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Host resistance to bacterial infections

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Introduction

Infectious diseases are a major concern in modern swine production. In spite of current prevention and control methods, swine diseases continue to have a negative impact on growth, reproduction, and animal welfare. Resistance to several diseases has a documented genetic component that can involve immune or non-immune mechanisms. Selecting pigs that are resistant to disease will provide an alternative to the current methods of disease control.

Selection of resistant pigs will impact pig production in different ways. The most tangible benefit will be improved performance in the face of disease, i.e., lowering the cost of production. Other benefits include possible reduction in antibiotic use, which may reduce the risk of developing antibiotic resistance in human and animal pathogens. Pigs with reduced carriage of zoonotic pathogens could reduce endpoint bacterial contamination in carcasses, providing a new tool to enhance food safety programs. Disease resistance will also improve pig welfare under confinement as well as traditional management systems. In summary, the ability to select disease-resistant pigs will benefit pigs, producers, and, ultimately, consumers.

Evidence linking disease resistance and susceptibility with host genetics has been observed in inbred and outbred populations of humans[1], mice[2], cattle[3], poultry [4], and pigs[5]. These studies indicate that genetics are an important component in the capacity of the animal to respond to several pathological processes including infectious diseases.

Selection for disease resistance requires an understanding of the mechanisms of disease resistance.

Mechanisms of disease resistance

Microbial attachment

One of the most important mechanisms of resistance is related to the ability of the microorganism to initiate infection in the host, or in other words, the ability of the host to facilitate pathogen attachment. The lack of a receptor for K88 and F18 *E. coli* confers resistance to infection in pigs due to lack of attachment of *E. coli* to susceptible intestinal cells[6,7]. In both examples, single genes are responsible for the infection component of the disease. However, it is likely that several genes participate in the development of disease after infection. For example, it appears that more than one receptor may be involved in PRRSv infection of the macrophage, the target cell. Antibody-dependent enhancement supports the theory of the importance of the Fc receptors in viral entry into the target cell, and recent evidence indicates that other receptors may also be involved. This suggests that multiple genes may be involved in a single aspect of infection.

Many receptors involved in the pathogenesis of virus or bacteria are integral parts of important body functions. The Fc receptor may be an important mechanism for entry into alveolar macrophages during PRRSv infection but it is also the attachment site for the immunoglobulins, which are indispensable for immune functions of the host. Blockage of this site will likely have detrimental effects in the host. The removal of the receptor for Aujezsky's disease virus from the host had critical effects in fetal development. The FMD virus seems to have not one but multiple receptor sites for viral invasion and most of them are likely to be necessary for normal cell interactions in the host. Genes are not there to cause diseases—they usually have other important functions. Caution has to be exerted when evaluating if the absence of the gene has a negative effect. Selecting favorable genes or selecting out undesirable genes can be accomplished from current pig populations that produce satisfactorily.

Host responses

Generalized

Response to infection requires the cooperation of several components of the immune system. Immediately after pathogen invasion, innate immune mechanisms are crucial for control of the pathogen, and, as the disease progresses, cell immunity and antibody production become more relevant to control of the disease. To target general resistance, humoral, cell-mediated, and innate resistance factors have been combined in an immune index for selection in pigs[8]. Using the index, high and low responders were grouped and challenged with *Mycoplasma hyorhinis*[9]. High responders had higher serum antibody titers and less peritonitis, pleuritis, and pericarditis, but also had greater arthritis. This points out the com-

plexity of selecting for an appropriate immune response rather than simply and elevated response. Using the same index in an APP vaccination trial, the frequency of non-responders was smaller in the high responder group to some but not all antigens[9]. Pigs in the high responder group took fewer days to reach market weight. The use of indexes could be an alternative tool for selection for general resistance but more work is needed to see if the potential of this approach is realized in commercial settings. Targeting specific diseases with a specific index may be an interesting alternative.

Innate

Resistance in pigs can be associated with non-specific immune mechanisms. In mice, natural resistance to Salmonellosis is regulated by a single, dominant, autosomal gene initially called Bcg/lsh/ity (more recently denominated NRAMP). In addition to *Salmonella typhimurium*, the NRAMP gene also confers resistance to other antigenically distinct intracellular pathogens including *Mycobacteruium bovis* and *Leishmania donovani*. A second example of a non-specific immune mechanisms is the Mx gene. The Mx gene is a single automosmal dominant gene located in chromosome 16 in mice. The Mx gene is an interferon (IFN) inducible gene that confers resistance to strains of influenza virus. The gene is present in some inbred strains of mice, in particular A2G, in which the resistance trait was first noticed, but absent from the majority of laboratory strains. In addition to orthomyxovirus, the Mx gene also confers resistance to dhori virus and thogoto virus infections indicating that Mx protein has a broader spectrum of antiviral activity. The NRAMP and Mx genes are two examples where resistance is associated to non-specific mechanisms and with a broader spectrum of protection that include several pathogens.

Likewise, other non-specific components of the immune response such as IFNs, lysozymes, neutrophils, and complement production could be involved with a more generalized resistance mechanism.

Specific

Resistance can also be associated with specific immune mechanisms. The Major Histocompatibility complex, called SLA in swine, is part of the specific immune mechanisms in the pig, and is partly responsible for resistance to specific diseases. The MHC is a chromosomal region that includes a group of closely linked genes. It has been found that MHC haplotypes (that is how specific MHC genotypes are called) influence susceptibility to disease in chicken, man, horses, cattle, and pigs. In pigs, association between SLA haplotypes and complement levels[10], anti-lysozyme responses[11], bacterial phagocytosis and killing[12], cell-mediated responses[13], and responses to vaccination against several antigens[14] have been reported. SLA has been also linked to disease processes like malignant melanoma[15] and susceptibility to *Trichinella spiralis* infection[16].

One of the best-documented associations between MHC and susceptibility to disease in found in Marek's disease in chicken. Specific MHC haplotypes are clearly associated with susceptibility to Marek's disease[17]. Although, MHC haplotypes make a substantial contribution to resistance to Marek's disease, other genes also contribute to resistance. In the case of Marek's, it is probable that a significant element of genetic resistance, whether MHC-associated or not, results from control of viral replication in the early stages of infection.

The MHC is an important region to target for disease-resistance studies and warrants further investigation. For practical purposes, selection of specific MHC haplotypes could bring up some complications. It is generally believed that the great variation naturally found in the MHC region is an evolutionary advantage. From the population point of view (rather than from that of the individual) the advantage of the variation in the MHC region is related to protection against a wide rage of pathogens ensuring survival of at least some animals and continuation of the species. Therefore, selection base on specific MHC haplotypes needs to be evaluated carefully. An alternative to selection of favorable MHC haplotypes could be the removal of some haplotypes associated with susceptibility to lessen the impact of a particular disease.

Natural selection of resistant genes

So why haven't genes that have detrimental effects related to disease disappeared? One hypothesis could be that different versions of genes rise and fall driven by the rise and fall of diseases. Or, perhaps, because newer diseases have not been around long enough (in evolutionary terms) to exert such a pressure to select out those susceptible genes, they are still there. It is probable that human control on pig farms interferes with "natural selection". Pigs that will provide the gene pool for succeeding generations are not selected by survival therefore there is no real evolutionary pressure. An alternative explanation is that there is a constant turnover of genes without adaptive significance. One issue of concern with regard to selecting for disease resistance is the possibility that the pressure put on pathogens by the presence of resistance pigs will mean that pathogens will evolve to overcome resistance. Experience with massive vaccination, where a lot of pressure is put on a pathogen, as with polio in humans, did not necessarily end in strains turning more virulent. This is an area that has to be carefully considered.

Practical implications

Breeding for disease resistance requires tools such as indicator traits or genetic markers that can be used for se-

lection. Common approaches used to identify these traits/ markers include comparative genetics, candidate genes, in vitro tests, genome-wide analysis, transgenics, genomics, and proteomics.

Selection for disease resistance has been implemented in various domestic species, including Marek's disease in chicken, nematode parasites and scrapies in sheep, and mastitis in cattle. In swine, susceptibility to *E. coli* neonatal diarrhea is inherited by a dominant receptor allele to K88 that maps to chromosome 13[6]. For *E. coli* edema disease, susceptibility is dominantly inherited and the locus maps to chromosome 6. Variation (called polymorphism) in the FUT1 gene co-segregates with *E. coli* F18 adhesion. The polymorphism is due to a mutation at the bp 307[7]. The FUT1 is a good marker for selection of resistant pigs.

For those particular farms where edema disease represents a problem the percentage of resistant pigs can be improved by incorporating a higher number of pigs lacking the susceptible genes. Management practices, diet modification, vaccines, and antibiotics are use to control death loss but not to eliminate the disease.

How can resistant genes be introduced in a herd?

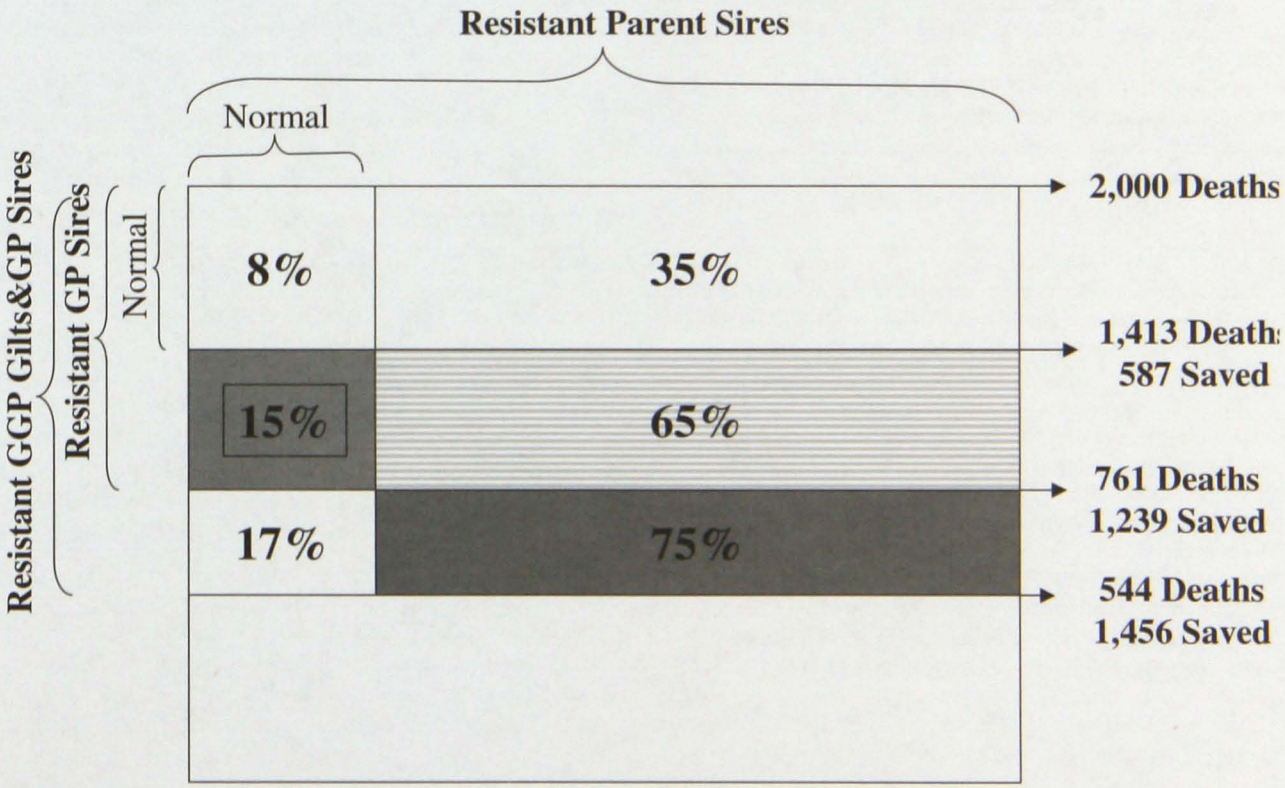
The introduction of resistant genes in a herd depends on weather the gene is dominant or recessive, the frequency of resistant genes in the current population, and the percentage of resistant animals required in the herd. In **Figure 1**, I explore the ways that resistance genes can be introduced in a herd using an example scenario with Edema disease.

To determine what proportion of the pig population should be resistant to a given disease, theoretical models could be created. The models should take into consideration the transmission of the disease through populations that show variations of host genotype. It may not me necessary to have 100% of the herd be resistant. Presumably, a higher proportion of resistant pigs may be needed for diseases that are highly infectious.

Conclusion

It is possible to detect animals that are resistant or that show reduced susceptibility to diseases. DNA and/or in vitro markers will become the tools for selection of supe-

Figure 1. Benefits of introduction of resistant F18 *E. coli* genes



Example scenario of a 1,000-sow herd operation producing 20 p/s/y and total nursery death of 10%. The farm has a frequency of 8% of resistance genes under normal conditions. Options: Use all F18 R (resistant) parent sires or semen, or b) Use F18 R GP sires or semen from the maternal side and c) Use F18R GGP gilts and GP sires.

rior pigs. Molecular technology is promising, particularly for resistance mechanisms controlled by single genes. Work is in progress to understand polygenic resistance mechanisms in pigs. Pigs resistant to specific disease may be used for specific herds with specific problems. In the upper layers of the breeding pyramids, selection for disease resistance can become another selection trait with an economic value attached to the overall estimated breeding value index of a pig. Selection for disease resistance is becoming a reality for disease control in swine.

References

1. Bellamy RJ, Hill AVS. Host susceptibility to human tuberculosis. Proceedings of Novartis Fundation Symposium (1998): Wiley, Chichester, 3-23.
2. Bumstead N. Genetic resistance to avian viruses. Review of Scientific Technology Office of International Epizootics (1998): 17 (1), 249-255.
3. Skamene E, Gros P, Forge A, Kongshawn PAL, St Charles C, Taylor B. Genetic regulation of resistance to intracellular pathogens. Nature (1982): 297,506-509.
4. Feng J, Li Y, Hashad M, Schurr E, Gros P, Adams LG, Templeton JW. Bovine natural resistance associated macrophage protein 1 (Nramp1) gene. Genome Research (1996): 6, 956-964.
5. Hutt FB. Genetic factors influencing atrophic rhinitis in the pig. In Genetic resistance to disease in domestic animals. Comstock, Ithaca, NY. Animal Production (1958): 30,277-283.
6. Sellwood R. Escherichia coli diarrhoea in pigs with or without the K88 receptor. Veterinary Record (1979): 105,228-230.
7. Meijernk E, Fries R, Vogeli P, Masabada J, Wigger G, Stricker C, Neuenschwander S, Bertschinger HU, Stranzinger G. Two alpha fucosyltranferase genes on porcine chromosome 6q11 are closerly linked to the blood group inhibitor (s) and Escherichia coli F18 receptor (ECF18R) loci. Mammalian Genome (1997): 10,736-741.
8. Mallard BA, Wilkie BN, Kennedy BW, Quinton M. Use of estimated breeding values in a selection index to breed yorkshire pigs for high and low immune and innate resistance factors. Animal Biotechnology (1992): 3, 257-280.
9. Magnusson U, Wilkie BN, Mallard, BA., Rosendal S, and Kennedy B. Mycoplasma hyorrhnis infection of pigs selectiverly bred for high and low immune response. Veterinary Immunology and Immunopathology (1998): 61, 83-96.
9. Magnusson U, Bosse J, Mallard BA, Rosendal S, Wilkie BN. Antibody response to Actinobacillus pleuropneumoniae antigens after vaccination of pigs breed for high and low immune response. Vaccine (1997): 15(9),997-1000.
10. Vaiman M. Hauptman G, Mayer S. Influence of the major histocompatibility comples in the pig (SLA) on haemolytic complement levels. Journal of Immunogenetics (1987a):5, 59-63.
11. Vaiman M, Metzger JJ, Renard C, Vila JP. Immune response genes(s) controlling the humoral anti-lysozyme response (Ir-Lys) linked to the major histocompatibility complex SL-A in the pig. Immunogenetics (1987b): 7:231-238.
12. Lacey C, Wilkie BN, Kennedy Bw, Mallard BA. Genetic and other effects on bacterial phagocytosis and killing by cultured peripheral blood monocytes of SLA-defined miniature pigs. Animal genetics, (1989): 20, 381-382.
13. Mallard BA, Wilkie BN, and Kennedy BW. Genetic and other effects on antibody and cell mediated immune response in swine leucocyte antigen (SLA)-defined miniature pigs. Animal Genetics (1989): 20, 167-178.
14. Rothschild MF, Chen HL, Christian LL, Lie WR, Venier L, Cooper M, Briggs C, Warner CM. Breed and swine lymphocyte antigen haplotype differences in agglutination titers following vaccination with B. bronchiseptica. Journal of Animal Science (1984): 59,643-649.
15. Banglero J, Tissot RG, Beattie CW, and Amoss MS. Genetic determinants of cutaneous malignant melanoma in Sinclair swine. British Journal of Cancer (1966): 73, 667-671.
16. Lunney JK Murrel KD. Immunogenetic analysis of Trichinella spiralis infection in swine. Veterinary Parasitology (1988): 29, 179-193.
17. Cole RK. Studies on genetic resistance to Marek's disease. Avian Disease (1968): 12, 9-28.