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GENETIC BASIS OF MASTITIS RESISTANCE IN DAIRY CATTLE – A REVIEW*

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Abstract

Mastitis is one of the most important mammary gland diseases impacting lactating animals. Resistance to this disease could be improved by breeding. There are several selection methods for mastitis resistance. To improve the natural genetic resistance of cows in succeeding generations, current breeding programmes use somatic cell count and clinical mastitis cases as resistance traits. However, these methods of selection have met with limited success. This is partly due to the complex nature of the disease. The limited progress in improving udder health by conventional selection procedures requires applying information on molecular markers of mastitis susceptibility in marker-assisted selection schemes. Mastitis is under polygenic control, so there are many genes that control this trait in many loci. This review briefly describes genome-wide association studies which have been carried out to identify quantitative trait loci associated with mastitis resistance in dairy cattle worldwide. It also characterizes the candidate gene approach focus on identifying genes that are strong candidates for the mastitis resistance trait. In the conclusion of the paper we focus our attention on future research which should be conducted in the field of the resistance to mastitis.

Key words: dairy cattle, mastitis, genetic markers

Mastitis is one of the frequent mammary gland diseases impacting lactating animals. Economically, it is considered the most important disease in dairy cattle. Mastitis is a difficult problem to comprehend because it is caused by many factors acting simultaneously. Microorganisms are responsible for the infection. However, for bacteria to enter the mammary glands and establish themselves to the point that they cause an infection, a multitude of other factors may be involved: hygiene, housing,

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climate, milking machines, feeding and genetic factors. It is even more difficult to generalize about the relative importance of each one, as certain factors affect certain microorganisms in particular. The immune response of the cow to the pathogen is complicated. The innate immune system is ready to respond immediately to the earliest stages of infection and to recognize pathogens that have not been encountered previously. In contrast, the adaptive immune system requires several days to become capable of exerting a protective response to infection (Uthaisangsook et al., 2002).

Mastitis resistance is a complex trait, depending on a genetic component but also on physiological and environmental factors. On the most global scale resistance could be defined as the ability to avoid any infection of the udder, or quick recovery from any infection. Most genetic studies have focused on milk somatic cell count (SCC) and clinical mastitis (CM) as phenotypic measure to predict inflammation of the udder. The goal of the standard mastitis programme is to reduce mastitis incidence rates on farms. One of the methods for reducing the incidence of mastitis in dairy cows is genetic selection. It is well known that heritability estimates of mastitis are generally low (Nash et al., 2003; Heringstad et al., 2003; Zwald et al., 2006). It is often misinterpreted that genetics has little role to play, and that improvement of management is the only option to reduce mastitis. This is not true as long as there is no improvement in reducing the number of new infections, which is what we face in reality.

There are several selection methods based on phenotype and genotype to select for mastitis resistance. In the phenotype selection estimated breeding values are used, and selection is either direct or indirect. The direct selection of dairy bulls for mastitis resistance is based on clinical cases of mastitis of their daughters. Indirect selection refers to selection applied to a trait that is correlated to the trait of interest. Since mastitis is an inflammatory response to invading pathogens, a trait related to the response to infection, or the innate defense mechanisms of a cow, are of particular interest. The most suitable parameter for indirect selection based on phenotype to reduce the incidence of mastitis proved to be SCC. Selection can also be based on genotype. Enhancing the genetic progress of quantitative traits can be indirect or direct. Indirect selection based on genotype, similar to indirect selection based on phenotype, uses a trait that is correlated to the trait of interest. In this type of selection the emphasis is placed on quantitative trait loci (QTL) associated with mastitis resistance. Direct selection based on genotype is looking for genes directly related to mastitis resistance.

Current breeding programme

To improve the natural genetic resistance to udder pathogens in succeeding generations, resistance traits such as SCC and CM are being used in the current breeding programme. These traits as selection criteria measure the capacity of the cow to resist infection by udder pathogens. Therefore, many countries have included SCC, CM or both in their breeding programme as a way to improve resistance to intramammary infections. SCC is the trait most often used to evaluate susceptibility to mastitis (Rupp and Boichard, 2003). It is included in the breeding goal and routinely published in several countries. SCC has a higher heritability (0.08–0.19) than

CM, allowing more effective genetic progress (Heringstad et al., 2003). Additionally, the genetic correlation between SCC and incidence of CM has been demonstrated (0.6–0.8) (Heringstad et al., 2003, 2006; Nash et al., 2003; Zwald et al., 2006). This is a relatively high genetic correlation and indicates that progress can be made in the reduction of CM by selecting for decreased SCC. Clinical cases of mastitis are also treated as a selection trait in the breeding programme for improved udder health. Cows with less frequent and less severe cases of mastitis are selected as parents for the next generation. But only Scandinavian countries conduct genetic selection for udder health based on CM records because all veterinary treatments are recorded in those countries (Heringstad et al., 2007). Inclusion of these records in sire evaluation and selection has led to a lowered genetic trend for CM in these countries. Unfortunately, heritability of this trait is relatively low (0.01–0.15), with the greatest genetic contribution observed in the first lactation (Heringstad et al., 2003; Nash et al., 2003; Zwald et al., 2006). Additionally, mastitis is a very complex disease and the measurements of clinical cases allows detection of a narrow spectrum of the total disease process. Under field conditions, assessment of clinical cases is difficult, time consuming and variable in its effectiveness. The most suitable parameter for indirect selection based on phenotype to reduce the incidence of mastitis proved to be SCC. However, these methods of selecting cows and sires with daughters that display phenotypic ability to resist mastitis have met with limited success. This is partly due to the complex nature of the disease, which is caused by more than 100 different organisms that differ in how they interact with the immune response. As a result, clinical and subclinical infections can be short, intermediate and long in duration (Pighetti and Elliott, 2011). Genetic selection by SCC or CM, which have low to moderate heritability, has been slow in the face of selecting for milk yield. Intense selection for milk yield, a highly heritable trait (Nash et al., 2003), leads to an increase in disease prevalence in the population due to a positive genetic correlation between milk yield and mastitis (Fleischer et al., 2001).

Molecular markers of mastitis resistance

Due to the limited progress in improving udder health by conventional selection procedures using indirect traits, demand increased for information on molecular markers for mastitis resistance to be included in marker assisted selection schemes. Researchers have focused on identifying more informative genetic markers to allow faster and more accurate selection of cattle resistant to mastitis (Wiggans et al., 2011).

Mastitis is under polygenic control, so there are many genes that control this trait in many loci. The major challenge that molecular genetics faces is to identify markers for genes that control the phenotypic variation in mastitis resistance. Two types of markers can be considered. First there are linked markers. They are sufficiently close to the gene (or quantitative trait loci) on the chromosome and alleles at the marker and trait gene are inherited together. The second type of marker is a functional polymorphism in the gene that controls variation in the trait. These markers are called direct markers. Once the functional polymorphism is known, it is possible to predict the effect of particular alleles in a population. Direct markers are more useful than

linked markers for predicting the phenotypic variation of the trait, for example mastitis resistance, within the population. However, the variation in quantitative traits like mastitis resistance is controlled by several loci, each of which is responsible for a small amount of the overall variation. All markers can be used in selection for mastitis resistance using marker-assisted selection schemes.

Two main approaches are available to look for markers, preferable major genes for mastitis resistance. The first is to detect and to localize QTL. The second is the candidate gene approach, which looks for single nucleotide polymorphisms (SNP) in the genes that are connected to mastitis.

Detection and localization of QTLs

During the past several years many QTLs affecting mastitis have been identified in cattle. QTL detection does not require any prior knowledge about the genes, but it does require appropriate family structure with parents heterozygous for the QTLs and for the linked marker, and progeny with phenotypic and marker information. Several multiple genome-wide association studies have been carried out to identify QTLs associated with mastitis resistance in dairy cattle. Mastitis resistance has been studied using either SCC or SCS (somatic cell score), or less frequently CM events as phenotypes (Heyen et al., 1999; Klungland et al., 2001; Kuhn et al., 2003; Ashwell et al., 2004; Holmberg et al., 2004; Ron et al., 2004; Schulman et al., 2004, 2009; Schrooten et al., 2004; Lund et al., 2007, 2008; Sahana et al., 2008; Sorensen et al., 2008; Baes et al., 2010; Tal-Stein et al., 2010; Sodeland et al., 2011; Minozzi et al., 2011; Meredith et al., 2012; Wijga et al., 2012). QTLs have been found on almost all chromosomes, and several have been confirmed by at least two independent studies. There are QTLs for SCC or SCS on *Bos taurus* autosome (BTA) 1, 2, 4, 5, 6, 8, 9, 10, 11, 14, 15, 18, 20, 21, 23 26 and 27 (Khatkar et al., 2004, 2005; Minozzi et al., 2011; Meredith et al., 2012; Wijga et al., 2012) and for CM on chromosomes 2, 3, 6, 8, 9, 11, 14, 18 and 20 (Klungland et al., 2001; Holmberg et al., 2004; Schulman et al., 2004; Mai et al., 2010; Sodeland et al., 2011). Usually the QTLs for SCC and CM present on the same chromosome do not overlap (for example BTA8). Few chromosomes exhibit QTLs for both SCC and CM, for example on BTA18 (the same location), BTA11 and BTA14 (not in the same location). In contrast, QTLs for SCC and CM on BTA9 and BTA11 were within 20 cM of each other in Swedish cattle (Klungland et al., 2001; Holmberg et al., 2004; Schulman et al., 2004). Recently, Meredith et al. (2012), using data from Irish Holstein- Friesian cattle, found that nine SNPs were significantly associated with SCS. Three of these were located within known QTL regions for SCS on BTA6 and 10. The remaining six SNPs, located outside known QTL regions for SCS, were spread across chromosomes 6, 15 and 20. Three SNPs on BTA20 were associated with decrease in milk yield and SCS (Meredith et al., 2012). This observation agrees with the well-known positive correlation that exists between milk yield and SCS. QTL regions such as this may help elucidate how to select for increased milk yield without the associated detrimental effect on resistance to mastitis.

Ogorevc et al. (2009) developed an extensive database of candidate genes and genetic markers for mastitis related traits. Functional traits of the mammary gland

have been studied using different approaches, including the QTL approach, association studies and the candidate gene approach. For identification of candidate loci data from seven different research approaches were exploited (Ogorevc et al., 2009).

QTLs associated with mastitis resistance in dairy cattle are updated regularly in the cattle QTL database (http://www.animalgenome.org/cgi-bin/QTLdb/BT/index) (Hu et al., 2010). These results reflect the fact that mastitis resistance is a complex function that involves many molecules and pathways that can be regulated by many different genes. Results seem to be specific to the trait and population considered. Environmental conditions like exposure to pathogens and the genetic background of the studied population and breed may greatly influence the links between genes and phenotypes. One of the limitations of QTL-based approaches is the need for a large effect in order to identify loci associated with the phenotype of interest (Cole et al., 2009; Hayes et al., 2010).

In the past, the most commonly used genetic markers were microsatellites. Since new genetic tools came into use, QTLs for mastitis resistance can be detected by whole genome scans. Using this new genetic tool it is possible to identify 50 000 SNPs with microarray. The identification of a very large number of SNPs has helped in the use of genome-wide association studies to detect alleles that are associated with mastitis resistance. This allowed the discovery of differences in DNA between animals for which we know estimated breeding value (EBV) for mastitis resistance. The most important thing at this stage is to use the correct statistical methods to evaluate the relationship between SNPs and mastitis resistance. This is to find predictive equations. These predictive equations allowed estimation of the effect of each allele or haplotype, and no pedigree or family history is needed to estimate mastitis resistance for one genotyped animal. Animal breeding value for mastitis resistance is the sum of the effects of all alleles. The advantages of this method are the very low cost of breeding value estimation in comparison to traditional methods, and the possibility to estimate mastitis resistance for very young animals. Marker haplotypes associated with mastitis resistance constitute confidential information, but breeding companies are very interested in the implementation of marker technology in their existing and future breeding schemes. Genome-wide selection is already used in breeding programmes in France, the Netherlands, Australia, New Zealand and the United States. It is going to be used soon in Canada, Germany, Ireland, and Scandinavian countries.

Candidate gene approach

The candidate gene approach focuses more on identifying genes that are connected to mastitis, causing organisms' recognition, leukocyte recruitment, pathogen elimination and resolution. This is possible with the use of knowledge on functional candidate genes. In this case we are looking for a functional polymorphism in the gene that controls variation in the trait. For poorly defined traits, such as mastitis resistance, it is difficult to select candidate genes that may control the trait because of the large number of different pathogens and physiological mechanisms contributing to the observed variation. Complex traits are also determined by many genes with little effect, versus a limited number of genes with large effect, once again limiting

the ability of genome-wide association studies to identify these genes (Hayes et al., 2010).

During the last 10 years the genes associated with the immune response have been investigated for the presence of SNP and associations with mastitis related traits. TLR 4 (toll-like receptor 4), responsible for initial recognition of invading organisms, has received the greatest attention as a candidate gene for mastitis susceptibility. The bovine TLR family contains members 1–10 and enables recognition of bacterial, viral and danger signals by individual cells (Ingham and Menzies, 2006). TLR4 recognizes lipopolysaccharide, a component of the cell wall of Gram-negative bacteria such as *E. coli* and Klebsiella, common causes of mammary infections in dairy cattle (Bannerman, 2009). Bovine TLR4 is highly polymorphic, with 36 SNPs discovered across 14 breeds of cattle (Sharma et al., 2006; Opsal et al., 2006; Wang et al., 2007). Of these, several SNPs were identified to have association with phenotypic or EBV for somatic cell count (Opsal et al., 2006; Sharma et al., 2006). Also SNPs for NLR (nod-like receptor), which represents an intracellular family of viral, bacterial and danger sensors, has been proven to be connected to mastitis resistance (Pant et al., 2007).

The chemokin IL-8 is released during infection by neutrophils and other cells in response to invading pathogens. Subsequent binding of IL-8 to CXCR1 or CXCR2 induces migration, regulates cell survival, modifies cytokine production, and increases phagocytosis and reactive oxygen species generation (Mitchell et al., 2003; Lahouassa et al., 2008). Studies examining the relationship of CXCR1 with common indicators of intramammary infections have provided mixed results (Youngerman et al., 2004; Leyva-Baca et al., 2008; Goertz et al., 2009; Beecher et al., 2010; Zhang et al., 2012). Several candidate pathways were also found in the study on integrated genomic data from genome-wide association mapping in cattle, and transcriptomic data from microarray studies on mastitis pathogens. Of great interest are IL-17 and IL-8 signaling pathways (Lewandowska-Sabat et al., 2012). Sodeland et al. (2011) found that on the basis of a genome-wide association study SNPs highly associated with CM lie near both the gene encoding interleukin 8 on BTA6 and the genes encoding the two interleukin 8 receptors on BTA2.

Among genes associated with reduced mastitis incidence particular attention is being paid to the BoLA-DRB3 gene because of the role this gene plays in the immune system (Sender et al., 2008, 2010; Oprządek et al., 2012). The *BoLA-DRB3* gene belongs to the major histocompatibility complex (MHC) genes. The exon 2 *BoLA-DRB3* locus is especially highly polymorphic. This region encodes the antigen adhesion side of MHC molecules and plays an essential role in regulation of the immune response to pathogens. Several studies have demonstrated that the *BoLA-DRB3.2*24* allele tended to be associated with mastitis susceptibility and *BoLA-DRB3.2*3* tended to be associated with mastitis resistance (Starkenburg et al., 1997; Rupp and Boichard, 2003). However, it should be noted that contrasting results have also been obtained. Galal Abdel Hameed et al. (2008) found that cows carrying allele *16* had a significantly lower EBV of SCC than cows carrying allele *23*. Also an increase in the prevalence of sub-clinical mastitis caused by *S. dysgalactiae* was associated with cows carrying allele *23* (Galal Abdel Hameed et al.,

2008; Sender et al., 2008). This indicates that alleles of some genes may be related to resistance or susceptibility with the influence of environmental conditions (present pathogens), which may be different in different studied populations.

The lactoferrin gene has received some attention as a candidate gene for mastitis resistance. Due to the connection of this protein with innate immunity, lactoferrin could be a promising candidate gene for mastitis resistance. Polymorphisms occurring in the regulatory region of the gene seem to be particularly interesting because they may affect gene expression (Pawlik et al., 2009).

In cattle, the growth hormone receptor located on BTA20 is highly polymorphic, with at least 39 SNPs identified in this gene. Four SNPs were observed to be significantly associated with SCS in the daughters of 848 Irish Holstein-Friesian sires (Waters et al., 2010).

Analysis of the osteopontin or the secreted phosphoprotein 1 (SPP1) gene revealed four SNPs associated with SCS EBV in the third lactation. One SNP located in the promoter region of the SPP1 gene was significantly associated with SCS EBV across all three lactations in daughters of Canadian Holstein sires (Quirion et al., 2009).

Recently, several new SNPs have been evaluated for relations to mastitis resistance. Three SNPs of mannan-binding lectin (MBL) linked to greater risk of *S. aureus* infections were associated with SCS in Chinese Holstein and Luxi Yellow cattle (Wang et al., 2011, 2012). Also, in Chinese Holstein dairy cows it was found that polymorphism of the *ATP1A1* gene, which encodes the bovine Na^+, K^+ ATPase α1 subunit is associated with mastitis (Liu et al., 2012). Yang et al. (2012) reported that polymorphism of the bovine complement component 4 (C4A) gene was also related to mastitis resistance. There are many other genes whose relationship to mastitis could be proved, but it is impossible to mention all of them in one review paper.

Conclusion

We can conclude that attention should be paid to two aspects of research on genetic determinants of resistance to mastitis.

Firstly, one important aspect of this research is the choice of features of resistance to mastitis. Most of the research on resistance to mastitis is based on SCC as an indicator of mastitis or the occurrence of CM. In only a few studies has resistance to mastitis been evaluated on the basis of the occurrence of bacterial infections of the udder. However, it seems that a large-scale study of the genetic determinants of infection of the mammary gland would answer many questions related to resistance to mastitis.

Secondly, another important aspect of the research is the choice of method of selecting animals resistant to mastitis. We can carry out the selection of animals which have favourable alleles (if we identify a few genes with a large effect on resistance to mastitis) or we can choose the best cumulative effect of many genes (in the case of finding genes with a small effect on resistance). The best cumulative genotype does not identify individual genes, and animals are selected based on the estimated cumulative impact of multiple genes on resistance to mastitis. In both methods of selection the aim will be to breed animals resistant to infection and inflammation of the udder.

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Podstawy genetyczne odporności krów mlecznych na zapalenie wymienia – artykuł przeglądowy

STRESZCZENIE

Zapalenie wymienia (mastitis) jest jedną z najważniejszych chorób bydła mlecznego. Poprawa odporności na tę chorobę jest możliwa dzięki wykorzystaniu metod hodowlanych. Aby poprawić odporność krów mlecznych na mastitis, dopuszczalne jest wykorzystanie kilku metod selekcyjnych, które zostały omówione pokrótce w niniejszej pracy. Programy hodowlane, obecnie stosowane na świecie, wykorzystują jako kryterium selekcyjne zwierząt odpornych na mastitis, liczbę komórek somatycznych w mleku krów lub częstość występowania przypadków klinicznych. Programy te jednak tylko częściowo przyczyniły się do poprawy odporności krów na zapalenie wymienia. Jednym z powodów małej ich efektywności jest złożona etiologia tej choroby. Aby zwiększyć efektywność programów hodowlanych w odniesieniu do odporności na mastitis, w ostatnich latach podjęto badania nad markerami genetycznymi tej choroby i ich wykorzystaniem w selekcji wspomaganej markerami. Na zapalenie wymienia wpływa wiele genów. W niniejszej pracy dokonano przeglądu badań nad poszukiwaniem markerów związanych z odpornością na mastitis i genów do niej kandydujących. W podsumowaniu wskazano kierunki dalszych badań.