Review article

Genetic aspects of mastitis resistance in cattle

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Abstract. Cattle breeding program for improvement of milk traits is accompanied by intensive changes in the structural and functional specificity of the animal organism. Assuming the hypothesis that the biological role of the female is to rear her progeny, it may be concluded that the extremely high milk productivity of the modern cow many-fold exceeds the physiological normal range. The mammary gland as a milk-producing highly effective bioreactor is exposed to the particularly strong influence of external and internal factors. Therefore, susceptibility to udder dysfunction generally called „mastitis" causes great economical losses in highly productive cows. Mastitis is usually induced by a bacterial infection conveyed through the teat canal. The high variability of pathogens and diversity of environmental conditions cause difficulties in mastitis treatment. Antibiotic therapy does not give satisfactory results. Scientific research aims to recognize the heritable specificity of organism defence systems. Still, the currently used breeding selection procedures cannot be successful because natural resistance treated in categories of quantitative genetic variation shows a very low heritability and non-additive genotype-environment interaction. To overcome this problem, an alternative approach to detect a single gene with a high protective expression can be effective. The topics presented in this review include expression of lysozyme and lactoferrin in mammary gland tissue regarded as candidate gene for mastitis resistance as well as BoLA histocompatibility complex and milk protein polymorphic systems proposed as potential genetic markers of natural resistance in cattle.

Key words: cattle, genetic markers, mastitis, natural resistance

Cow udder, as a highly effective milk-producing organ is particularly strongly affected by internal and external factors. During 305 days of lactation a cow weighing 650-700 kg produces more than 8-10 tons of milk containing 350-400 kg fat, over 300 kg protein, 450-500 kg lactose, and 60-80 kg mineral constituents.

So far, over 100 components giving milk its specific biological properties have been recognized.

Milk components are directly or indirectly derived from blood. Production of one liter of milk requires participation of around 500 litres of blood flowing through the capillary vessels surrounding mammary gland vesicles. Assuming that the biological function of a female is to rear her progeny, it may be concluded that milk productivity of a modern cow many fold exceeds the physiological normal requirement.

A breeder, using a given system of cow-house keeping, feeding, prophylaxis and therapy, undertakes treatment allowing to maintain the functional effectiveness of animals selected due to the extremely high milk productivity. Optimally, from the economic and technological point of view, the standard of environmental conditions differs significantly from the set of factors that provide the comfort of homeostasis of a biologically active female. The occurrence of udder disorders generally called „mastitis" is not a uniform condition, each incidence may be caused by different reasons as well as be characterized by various functional aberrations. The pathogenic factors are usually bacteria conveyed through the teat canal. A commonly accepted indicator of udder health is the somatic cell count (SCC) of milk. Milk derived from a healthy udder contains 10-30 thousand cells/mL, of which 80-90% are mammary gland epithelium and drain canal cells, around 8% are leukocytes and below 1% are macrophages. The udder infection is a factor stimulating the activity of protective mechanisms of the organism (HARMON 1994, SORDILLO et al. 1996). In mastitis cases, as the SCC score in milk increases, the leukocyte score greatly increases and epithelial cells increase relatively slightly.

The dynamics of mastitis development assumes different forms: SCC score shows a broad scope of variability from a few thousand in healthy cows to millions in cases of acute mastitis. A detailed udder diagnosis includes several stages: a healthy udder secreting milk containing a few thousand SCC, 15% of which are leukocytes; latent udder infection characterized by the presence of pathogens and at the same time the regular SCC; subclinical mastitis, diagnosed in cases when the SCC is increased, including 50% leukocytes; clinical mastitis characterized by fever, swelling and tenderness as well as noticeable changes in milk properties; and finally subacute and acute cases in which the SCC increases to above one million cells, of which 75% are leukocytes. Classification of pooled milk for processing is done on the basis of technologically relative norm up to 100 thousand SCC/mL – satisfactory sanitary standard, 100-250 thousand cells/ml – permissible standard (HERZOG 1987).

The relationship between mastitis and milk yield efficiency is obvious, but difficult to verify statistically. Highly-productive cows are usually more susceptible to mastitis. However, udder infection is accompanied by a decrease in milk productivity caused by destruction of milk-secreting cells that can be renewed only during the dry period before next calving. Mastitis causes characteristic changes

in milk composition and technological properties such as a decrease in the amount of lactose, an increase in chlorides, aberrations in the physiological milk protein equilibrium, an increase in the level of immunoglobulins conveyed via the circulatory system, a decrease in casein fraction, as well as aberrations in proportions between mineral components like calcium and phosphorus, sodium and potassium, and in consequence unfavourable changes of milk acidity, coagulation ability and heat stability indices limiting the consumption and processing usefulness of milk (POLITIS, NG-KWAI-HANG 1988, HARMON 1994).

Mastitis causes economic losses far larger than those caused by other cattle diseases. The costs of diagnosis, prophylaxis, treatment, too early elimination of animals, decreased productivity and disqualification of sick cows' milk are very high. The easy to recognize clinical mastitis cases include 1-2% of animals, while the main threat comes from subclinical cases including on average 30-50% of cow population. Difficulties in the treatment of mastitis are caused by the high variability in pathogenic factors and different environmental conditions. Antibiotic therapy did not give satisfactory results. Only the type of pathogenes changed: mastitis caused by *Streptococcus* was eliminated but the range of *Staphylococcus* infections widened. Application of antibiotics specifically reducing the growth of *Staphylococcus* was also not successful, either due to escalation of *Corynebacterium* infections or non-bacterial, mostly fungal infections. Introduction of antibiotic therapy destroys the saprophytic microflora participating in milk fermentation processes and causes unfavourable tolerance symptoms in animals and people consuming the milk.

Detection of genetically controlled natural defence systems destroying pathogenic factors has actually been a center of scientific and breeding interests (LIE 1985, PAAPE et al. 1985, LEWIN 1989, LYONS et al. 1991, COLLEAU, BIHAN-DUVAL 1995, KELM et al. 1997). Natural resistance is the most important in the overall functional efficiency of the organism. Animal selection for improving natural resistance as a polygenic quantitative trait is difficult due to very low heritability (h^2), non-additive genetic interaction and a high variability in the forms of expression (JENSEN et al. 1985, SHOOK 1988, WALAWSKI et al. 1993b, URIBE et al. 1995, WALAWSKI, CZARNIK 1995, EMANUELSON et al. 1998). Another difficulty is due to the diversity of susceptibility and resistance symptoms in sick and healthy animals. The resistance expression is lack of disease symptoms, e.g. low and stable level of SCC, but also natural ability to stimulate the immune system, manifested in fluctuation of SCC score which returns to normal values without therapeutic intervention.

Current breeding programs include more or less detailed parameters of udder dysfunction. Efficiency of used selection procedures evokes basic controversy. Low h^2 of mastitis resistance as well as negative correlation between mastitis and milk productivity and milk protein contents are considered. Oversimplification of binary susceptible/resistant animal classification system is critically discussed. However, good aspects such as a positive correlation between mastitis resistance

and the breeding value of general milk traits and resistance to other diseases are also emphasized.

Attempts have been made to introduce a non-direct selection method for mastitis resistance. The relationship between udder morphology and performance had been noticed long before the appearance of the scientific animal breeding theory. It was considered obvious that defects in udder conformation may cause functional aberrations. Breeders' intuition was confirmed by scientific results. It was found that udder morphology indices are characterized by a relatively high h^2 and show a significant correlation with milk performance traits (BATRA, MCALLISTER 1984, SEYKORA, MCDANIEL 1986, ROGERS 1993, CZARNIK 1994). The attempts to optimize criteria specifying udder morphology indicate that cows resistant to mastitis are characterized by a high udder carriage and fore attachment as well as regular placement of teats, equally long and wide. Results of the so-called quarter milking test may be also useful as indirect selection factors, particularly indices of balanced milk efficiency of individual udder quarters, the speed of milk flow, the length of the dry period, the last one being a main cause of mechanical damage of teat canal. The indices of udder morphology and efficiency are considered in sire breeding evaluation and sire mothers selection programs.

Cattle breeding programs are constructed on the basis of theoretical assumptions of quantitative trait genetics. Genetic parameters used in animal evaluation are statistical estimators whose precision is limited by the real possibility of direct classification of different genetic and non-genetic factors. Parameters estimating natural resistance, adaptability and reproduction efficiency show a stable tendency resulting from biological properties shaped by evolution and consequently protected. Natural selection mechanisms counteract radical changes in the genetic structure of populations. In this case the polygenic statistical model of animal improvement is generally doubtful. The alternative approach is to detect single genes with large phenotypic effects. Recognition of major genes is the theoretical basis of of Marker Assisted Selection (MAS) (JENSEN et al. 1985, LEWIN 1989, MEUWISSEN, ARENDONK 1991, DENTINE 1992), as well as Quantitative Trait Loci (QTL) and Economic Traits Loci (ETL) programs (ASHWELL et al. 1997, HALEY, ANDERSSON 1997, BOICHARD 1998) constituting a compilation of population verified methods of quantitative trait genetics and application of achievements of molecular genetics referring to phenotypic effects of selected genome fragments and phenotypic effects of single gene loci in economically important breeding efficiency.

Genetic markers include DNA restriction fragments, highly polymorphic microsatellite DNA sequences as well as polymorphic gene products such as: erythrocyte antigen systems, histocompatibility complexes, lipoprotein and immunoglobulin allotypes as well as erythrocyte, leukocyte, blood serum and milk protein systems. The progress of the cattle genome mapping program realized in cooperation by many scientific centers is very fast. So far over 3300 genetic mark-

ers have been identified, including 1200 loci and DNA anonymous sequences (EGGEN, FRIES 1995, BARENDSE et al. 1997).

Many processes participate in mastitis resistance. Relatively well documented is the role of non-specific cell defence factors (REITER 1985, WOLFSON, SUMMER 1993, HARMON 1994, SORDILLO et al. 1996). The progress in recognizing the structure, organization and expression of identified genes allowed for pointing to potential natural resistance markers. Actually, research on the structure and expression of the lysozyme gene (HENKE et al. 1996, SEYFERT et al. 1996, PAREEK et al. 1998a,b) is most advanced.

Lysozyme (E.C.3.2.1.17) may function as a muramidase, which is manifested by hydrolysis of beta-glycoside bonds (1,4) appearing between N-acetyl-muramic acid and N-acetyl-glucosamine. Destruction of murein walls constituting the external covering of bacterial cells leads to their inability to stabilize the difference in osmotic pressure between bacterial cell and its external environment. Bacteria undergo lysis followed by enzymatic destruction. Gram-positive bacteria are particularly susceptible to lack of the protective lipid membrane (PAAPE et al. 1985, REITER 1985). The activity of lysozyme is measured by lysis power estimation of the standard *Micrococcus_lysodeicticus* strain. However, the bactericidal activity of lysozyme was proved also in relation to many other pathogens, including *Salmonella, Shigella, Brucella, Neisseria, Escherichia, Kleibsella, Staphylococcus aureus, Listeria monocytogenes* and *Clostridium botulinum*. Additionally, the non-enzymatic function of lysozyme has been studied, particularly as an antiviral and anticarcinogenic factor (OSSERMAN, LAVIOR 1996).

Genetic aspects of lysozyme activity were analyzed in research carried out on Red-and-White cattle in Norway (LIE 1980, LIE, SOLBU 1983, MAO et al. 1992, OLSAKER et al. 1993), and in Black-and-White cattle in Poland (WALAWSKI et al. 1999). Using a statistical procedure the presence of a hypothetical high lysozyme activity gene LZM$^+$ was detected, and the sires alternatively segregating high and normal lysozyme activity were identified. Original research (WALAWSKI et al. 1999) pointed to a clearly visible LZM$^+$ allele effect manifested in a three times higher bacterial lytic power. An exception to this rule is a significantly smaller difference in lysozyme activity in calves tested right after birth in which the genetic influence of the sire is diminished by dam's effect transferred most probably by the lysozyme present in colostrum.

The lysozyme gene recognized as a Lys1, Lys2, Lys3 multiple gene cluster (IRWIN et al. 1984) has been localized on 5q23 chromosomal position (GALLAGHER et al. 1993). Lysozyme cDNA (3.5 kb fragment) was found in macrophages (BRUNNER et al. 1994), whereas the coding and non-coding sequences and a polymorphic microsatellite (Lys-mic) fragment were identified (HENKE et al. 1996). Macrophage expressed Lys-mic polymorphism, which was manifested in the appearance of 12 variants, including 5 variants identified in Holstein-Friesian cattle (WEIKARD et al. 1996). In a Polish Black-and-White cattle population two additional Lys-mic 7 and Lys-mic 10 variants were found

(PAREEK et al. 1998a, WALAWSKI et al. 1999). Lys-mic 7 was directly identifiable with the phenotypically recognized LZM$^+$ allele (PAREEK et al. 1998b). Bulls inheriting alternatively high or normal lysozyme activity were genotyped as Lys-mic 3/7 heterozygotes.

An immuno-relevant cDNA lysozyme gene fragment was also found in mammary gland tissue (STEINHOFF et al. 1994), and as a consequence the lysozyme gene was pointed out as a candidate gene of mastitis resistance in cattle (SEYFERT et al. 1994).

On the basis of population analysis including almost 10 thousand individuals of Black-and-White cattle, it was found that LZM$^+$ frequency is very low (WALAWSKI et al. 1999). The unbalanced genetic structure of breeding herds does not allow to carry out methodologically correct research verifying Lys-mic polymorphism as a mastitis resistance factor. An attempt was projected on experimental herds to equalize the number of Lys-mic genotype groups. Bulls identified as LZM$^+$ carriers (Lys-mic 3/7 heterozygote) and their offspring were used for individual mating which are supposed to bring the so far unregistered Lys-mic 7/7 homozygote animals, as well as contemporary animal groups of other Lys-mic genotypes.

In the mammary gland, lactoferrin gene expression was also identified. (GOODMAN, SCHANBACHER 1991, SEYFERT et al. 1996). Lactoferrin does not show any genetically controlled polymorphism, but it is linked with polymorphic transferrin and ceruloplasmin polymorphic systems. Furthermore, a few DNA non-coding fragments specifically digested by restriction nucleases were identified. So far no information specifying the relationship between the polymorphism of non-coding lactoferrin gene fragments and mastitis resistance in cattle have been confirmed.

Intensive research has been focused on finding the relationship between the histocompatibility complex and immunological reactivity processes. In cattle, MHC system found in chromosome 23 includes about 10 BoLA class I loci, which appear in 17 allele variants and creates over 50 haplotypes as well as BoLA class II-DQ, DR, DY, DO, DI loci (ANDERSSON 1988, GROENEN et al. 1990), including the highly polymorphic DRB3 locus (van EIJK et al. 1992) and an unspecified number of BoLA class III loci (ANDERSSON, DAVIES 1994). The BoLA complex is closely linked with M blood groups system (LEVAZIEL, HINES 1984). Antigen M was recognized as a direct BoLA W16 haplotype marker which is negatively correlated with mastitis resistance (SOLBU et al. 1992, LARSEN et al. 1985). Original research was carried out on a herd of Black-and-White cows (WALAWSKI et al. 1993a, 1995). In the subsequent stages of I, II and III lactation, milk and blood diagnostic indices were registered. On the basis of serological tests M-positive and M-negative groups of cows having the same father were distinguished. The negative influence of M antigen manifested itself in a higher SCC score in milk and in pathological changes in milk properties. Differences in the leukogram and blood serum protein-gram were also found. M-positive cows were characterized by higher score of monocytes and eosinophils. The registered changes in blood di-

agnostic indices are typical for bacterial infections and may also be recognized as genetically controlled natural resistance symptoms. Research was also carried out to describe the relationship between mastitis susceptibility and BoLA class III polymorphism. In Holstein-Friesian sires a negative correlation between BoLA DQ1A and DRB3 (LUNDEN et al. 1990) as well as DRB 3.23 haplotypes (KELM et al. 1997) and the mastitis resistance index was found. Moreover, groups of cows with BoLA DRB3.23 were characterized by a higher frequency of clinical and subclinical mastitis cases, which still does not change the SCC score in milk (SHARIFF et al. 1998).

Statistically significant, but hard to interpret results were obtained in research on the relationship between subclinical mastitis and milk protein polymorphism (WALAWSKI et al. 1997). It was found that cows with beta lactoglobulin (LGB) AA genotype have a higher SCC score and show pathological changes in milk properties and composition in mastitis-related cases. At the same time significant differences in the leukogram, and protein-gram composition, as well as the lysozyme activity in blood serum were observed. The obtained data does not prove whether the differences in blood indices are the cause or effect of udder dysfunction. Hypothetically it was assumed that LGB gene expression might occur in cells participating in immunological processes localized outside udder tissue. Initial research carried out on calves indicates that the LGB genotype is the factor which changes the leukogram and NBT reduction indices. A pleiotropic mastitis resistance effect was also found in the polymorphic kappa-casein (CASK) system. CASK AB heterozygote cows show a lower SCC score in comparison to CASK AA and BB heterozygote contemporaries reared in the same herds (WALAWSKI et al. 1994).

The potential marker of natural resistance is the alpha-lactoglobulin (LALBA) gene, similar in structure and function to the lysozyme gene (MCKENZIE, WHITE 1991). A genetic polymorphism of LALBA coding fragments is found only in *Bos indicus*; in European dairy cattle breeds this protein is monomorphic. Meanwhile, the polymorphism of the LALBA non-coding gene fragment has been discovered (MARTIN-BURRIEL et al. 1997), but its biological function has not been examined.

Theoretical considerations show that when looking for possible natural resistance genetic markers, polymorphic systems which show expression in white blood cells may be important. Particular attention should be paid to research on the structure and organization of the beta2-integrin gene (ITGB2) (CZARNIK, KAMIŃSKI 1997, KRIEGESMANN et al. 1997), where the D128G lethal recessive mutation (BLAD) shows at the same time a decidedly beneficial pre-selection effect for milk performance traits (CZARNIK, WALAWSKI 1998). The other area of research includes polymorphic enzymes, such as leukocyte alkaline RNA-ase (WALAWSKI, PRUSINOWSKA 1981) and leukocyte acid phosphatase (KACZMARCZYK, WALAWSKI 1992) participating in degradation of bacterial pathogens.

Currently research on genetic determination of mastitis is developing dynamically, which is related to application of achievements of molecular genetics. The structure and organization of non-specific monogenic resistance factors are soon to be identified. However, theoretical research should be accompanied by breeding experiments verifying the practical benefits of the identified genetic markers.

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