PROGRESS AND PROSPECTS IN RESISTANCE TO DISEASE

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SUMMARY

Research on resistance to disease and its applications fall into four overlapping epochs: (I) Starting from the 1930's, genetic variation in resistance to disease had been recognized and feasibility of genetic selection for resistance demonstrated. Estimates of genetic parameters indicated that selection for resistance to specific pathogens had good prospects. (II) Subsequently, progress in the understanding of resistance mechanisms resulted in practical applications, such as indirect selection for resistance based on haplotypes of the major histocompatibility complex. (III) More recently, molecular genetics started to elucidate the DNA bases of disease resistance traits e. g. by gene cloning and identification of quantitative trait loci within resistance polygenes. (IV) First experiments in genetic engineering of new resistance mechanisms indicate potential usefulness of this approach. It is concluded that considerable progress in disease resistance has been achieved at both the scientific and practical levels. Conventional breeding methods will remain the principal approach to improvements of resistance to disease but in some instances, genetic engineering of resistance mechanisms will be justified. Genetic resistance will gain importance as the most environmentally desirable method of disease control.

Key words: *Genetic resistance to disease*

INTRODUCTION

World population is increasing by some 80 million annually and 30 million tonnes of additional staple foods are required just to meet the demand created by the increase. Despite all advances in disease control, significant economic losses due to disease persist in poultry production. For example, even with successful vaccination programs, Marek's disease alone causes global losses of about US $ 1 billon annually (Purchase 1985). Elimination or reduction of mortality and decreased performance due to disease leads to increased production without a need for additional resources and such increase can contribute towards meeting the rising demands. Hence the interest in disease prevention and control persists throughout the world.

Methods of disease prevention and control available to the poultry industry can result in either complete elimination of a pathogen from poultry populations or introduction of disease tolerance that allows birds to function and produce despite of pathogen presence. Either outcome can be accomplished by genetic and non-genetic means. A pathogen can be eliminated by eradication or by genetic change in the host making the host resistant to infection. To induce disease tolerance, poultry can be vaccinated or bred for an ability to minimize effects of the pathogen on performance and survival.

Parasitism in the broad sense is so widespread in nature that every organism is either a parasite or a host, or both. Host-parasite relationships should be viewed as co-evolutionary systems. A disease of the host is not an evolutionary goal of the parasite. From the evolutionary point of view, a balance of the host and its parasite is preferable to incompatibility. There is no selective advantage to the parasite in making the host ill, unless the disease aids in the transition of the parasite to new hosts, such as in the case of diarrhoea. It has been pointed out that highly virulent parasites that often result in epidemics and pandemics are those that became associated with the host relatively recently (Klein and O'Higin 1994). Parasites associated with the hosts for evolutionarily longer periods would tend to result in harmless subclinical infections, although there is evidence that some subclinical infections may cause significant economic losses (Gavora 1980). An important aim of poultry breeders is to upset the balance of host-parasite systems in favour of the host.

Work on genetic resistance to disease in poultry has been, perhaps because of the suitability of birds as an experimental model, in the forefront of such efforts in livestock. This communication will review disease resistance genetics in poultry and approaches to its study and improvement by dividing the past, present, and future developments of this area into four overlapping epochs: (I) Evidence for the existence of genetic variation in resistance to disease, quantitative genetic analysis of resistance, and conduct of selection experiments. (II) Search for and studies of mechanisms underlying disease resistance, particularly in immunology and development of indirect selection for resistance. (III) Studies of molecular bases of resistance to disease, mapping of resistance genes and marker assisted selection. (IV) Genetic engineering of new disease resistance mechanisms.

I. GENETIC VARIATION, GENETIC PARAMETERS, SELECTION EXPERIMENTS

Early evidence of genetic variation in resistance to disease emerged in the early thirties from research on Marek's disease (MD), a viral lymphoproliferative disease of chickens (Asmudson and Biely 1932), and salmonellosis (Hutt 1935). Hutt's and Cole's (1947) demonstration that resistant and susceptible chickens can be selected using natural exposure to the MD virus marks the start of similar selection studies over the next 40 years. Because of its economic importance, MD remained the focus of these studies. Rapid response to such selection provided evidence, now supported by immunogenetic data and gene mapping, that a large portion of genetic variation in MD resistance is likely based on relatively few genes (Cole 1968). It was also shown that simultaneous selection for MD resistance and egg production traits is feasible (Gavora and Spencer 1983).

Gavora (1990) reviewed estimates of heritability of general viability and resistance to specific diseases and found that heritability of the rather poorly defined trait "total mortality" is low - generally less than .1, while heritability of resistance to specific diseases is higher, e.g. .06 to .67 for MD, .07 to .17 for Newcastle disease, and .06 to .26 for resistance to mites. Similarly reviewed estimates of genetic correlations of viability and disease resistance traits with production characteristics were generally favorable when considering selection in egg chickens, while there were indications that selection for rapid growth may reduce MD resistance.

This period marks the beginning of efforts by commercial breeders to include selection for disease resistance in their breeding programs. Besides selecting for general viability, breeders also included selection for resistance to MD, based on MD challenge tests of sibs or progeny. These efforts were somewhat reduced immediately after vaccines for MD became available in the early 1970's but resumed later with the emergence of MD viruses of high virulence.

II. MECHANISMS UNDERLYING RESISTANCE TO DISEASE

The efforts to understand the physiological and genetic basis of disease resistance started in the later part of the above described epoch of disease resistance research. Intensive studies were conducted particularly in immunology and immunogenetics, aiming primarily at human diseases, but the avian branches of these disciplines also moved forward rapidly, powered by both the advances in the general field and work specifically targeted at poultry.

The most fruitful research area in this period were studies of the major histocompatibility complex (MHC). A comprehensive review of these studies by Bacon (1987) showed that MHC haplotypes are associated with resistance to viral, lymphoproliferative diseases (MD, sarcoma, erythroblastosis, lymphoid leukosis (LL)) and infectious bursal disease, as well as a bacterial disease (fowl cholera), and a parasitic disease (coccidiosis). The most intensive studies involved again MD, and provided strong evidence of the association of at least two MHC haplotypes(B^{21} and B^{2}) with MD resistance. Retrospective analyses of earlier selection experiments confirmed the above associations when it was found that frequency of "resistant" MHC haplotypes was significantly increased by selection for MD resistance (Briles *et al.* 1975, Gavora *et al.* 1986). It has been also shown that similar to the situation in mammals, both cellular and humoral responses play important roles in resistance to disease in birds (Gross *et al.* 1980).

An example of the complexity of resistance mechanisms was provided by a number of studies that, taken together, demonstrated the existence of two levels of resistance to LL (Crittenden 1975): cellular resistance, also referred to as the first line of defence, is based on the absence of suitable cell surface receptors for LL virus that can prevent the entry of the virus into the chicken and, the second line of defence, resistance to tumor development.

As a consequence of these advances, most of the major breeding companies started in the 1970's indirect selection for MD resistance. They included MHC haplotypes among their selection criteria and this led to the increase of the frequency of the "desirable" haplotypes in their commercial hybrids, particularly leghorns. It now seems safe to assume that most, if not all of today's commercial leghorns carry at least one of the MHC haplotypes associated with MD resistance. Some commercial breeders also used the new knowledge about resistance to LL to select for cellular resistance to infection with LL virus. This selection was applied in meat chickens because genes for such resistance are almost entirely absent from leghorns. The findings about negative effects of subclinical infections with LL virus in genetically susceptible birds provoked worldwide efforts by the poultry breeding industry to eradicate LL viruses from commercial chickens. There is little doubt that these three instances of application of scientific advances in practical breeding significantly contributed to the improved health status of today's commercial chickens.

III. MOLECULAR BIOLOGY OF RESISTANCE AND GENE MAPPING

The advent of molecular biology techniques resulted in rapid advances in the understanding of the molecular bases of disease resistance traits. The list of significant findings includes the successful cloning of the cellular receptor for LL virus (Bates *et al.* 1993), extensive studies of endogenous viral genes (for review see Crittenden 1991) and demonstration of their association with susceptibility to LL (Critteneden *et al.* 1982; Gavora *et al.* 1995), and reduced egg production (Gavora *et al.* 1991), analysis of gene NRAMP, associated with properties of lymphocytes important in response to pathogens (Hu *et al.* 1994), and evidence of the involvement of the growth hormone gene in resistance to lymphoproliferative diseases (Kuhnlein *et al.* 1996).

Development of the genetic map of the chicken (Cheng *et al.* 1995) provided the basis for the identification of quantitative trait loci (QTL) as components of polygenes. The recently completed analysis of MD susceptibility in an F_2 cross of two inbred lines of leghorns, identical for the MHC B^2 haplotype but greatly different in MD susceptibility, provides the first insight into a polygenically inherited disease resistance trait in an animal species (Vallejo *et al.* 1997). The study revealed the existence of three to five QTL loci that collectively explained 32 to 68% of genetic variance in MD susceptibility. This new information, together with the involvement of MHC in MD susceptibility well established earlier, clearly indicate that the polygene governing susceptibility to MD is not of an infinitesimal nature. It is more likely that, as suggested earlier (Gavora 1992), the polygene consists of a small number of genes of major and medium size effects, as well as a large number of genes of indiscernible, small effects.

Disease resistance appears to be particularly well suited for the application of marker assisted selection. The finding that most of the QTL identified (Vallejo *et al.* 1997) are dominant for MD resistance should facilitate their use in practical breeding programs. It can be expected that in the future, the use of QTL or their markers will increasingly find its way into practical poultry breeding programs.

IV. GENETIC ENGINEERING OF NEW RESISTANCE MECHANISMS

This epoch in the evolution of investigations of genetic bases of resistance marks a major leap: from analytical studies and conventional techniques aiming at improvement of existing disease resistance mechanisms, to the introduction by genetic engineering of new mechanisms of resistance. The same techniques can also be used to modify existing resistance mechanisms to the advantage of the host or disadvantage of pathogens.

The first successful introduction of pathogen-mediated resistance to disease by genetic engineering in animals was reported by Salter and Crittenden (1989). They produced several lines of chickens, each with an insert of a recombinant avian leukosis retroviral genome at a different locus within the host genome. The transgenic birds that expressed only the viral envelope coding region of the recombinant genome were resistant to the avian leukosis virus and it is assumed that this resistance is due to a blockage of the virus receptors by the viral envelope proteins produced by the transgene.

There is increasing evidence that, similar to plants, a number of approaches can be used to genetically engineer new disease resistance mechanisms in animals. The murine Mx1 is a protein with activity against the influenza virus. Garber *et al.* (1991) inserted cDNA encoding the murine Mx1 protein into chicken embryo fibroblasts and the cells were resistant to infection with avian, as well as human influenza viruses. Clements *et al.* (1994) produced sheep that carry transgenes expressing the envelope genes of the visna virus, and Gavora *et al*, (1994) transferred genes that code for bovine rotavirus capsid proteins into the genomes of susceptible cells in culture and into genomes of laboratory mice. However, insertion of a transgene in animal cells can also have consequences other than the desired disease resistance and thorough testing of individuals containing such transgene is required. Prospects for development and use of new, genetically engineered mechanisms of resistance to viruses were further discussed by Gavora (1996).

CONCLUDING REMARKS

Poultry genetics and breeding made remarkable progress over the last 60 years: From the early realization that genetic variation in resistance to disease exists and can be utilized in breeding, through the employment of a variety of direct and indirect selection techniques to improve resistance to disease and general survival, to the first attempts to genetically engineer new resistance mechanisms.

Conventional breeding methods, increasingly enhanced by information flowing mainly from immunology and QTL mapping, will remain the principal approach to the improvement of disease resistance. In some instances introduction of new genetically engineered resistance mechanisms will be justified. Genetic engineering strategies that prevent viral entry into hosts are expected to be the most valuable and the desirability and usefulness of new resistance mechanisms will likely diminish as their action distances itself from the point of viral entry into the host.

It is likely that in the 21st century, the poultry industry will experience additional improvements of genetic resistance that will gradually gain further importance as the most environmentally desirable and preferred method for disease control. Sooner or later, poultry industry will start using birds with genetically engineered resistance to disease. However, the benefits derived from such resistance will have to strongly outweigh the risks perceived by the consumer.

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