Prospects For Enhancing Genetic Resistance to Disease in Dairy Cattle.

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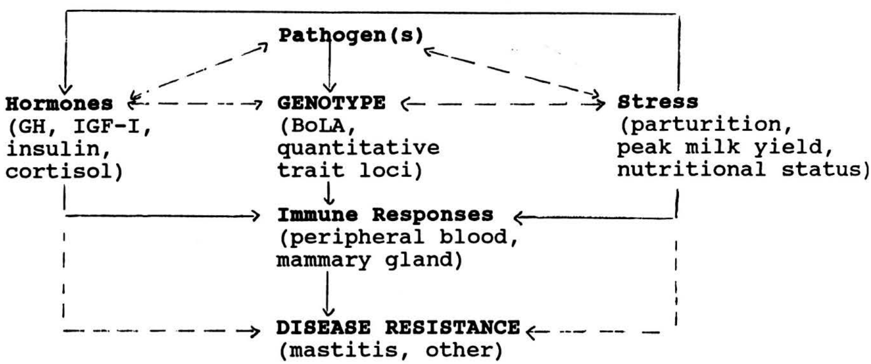
There is now substantial evidence that genetic selection in dairy cattle, soley for improved production, is associated with rising disease incidence (1,2a,b). Diseases such as mastitis are multifactorial with complex etiology (fig 1.), which despite elaborate farm management schemes, costs the US dairy industry approximately $2 billion annually, and the Canadian industry between $500-700 million (3). Direct losses result from cow deaths, culling, milk discard, and antibiotic therapy of clinical disease. Although dollar losses from subclinical mastitis are much more difficult to estimate, these may be the most significant due to chronically reduced milk yields and altered milk composition of affected cows (4). Unfortunately, effective vaccines for the prevention of complex diseases such as mastitis, have not yet been realized (5). In addition, the relative lack of understanding of how genetic and physiological host factors influence immunological defense has hampered progress in the development of effective alternate preventatives. However, there is now evidence from numerous species that immune responsiveness and disease resistance are partly genetically regulated traits, and that enhancement of these traits based on genetic selection is feasible (6, 7, 8). In cattle, several genetic markers and immune response traits have been identified which have some association with mastitis or other economically relevant diseases, but these require confirmation in the context of breed and pertinent physiological status of the cow prior to use in selection schemes (2a, 9, 10, 11, 12, 13, 14).

Several researchers have suggested immune responsiveness as an effective indicator of disease resistance, and that the ability to respond immunologically is determined in part by the highly polymorphic major histocompatibility complex (MHC) genes (15, 16, 17, 18), as well as by other non-MHC quantitative trait genes (19, 20). For instance, associations between various alleles of the bovine MHC, called BoLA (bovine leucocyte antigens), and specific diseases have been described. The relationship between these genes, immune response traits, disease resistance, and productivity are currently being investigated in cattle (10, 14, 17, 18, 21, 22), and certain of these genes may be suitable markers for selection. Many associations are however breed specific (9), and relationships may need to be established within each breed. Nonetheless, associations between specific BoLA antigens and mastitis, tick resistance, enzootic bovine leucosis, milk fat percent, milk protein yield and weight gain have been reported (reviewed in 9). A recent Canadian study involving 179 Holstein cows and 271 progeny tested bulls reported a significant influence of specific BoLA class I alleles on economic traits using a gene substitution model (21). Two alleles were of particular interest, W6.1 and W20A, because of their relatively high frequency in the Holstein bulls examined (26 and 15% respectively). While both alleles were associated with comparatively high 308 day milk and protein yields, those animals expressing the W6.1 antigen had much higher disease treatment costs over the first lactation ($35.84 vs $1.43). These results now need to be extended and independently confirmed, and their precise relationship with host defense mechanisms examined. Another study involving 196 progeny tested Swedish Red and White dairy bulls, has reported an association between the bulls' breeding value (EBV) on progeny testing for disease resistance and BoLA class II polymorphisms (23). In this case the DQ^{1A} haplotype was associated with susceptibility to clinical mastitis. Associations between other BoLA specificities and mastitis have also been reported (16, 24). Some of these associations may derive from the ability to mount a beneficial immune response during periods of known stress, such as peripartum, when mastitis incidence is high (25a,b). In addition, influential genotype by endocrine interactions may occur between calving and peak lactation since concentrations of growth hormone, IGF-1, insulin, and cortisol are also altered during these stress periods (26a,b,c). This hypothesis seems credible since recent studies in mice and humans report genetic regulation of stress responses which effect the immune system (27, 28). Still, substantial gaps exist in knowledge regarding meaningful associations between genotype, inherited immune response traits, stress, and disease resistance (Figure 1).

Figure 1. Host factors influencing genotype-disease associations.



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The immediate research goal may be to determine if meaningful interactions exist between genotype, immune response, hormones, and disease in order to improve periparturient cow health, and then to recommend suitable marker traits for genetic improvement of broad-based inherent resistance to infectious diseases (with emphasis on mastitis) in dairy cows.

Recently, there has also been a great deal of effort by the dairy industry to reduce somatic cell scores (SCS) as an indicator of improved milk quality and reduced mastitis (2a,b). Again, serious regulatory, public health, and consumer concerns about the quality of dairy products has added credence to the genetic approach (3). Genetic correlations between SCS and clinical mastitis vary around 60% (2b). This combined with the fact that SCS has a heritability of 10-20%, and can be easily and accurately measured at a low cost make it an attractive genetic marker (2b). However, ultimately selection for reduced SCS could have detrimental effects on cow health since somatic cells are composed largely of lymphocytes, neutrophils and macrophages which are recruited to the gland in response to infection and which mediate many of the protective mechanisms (29). Theoretically, extended selection for lowered SCS could compromise immunity both in the mammary gland and the periphery. Consequently it is paramount to determine appropriate selection cut-off points, and the relationships between reduced SCS and other resistance-related mechanisms before introducing SCS as a selection criterion for improved cow health. To date these factors have not yet been adequately evaluated.

It is also important to realize that one marker is unlikely to suffice for increasing broad-based immunity or disease resistance. Therefore the rapid progress in mapping the bovine genome increases the possibility of locating additional marker traits useful in selection (30, 31, 32). These may include cytokine, complement, regulatory genes, and other loci which influence disease outcome . For instance, reports establishing the use of immunoglobulin variable region gene (Ig v-gene) families in different MHC strains of mice suggest that preferential use of v-genes may influence immune response and disease status (33, 34). Ig-v genes seem to be conserved in pigs and cattle (35), and therefore may serve as additional markers of immune function. Molecular identification of the many genes which effect economic traits (such as disease resistance), the so called "Economic Trait Loci" or "Quantitative Trait Loci", is a longterm goal which should improve genetic response through increased accuracy of selection (31). However the integration of currently available molecular techniques with traditional selection approaches, based on animal performance, should provide positive and immediate genetic gain in a number of livestock species (36).

The ongoing search for meaningful genetic markers or indicators of disease resistance, has sound and practical future applications for the livestock industry, particularly for the production of breeding stock with enhanced genetic resistance to infectious diseases. To date, livestock health maintenance has relied heavily upon exogenous methods, such as antibiotics, drug therapies, and elaborate management practices. It is now realized that these traditional approaches may not be cost effective in all instances and certain therapies may be severely curtailed because of consumer concern over animal and human well-being. However genetic adaptation to stress and enhanced immune response and disease resistance may be attainable by combining genetic selection for these traits with current selection programs to increase production. Non-traditional genetic approaches to improve livestock performance and health hold great promise as environmentally sound alternatives to improved animal health, which at the same time should help alleviate concerns over the hazards and costs associated with conventional disease and production management.

SUMMARY:

There is now substantial evidence that genetic selection in dairy cattle, soley for improved production, is associated with rising disease incidence. Diseases such as mastitis are multifactorial with complex etiology, which despite elaborate farm management schemes, costs the US

dairy industry approximately $2 billion annually, and the Canadian industry between $500-700 million. Direct losses result from cow deaths, culling, milk discard, and antibiotic therapy of clinical disease. Although dollar losses from subclinical mastitis are much more difficult to estimate, these may be the most significant due to chronically reduced milk yields and altered milk composition of affected cows. Unfortunately, effective vaccines for the prevention of complex diseases such as mastitis, have not yet been realized. In addition, the relative lack of understanding of how genetic and physiological host factors influence immunological defense has hampered progress in the development of effective alternate preventatives. However, there is now evidence from numerous species that immune responsiveness and disease resistance are partly genetically regulated traits, and that enhancement of these traits based on genetic selection is feasible. In cattle, several genetic markers and immune response traits have been identified which have some association with mastitis or other economically relevant diseases, but these require confirmation in the context of breed and pertinent physiological status of the cow prior to use in selection schemes. Nonetheless genetic approaches to improve livestock performance and health hold great promise as environmentally sound alternatives to improved animal health, which at the same time should help alleviate concerns over the hazards and costs associated with conventional disease and production management.

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