

Genetic Selection for Disease Resistance: Challenges and Opportunities

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Animal health and well being have become increasingly important issues for animal producers and consumers. Animal diseases causing morbidity and mortality significantly decrease profitability of animal production. Antibiotics that were once widely used to prevent or treat animal diseases are now administered more judiciously because of consumer fears of residual drugs in meat products and microbial resistance to commonly used antibiotics. Because no new class of antibiotics has been developed in the past three decades, the continued use of antibiotics may become more limited. Also, there has been an emergence of previously unknown diseases such as BSE (Binder et al., 1999) and emergence of infectious diseases in domestic livestock related to climatic changes, more intensive production, and transmission of diseases from wildlife to livestock and vice versa (Daszak et al., 2000). Current fear of a worldwide human influenza pandemic caused by transmission of avian influenza virus to humans has increased public awareness of a need to control animal diseases (Wong and Yuen, 2006). Therapeutic treatment costs for sick animals have continued to increase. Animal well being has become a significant concern among consumers who expect food animals to be well treated, raised in idyllic environments, and free of disease. Consumers also expect their meat products to be free of residual antibiotics and therapeutic drugs.

For these reasons, new approaches or alternatives to addressing animal diseases are needed. One approach is genetic selection for animals resistant to disease. It has been well established that rarely will all animals in a population, when exposed to an infectious

disease, exhibit clinical symptoms. Breed differences for disease related traits have been documented in many different species (i.e., pinkeye incidence in cattle, Snowden et al., 2005a; bovine respiratory disease (BRD) incidence in cattle, Muggli-Cockett et al., 1992; Snowden et al., 2005b, 2006; *Bordetella bronchiseptica* infection in swine, Rothschild et al., 1984; immune response in chickens, Zekarias et al., 2002). However, it is difficult to determine why some animals become sick while others remain healthy. Animal health is influenced by many factors including genetics, nutrition, age, stress, management system, season, pathogen dosage, immunological background, epidemiology, animal biological status, and many other variables. These factors interact, thus confounding our ability to understand the mechanisms of disease resistance.

Challenges of Selecting for Disease Resistance

Identifying the phenotype for disease resistance is difficult. It is a false assumption that in a population of sick and healthy animals all healthy animals are disease resistant. Some susceptible animals may not have been sufficiently exposed to the disease organism to get sick. Animals that appear healthy may have sub-clinical infections and represent pathogen reservoirs. Often the clinical expression of a disease can be confounded with a similar disease; for example pneumonia can be confused with bronchitis, emphysema, pleuritis, pulmonary adenomatosis, upper respiratory infection, and pleural fibrosis. Accurate disease diagnosis is costly and time consuming. The success of selection for disease resistance is

dependent on correctly identifying the phenotype for disease resistance.

Selection for disease resistance is much more complicated than selecting for production traits which can be measured directly or indirectly on each animal. In regards to selecting for disease resistance in livestock, it may not be ethical or cost efficient to challenge each animal with a pathogen to determine its level of disease resistance. (Alternatives to this selection approach will be discussed later.) Before breeding schemes for disease resistance can be developed, consideration of many different scientific areas such as microbiology, epidemiology, immunology, host-pathogen interaction, host biology, livestock production systems, etc., must be understood. For example, selection for animals resistant to a particular pathogen may result in indirect selection for a more virulent pathogen or, development of highly resistant animals to one specific pathogen may make the animals more susceptible to another pathogen. Keeping the host's immune defense system in homeostasis may be difficult. Also, selection for immunity without leading to autoimmunity may be a difficult balance to achieve.

Justification for including disease resistance in breeding programs can be challenging to establish. Most importantly, the economical cost of the disease must be sufficiently high to rationalize selecting for resistance. Certainly, if consumers shun a product because of its potential health threat from antibiotic residue or non-treatable communicable diseases (i.e., BSE, Avian Influenza) then selection may be a favorable alternative. If antibiotics and other drugs have become inefficient because of microbial resistance, selection for disease resistance may be logical. Genetic selection for disease resistance may be useful against diseases for which neither vaccines nor therapeutics have been found. Selection may also be of interest for diseases due to a variety of pathogens infecting the host in a similar manner or pathway. Organic meat production

systems that cannot use vaccines or therapeutics may also find it economically important to select for disease resistance.

However, selection for disease resistance may be unfavorable for animal production. If the genetic factors that improve disease resistance reduce production traits such as growth or feed efficiency then selection for disease resistance will decrease production. There is sufficient evidence that such negative genetic correlations do exist. Milk yield in dairy cattle has a positive correlation with many disease traits (Simianer et al., 1991; van Dorp et al., 1998). Selection for growth rate in turkeys increased their susceptibility to Newcastle disease (Sacco et al., 1994). In beef cattle, the genetic correlations of disease resistance with growth and feed efficiency traits are unknown. If these genetic correlations are unfavorable, then a selection index for total merit may be feasible to maintain production levels while selecting for disease resistance.

Perhaps, the biggest challenge of selecting for disease resistance is to accurately identify the phenotype for disease resistance and/or to have reliable genetic markers with high predictive values for a disease phenotype. For some diseases, disease resistance may include sub clinical and clinical infection while for other diseases only the clinical expression may be considered.

The objective of this review is to briefly summarize the genetics of disease resistance and to offer a broad understanding as to whether it is feasible to select for disease resistance or not.

Understanding the Immune System

Knowledge of the mode of disease infection and host response is essential to comprehend the complexity of selecting for disease resistance. A simplistic explanation is given here. First, the pathogen must be present in the host's environment. The pathogen must penetrate host cell barriers in sufficient numbers, attack target

cells and replicate. Sub-clinical or clinical expression of the disease is dependent on the pathogen's virulence and the interaction between pathogen and host characteristics.

The host has three immune defenses against infection: natural, innate, and acquired immunity. To maintain health all three must be present and functioning.

Natural immunity is the first barrier and is comprised of skin, hair, mucous membranes, secretions (tears, urine, stomach, saliva, mucous, skin secretions, etc.), grooming behavior (licking, dust rolling, tail swishing, etc.) and favorable microorganisms that compete directly or indirectly against pathogens. There are also nutritional components to natural immunity. Dehydration and malnutrition can decrease natural secretions making some tissue more susceptible to infection. Vitamin and mineral deficiencies result in suppressed immune systems. Genetic components to natural immunity are being identified as well. For example, some pigs are fully resistant to bacteria-induced diarrhea (*E. coli*) because they lack an intestinal cell receptor for the bacteria to attach (Gibbons et al., 1977). Fly infestation of livestock can be affected by hair/wool length, skin secretions, and hide thickness.

Innate and acquired immunity are co-dependent and form a complex network of cells and tissues that interact to detect and attack pathogens or associated antigens. The innate immunity refers to the immune system one is born with and is the initial response by the body to eliminate microbes and prevent infection. It commonly involves white blood cells (natural killer cells, neutrophils, eosinophils, monocytes, and macrophages), complement proteins (C1 - C4) that adhere to pathogens, and cytokines (interferons and chemokines) that attract immune cells to the site of infection. The innate immune system constantly searches for antigens (bacteria, fungi, and viruses). When an antigen is discovered, the innate system can attack it or illicit inflammation to attract immune cells. The

innate system is not specific to any one type of pathogen and has no memory of previous exposure to a pathogen or antigen. Breed differences in the innate immune system have been reported. A higher haemolytic complement activity in *Bos indicus* breeds was associated with their higher resistance to tick infestation and subsequent tick borne diseases when compared to *Bos taurus* breeds (Wambura et al., 1998).

The acquired immune system is developed from previous exposure to pathogens or vaccines and can recognize pathogens previously exposed to. Acquired immunity is antigen specific. There are two types of acquired immunity: the cell-mediated immunity is comprised of immune cells that directly attack pathogen infected cells, and the humoral immunity which is made up of antibodies (specific immune proteins) that are directed at the pathogens themselves. The acquired immune system is comprised of T and B cells, which are specialized white blood cells. The T cells destroy pathogen-infected cells. The B cells develop into specific antibody-producing cells.

Acquired immunity occurs in two forms: passive and active. Passive or maternal immunity is passed from the cow to the calf via colostrum containing high levels of antibodies. Passive immunity is temporary. Disease resistance of very young calves is highly dependent on passive immunity. This type of protection is short lived because soon after birth, the calf's intestinal tract has a significant reduction in its ability to absorb immunoglobulins (antibodies), and the cow's production of colostrum decreases as lactation progresses. Half of the colostrum antibodies absorbed by the calf will be excreted, broken down, or absorbed at 8 to 16 days postpartum and most will be gone by 30 to 60 days postpartum (Besser et al., 1988). There are genetic components of passive immunity in cattle and recently, DNA markers associated with failure of passive immunity have been reported (Laegreid et al., 2002; Clawson et al.,

2004). Therefore, it is important that the calf's own immune system (active immune system) develops at an early age to produce cell-mediated immunity and antibodies in response to antigens and vaccines to take over when passive or maternal immunity diminishes.

Genetic Selection for Disease Resistance

From a genetic perspective, understanding the natural, innate, and acquired immune systems is crucial in developing selection programs for disease resistance. For example, if the breeding goal is to reduce bacterial diarrhea in young calves, then selection traits might include the dam's genetic potential for producing specific colostrum antibodies (passive immunity) and the calf's genetic potential for developing an innate and acquired immune system early in life that responds to the diarrhea causing pathogen. There may be further problems because negative genetic correlations between the dam and calf resistance to some diseases have been estimated (i.e., BRD, Snowden et al., 2005b).

Selection for disease resistance is costly. Potential costs associated with measuring disease resistance include reduced production, mortality, decreased longevity, diagnostic costs, and therapeutic expenses.

Direct selection for disease resistance can occur in three different scenarios (Rothschild, 1998). First, animals may be observed in a given production system or environment for lack of clinical expression of a disease. Under this selection approach, it is assumed that the disease pathogen is constantly present. However, the expression of disease resistance is questionable. Animals with clinical expression of the disease may be identified with relative accuracy but not all healthy animals may be exposed to the pathogen or challenged equally. Also, disease exposure in natural environments is subject to temporal and spatial clustering of disease incidence. Diseases often occur in clusters of time (years, seasons, production cycles, etc.) and space (herd, pasture, farm, region, etc.). In

years when the disease incidence is high, there can be an increase in the accuracy of identifying animals with a high probability of being disease resistant but in years of low incidence the accuracy will be diminished (Snowden et al., 2005b). The second direct approach is to uniformly challenge all breeding stock with infection. This approach can be costly depending upon the pathogen's virulence and clinical expression of the disease but is a reliable measure of disease resistance. This may require isolation of the population to prevent transmission to non-breeding stock. A third approach is to challenge relatives or clones of the breeding stock, especially if the disease has a high mortality rate. This latter approach is also a reliable method of determining genetic resistance. The latter two approaches are not without error because immunological background (previous exposure to the pathogen) may vary among animals. Researchers will have to determine the significance of immunological background for biasing the observed animal response to a disease challenge. In cattle, direct selection for reducing brucellosis had a favorable response. Templeton et al., (1990) increased natural resistance to brucellosis in calves from 20% to 59% after breeding cows to a naturally resistant bull.

Ideally, such direct approaches of phenotyping animals for disease resistance would take place in a highly controlled and isolated environment. This is probably not practical for cattle associations but publicly funded institutions may develop such testing facilities in the future.

Indirect selection for disease resistance can also be achieved by selecting for indicators of disease resistance. Indicators of disease resistance include pathogen products (i.e., pathogen reproductive rates, pathogen by-products), and biological or immunological responses of the host. One of the most successful approaches of indirect selection for disease resistance has been reported in sheep by selecting for low fecal internal parasite egg

count (Woolaston et al., 1992). In dairy cattle, somatic cell count has been used as a selection criteria for reducing mastitis (Shook and Schutz, 1994). Immune responsiveness, challenging an animal with an antigen or vaccine and measuring antibody response or production, has been useful in poultry (Lamont et al., 2003) and swine (Mallard et al., 1992). Hernandez et al. (2003) suggested that immune responsiveness would be a useful indicator of disease resistance in cattle. Selection for immune response is generally beneficial when a single disease is targeted. However, studies in swine have indicated that selection for immune responsiveness can improve disease resistance to other diseases while, at the same time, increasing susceptibility to others (Wilkie and Mallard, 1998). For effective selection, indicator traits must be heritable, highly genetically correlated with resistance to the disease or diseases of interest, accurate to measure, and affordable.

Interactions between the genetics of the animal and the environment commonly exist. If the genetic by environmental interaction is significant, animals selected for improved disease resistance in one environment may be more susceptible to the same disease in a different environment. Therefore, selection programs may have to be environment specific with the selection environment matching the commercial production environment.

Gene Mapping

Sequencing of the mice and human genomes, and construction of similar maps in livestock have led to discovery of several genetic markers and even genes related to the immune system. Most genes related to disease resistance have been discovered using inbred strains of mice. Only a few genes have been linked to disease resistance in cattle. The *Nramp1* gene (natural resistance-associated macrophage protein) is associated with the innate immune system. *Nramp1* has been linked with resistance to brucellosis (Harmon et al., 1989), tuberculosis,

and salmonellosis (Qureshi et al. 1996). Homologues for *Nramp1* have been identified, sequenced and/or mapped in chickens, swine, and sheep (Adams and Templeton, 1998).

The major histocompatibility complex (MHC) genes are linked to specific immunological responses. MHC genes were some of the first mapped and sequenced genes related to disease resistance. The MHC have a high degree of polymorphism, more than one variant (allele) for a gene exists in a population. Over 50 MHC alleles have been identified (Adams and Templeton, 1998). The high degree of polymorphisms for MHC genes which is unique for each individual (over 100 million combinations possible) partially explains how the host immune system can attack such a great number of antigens which requires the ability to distinguish self from foreign. In dairy cattle, the bovine MHC complex has been linked to disease resistance of economically important traits (Batra et al., 1989). In chickens, MHC has been linked to resistance to Marek's disease and fowl cholera (Lamont, 1989).

Other examples of recently discovered single genes influencing disease resistance in livestock include the fimbriae F4 (K88) gene in swine for reducing *e. coli* intestinal infection (Moon et al., 1999), the prion protein (PrP) gene related to scrapie susceptibility in sheep (Bossers et al., 1996), and the TNC gene related to salmonellosis in chickens (Hu et al., 1997).

Polygenic Effects

The complexity of the immune system clearly infers that many genes are involved in disease resistance. It is highly doubtful that many single genes will be discovered and associated with major diseases. Chromosome mapping may lead to quantitative trait loci or regions related to disease resistance. Most recently, a region on chromosome 1 was associated with infectious keratoconjunctivitis (pinkeye) in cattle (Casas et al., 2006).

As the human and mice genomes are further investigated for disease related genes, it is highly plausible that quantitative trait loci (QTL) associated with disease resistant in livestock may also be identified in the near future. New and novel gene mapping approaches are being developed specifically for detection of complex disease loci (Pareek et al., 2002). Micro array technology is advancing rapidly to enable association of livestock DNA with human (Chitko-McKown et al., 2004) and mice DNA. Comparative genomics may make the identification of disease loci easier and more affordable. It may be possible to identify similar genes associated with disease susceptibility/resistance among human, mice, and livestock.

The Near Future

We do not know at this time to predict whether or not selection for disease resistance can be effective in livestock. Basic research into the complexities underlying diseases will likely reveal effective approaches for many disease problems. For example, the discovery that contagious keratoconjunctivitis (pinkeye) is heritable (Snowder et al., 2005) led to the discovery of a chromosomal region associated with its disease incidence (Casas and Stone, 2006). In the near future, it is likely that selection for disease resistance in most livestock species, especially cattle, will not be widely accepted by industry because of the lack of knowledge about how best to select for disease resistance and poorly understood genetic correlations between disease resistance and economically important production traits. Selection for disease resistance will be disease dependent. It may be possible to select directly against the disease, select for indicator traits (indirect selection), to select directly for the gene(s) that confer resistance or some combination of these approaches. The potential seems great for identifying breeding stock that is healthier because of their immune responsiveness. Although it may be difficult to select for animals resistant to a wide range of

diseases, it may be possible to breed or identify animals that are genetically more responsive to anti-viral vaccines or other therapies.

Certainly, genetic selection will not solve all of our livestock disease problems. Therefore, management, nutrition, vaccination, culling, therapeutic treatment, stress reduction practices and other measures must accompany genetic approaches to reduce the impact of livestock disease on profitability and animal well being.

Other Research Efforts by Immunologists, Bacteriologists and Virologists

Because of the complexity of the immune system, many researchers in the field of immunology, bacteriology, and virology believe that gene sequencing of the pathogen will lead to a more rapid method of reducing disease incidence than genetic selection of livestock. Identifying and sequencing pathogen genomes may help identify pathways in the pathogen or host that can be interrupted to prevent disease or the development of a new antibiotic. Although this paper has been focused on the genetics of disease resistance in the host, genetic research on the pathogen may lead to the pathogen's Achilles heel.

For further reading on the genetics of disease resistance readers are referred to previous reviews (Warner et al., 1987; Malo and Skamene, 1994; Muller and Brem, 1994; Adams and Templeton, 1998; Rothschild, 1998; Dettileux, 2001; Stear et al., 2001; Pareek et al., 2002).

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