pathogens. In livestock in Australia, for example, young calves have a lower resistance to respiratory and intestinal infections (viral and bacterial) and young sheep have a lower resistance to fleece rot, flystrike and gastrointestinal parasitic infections than more mature ruminants (16, 20, 21, 32). This lowered resistance has been characterised by hyporesponsiveness rather than increased pathogen burden.

Sexual maturity and castration/hormone treatment can also affect the immune response. Thus, genetic selection of resistant animals must address the changes which will occur during standard management practices in diverse production operations. The search to reveal those immunological parameters indicative of health status and increasing susceptibility has proved disappointing; however, these immunological parameters would most likely only represent another correlated phenotype rather than the genotype directly responsible for susceptibility.

Loci involved in resistance and susceptibility to infectious diseases

To investigate the loci involved in susceptibility to infectious disease, the mechanisms of such diseases need to be delineated. Laboratory models may not be applicable for this process since the mechanisms of colonisation and infectious process operational in the field and farm may be different from the parenteral injection of organisms. For instance, Fedorka-Cray et al. have demonstrated that the route of invasion may affect the pathogenesis of *Salmonella Typhimurium* infection (24). Hence, the incorporation of on-site studies which involve the normal infection of food animals with economically important pathogens into projects which identify chromosomal regions contributing to disease resistance will be essential.

The immune response associated with the host response to pathogens is a complex interaction of innate, specific and non-specific immune parameters (Table I) (41). This interaction involves the co-ordinate expression of cytokines during an inflammatory response for optimal clearing of the invading pathogen while minimising host tissue damage (22, 72). The possibility that the differential expression of specific cytokines may correlate directly with disease resistance phenotypes has been postulated (6). The genetic complexity which underlies infectious disease can also be illustrated by the knowledge that immune responses can be biphasic (49). Using a mouse model and bacillus *Bilié-Calmette-Guérin* (BCG) infection, Nadeau et al. demonstrated that natural resistance is initially controlled by the Nramp (natural resistance-associated macrophage protein) complex, whereas the latter stages of infection are controlled by major histocompatibility complex (MHC) polymorphism (49). Other lessons learnt from inbred mouse strains demonstrate that variation in inflammation can be observed in specific organ systems (respiratory system, central nervous system) and the scope of the response (quantitative) can be seen through cytokine variation.
Selection for production traits affecting immune responses

Although selective breeding for production traits has been successful in many instances, the process has also resulted in the emergence of unfavourable phenotypes. In many cases, selective breeding for increased production traits has compromised immune parameters of the individual (63). Lowered immune parameters were observed in turkeys selected for increased body weight (8). Increased milk production in Holstein cattle is associated with increased susceptibility to bovine leukemia virus infection and progression of the disease to a state of persistent lymphocytosis which results in lowered milkfat yields (19, 68). The compromised health status resulting from selection for increased production highlights the need to understand the genetics associated with each of these traits.

Table 1

<table>
<thead>
<tr>
<th>Types of resistance</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate resistance</td>
<td>Genes which control viral replication and those which encode receptors for pathogens (K88, Fv-1, IFN-α)</td>
</tr>
<tr>
<td>Non-specific immunity</td>
<td>Genes which regulate phagocyte uptake and killing (Nramp), genes which enhance the level and type of immune response (genes encoding cytokines and their receptors); and genes encoding complement proteins</td>
</tr>
<tr>
<td>Specific immunity</td>
<td>Genes encoding specific receptors which bind directly or indirectly to foreign antigens (TCR, IgH, MHC, TNF)</td>
</tr>
</tbody>
</table>

The level or specificity of host response in affording protection to pathogen infection is difficult to equate with in vitro measurements of immune responses (phenotypes). A related issue is the problem of selecting the stage during an infection at which to measure the immune response. As the majority of experimental observations are made late during the infection, it is not unexpected that certain immune parameters resulting from the progressing infectious process are lower than those found in control groups. However, the responses measured may not necessarily be the reason for the failure of the host to control and contain the infection. Those events undoubtedly occur earlier in the infection as a result of post-receptor/recognition steps which are highly regulated by several genes, thus complicating the identification of specific genetic components which contribute to host resistance.

Enabling technologies

Novel approaches to modify disease resistance or susceptibility in livestock are justified not only for economic and animal welfare reasons, but also through recent advances in molecular technologies (47). The control or elimination of infectious pathogens in farm animals has been achieved in the past by the use of vaccines, drugs, quarantine and eradication. However, new molecular approaches are emerging which will aid in understanding host responses to pathogens and the control and elimination of infectious pathogens.

Global gene mapping projects for swine, cattle, sheep and poultry have been highly successful. Landmark achievements include the identification of highly informative microsatellite markers and the integration of physical and linkage maps through collaborative workshops (9, 54). Furthermore, germline knockout mice have demonstrated that impaired inflammatory and immune responses, as well as lethal responses, can be attributed to the removal of a single gene. For instance, interferon-γ (IFN-γ) knockout mice are susceptible to sub-lethal Mycobacterium tuberculosis challenge, and tumour necrosis factor receptor 1 (TNFR1) knockouts are 1,000-fold more susceptible to Leishmania challenge (17).

Comparative genomics

Host resistance to infection appears to be controlled by numerous genes (45). A first step in determining which genes are involved in resistance is to establish a clear map location for loci which confer host resistance. Comparative gene maps are important tools for establishing such locations. These maps assist in the integration of mapping information between species, and can accelerate the identification of potential candidate genes which may contribute to phenotypes (5, 50, 64).
New polymerase chain reaction (PCR)-based technologies permit the rapid genotyping of candidate genes associated with immune responses, such as the MHC (61) and cytokines (6). High resolution genetic maps have been developed for economically important animals using highly polymorphic microsatellite loci (short tandem repeats which are easily detected by PCR) as well as expressed genes. These high resolution maps allow the association between chromosomal position and phenotype to be established. Thus, with rapid genome scanning of herds and flocks of animals, loci segregating with disease resistance can be identified. Such genetic information can then be incorporated into traditional breeding selection indices. As more information becomes available through gene mapping efforts, the means to access and distribute that information becomes an important issue.

Informatics systems will be required to provide insights into specific market needs for improved livestock which confer disease resistance, as well as needs for other production traits. Management practices will thus need to consider new approaches towards investigating decision-making processes among seedstock producers, farmers, processors, retailers and ultimately the consumer (65).

Marker-assisted selection for improving herd health

Changes in the agricultural industry towards large-scale vertical integration and increased global competition have stimulated the need for superior germplasm. This germplasm should contain the alleles essential for genetic enhancement of quantitative traits which will provide a strong return on-investment for seedstock companies and commercial producers. Quantitative traits, such as susceptibility and resistance to disease, are high priorities for both producers and consumers.

The process of genetically improving seedstock quality through the use of genetic markers requires knowledge of marker-identified chromosome loci which contain the genes effecting quantitative traits (Fig. 2). The identification of chromosome loci responsible for QTL, however, first requires the identification of genetic variation of the QTL of interest (Table II). This variation may be under genetic control at many different levels: between species, between races, breeds and lines of single species and between individuals (31).

Genetic variation in host response to nematode infection has been observed in various sheep breeds (2, 3, 10, 11, 30, 55, 73). Cauble breeds also exhibit different responses to trypanosomiasis infection. In this instance, the N'Dama breed of cattle are known to be tolerant to large parasite burdens while the Boran breed are susceptible (48). Breed variation in resistance to parasites suggests that large-scale applications for reducing parasite infections can be initiated, as seen in the sheep industry in Australia (10, 71, 74).

In order to identify the genes responsible for the genetic variation in host response to pathogens, genetic markers which segregate with chromosomal segments which account for a significant portion of the genetic variance need to be developed (Table III). A growing number of production and development QTL have been identified as a result of gene mapping efforts in domestic animals. In dairy cattle, markers associated with horn development (26) and milk production (12, 27, 59) have been identified. In sheep, the callipyge locus is associated with hind limb muscle development and growth.
Table III
Genetic elements associated with resistance and susceptibility to infectious agents in humans and mice, and the chromosomal location
(34, 35, 36, 69)

<table>
<thead>
<tr>
<th>Genetic element</th>
<th>Trait</th>
<th>Human Chromosomal location</th>
<th>Mouse</th>
<th>Cattle</th>
<th>Sheep</th>
<th>Pig</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nramp (Lsh and Beg)</td>
<td>Resistance to intracellular pathogens</td>
<td>2q35</td>
<td>1</td>
<td>2</td>
<td>2q41-q42</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mva</td>
<td>Influenza resistance</td>
<td>21q22.3</td>
<td>15</td>
<td>-</td>
<td>13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Xid</td>
<td>X-linked immunodeficiency</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IGH</td>
<td>Common variable immunodeficiencies</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TNF</td>
<td>Cerebral malaria, tuberculosis, malarial anaemia and leishmaniosis</td>
<td>6p21.3</td>
<td>17</td>
<td>-</td>
<td>7</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>FY</td>
<td>Resistance to malaria</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GSPD</td>
<td>Resistance to malaria</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
| HLA             | Resistance to malaria                      | 6p21.3                      | 17    | 23     | 20   | 7  | 20 |}

Nramp: natural resistance-associated macrophage protein
Mva: mutated viral antigen
Xid: X-linked immunodeficiency
IGH: Immunoreactive growth hormone
TNF: tumour necrosis factor
FY: Duffy blood group system
HLA: human leucocyte antigen
X: X chromosome
-: not available

(15), while in pigs, several associations between genetic markers and coat colour, growth and carcass characteristics have been identified (4, 14, 37, 57, 75).

The 21st Century: implications and opportunities

Biotechnology shifts the paradigm within which daily existence occurs. The historic human paradigm of the family farm is challenged by the need to feed an ever-increasing world population under diverse management and climatic conditions. Human evolution has advanced through the ability of mankind to harness the intrinsic genetics of plants and animals, through domestication and selection. The integration of bioinformatics and biotechnologies into integrated production systems will provide increasing opportunities to select animals for both superior production traits and disease resistance. Development of management systems (PigCHAMP™ and PigMON™) (63) and gene mapping databases will provide information which can be readily incorporated into real-time selection indices. Trademarked proprietary germplasms of cloned genetically identified and/or germline manipulated seedstock resulting from emerging methodologies, such as high throughput genotyping and animal cloning technologies, are also visible on the horizon (65).

During the coming years, research in animal production will continue to focus on unravelling the genetic components of disease resistance. Additional information on disease resistance, gene mapping and marker development related to animal production can be obtained from the Food Animal Biotechnology Center (http://fabctr.umn.edu).

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Vers une compréhension de la résistance génétique aux maladies infectieuses

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Résumé
La résistance génétique aux maladies revêt un intérêt tout particulier pour les espèces animales et végétales jouant un rôle important en agriculture. La sélection de plantes, animaux et insectes résistants à certains agents pathogènes montre que la résistance et la sensibilité à ces agents sont déterminées à la fois par des facteurs génétiques et environnementaux. Les loci intervenant dans la sensibilité ou la résistance immunitaire aux maladies sont actuellement inconnus. Toutefois, les nouvelles technologies moléculaires pourraient permettre d’élucider, d’une autre manière, les mécanismes génétiques de la réponse de l’hôte aux maladies infectieuses puis de sélectionner les gènes correspondant à la résistance.

Mots-clés

Desentrañar la clave genética de la resistencia a los agentes infecciosos

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Resumen
Los aspectos genéticos de la resistencia a la enfermedad constituyen un campo de gran interés por sus aplicaciones en especies animales y vegetales de importancia agrícola. La selección de plantas, animales e insectos resistentes a patógenos ha demostrado que la resistencia y la sensibilidad a los agentes infecciosos dependen de factores tanto genéticos como ambientales. Hoy en día se ignora cuáles son los loci inmunológicos que intervienen de manera causal en la sensibilidad y la resistencia a la enfermedad. Sin embargo, es de prever que las novedosas y potentes técnicas de biología molecular ayuden a encontrar nuevas vías para desentrañar los mecanismos genéticos de la respuesta del huésped a las enfermedades infecciosas y, en última instancia, a mejorar la genética de los ejemplares reproductores.

Palabras clave
Enfermedades animales – Genética – Resistencia a la enfermedad – Sensibilidad.
References


