AGRICULTURAL BIOLOGY,
2018, V. 53, № 2, pp. 235-247
(SEL'SKOKHOZYAISTVENNAYA BIOLOGIYA)

ISSN 2412-0324 (English ed. Online)
ISSN 0131-6397 (Russian ed. Print)
ISSN 2313-4836 (Russian ed. Online)

UDC 636.082:636.018:571.27

doi: 10.15389/agrobiology.2018.2.235eng
doi: 10.15389/agrobiology.2018.2.235rus

MOLECULAR MARKERS IN IMMUNE RESPONSE MANIFESTATIONS
(review)

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The author declares no conflict of interests
Received June 23, 2016

Abstract

Genetically controlled immune system is responsible for population heterogeneity on the immune response. This review focuses on molecular mechanisms of cell-mediated and antibody-mediated immune response and molecular markers for genomic selection. Genotypic differences between individuals in terms of tolerance/susceptibility to infectious diseases are characteristic of animal populations (S.C. Bishop et al., 2014). Data massive indicates multiple SNPs associated with high and low immune responses of animals, providing the possibility of calculating the coefficients of genomic breeding values for this attribute. There is a need to assess the dispersion of indirect genetic effects that help to open up new possibilities for the control of infectious diseases through selection. However, it should be noted that the quantitative genetic analysis based on individual animal disease status covers only part of the total genetic variation that affects the dynamics of infectious diseases in populations. Estimation of gene expression patterns in a particular immune response is considered as the most valuable (V.V. Firstova et al., 2010). Study of the major histocompatibility complex (MHC-B) 209296 bp region in birds with high-density SNP chips allowed the authors to determine 45 key genes which affect MHC-B diversity through recombination. The findings extend the understanding of the contribution of recombination to the diversity of MHC-B haplotypes, including the ability to identify hot spots and recombination estimation of recombination frequency (J.E. Fulton et al., 2016). The causative mutations related to the basic genetic variability of innate and adaptive immune responses in chickens are mapped (A. Slawinska et al., 2013). Search for causal mutations responsible for genetic variation in the immune response can be used as an approach to diagnostic tests. E.g., SNP associated with susceptibility to tuberculosis are detected (M.L. Bermingham et al., 2014). Immune response falls into a category of complex and quantitative traits that are under control of multiple genes with a noticeable influence of the environment. Obviously, some genes of common universal action may participate in innate and adaptive immunity. We can assume that such immunity has predominantly additive mode of inheritance (M. Siwek et al., 2015). Breeding for diseases resistance is greatly difficult because of low heritability and lack of estimates for comprehensive genetic assessment of the disease resistance variability. Growing genomic evaluations of the animals has created a basis for the use of molecular markers in breeding to increase animal resistance to diseases. Studies of the genome and the overall adaptive immune response associations in different species of farm animals provide an important starting point for the implementation of such plans. Identification of potential biological pathways and genes associated with immune response can assist in advancing the understanding of the important processes in animal resistance or susceptibility to diseases.

Keywords: immune response, antibodies, genome, single nucleotide polymorphism, SNP, disease, resistance, selection, quantitative traits, receptors, animals, heritability, associations, mutations

Infectious diseases are a big challenge for livestock farming and present a zoonotic threat to human health. Change of the nature of immune response in line with a characteristic of the pathogen effect provides main protection for the animals. Genotypic inter-specie differences in terms of tolerance/susceptibility to infectious diseases were found [1, 2]. However, one issue still pending is the possibility for inclusion of the characteristics of immune response into the selective indices to reduce frequency and severity of diseases in animals.

Over the past decade, genome valuation technique by genome-wide

screening of single nucleotide polymorphisms (SNPs) in animals was developed. The technique allows detecting of up to few millions SNPs, hundreds and thousands of which may serve as variation markers at detection of quantitative traits. Genome selection was successfully implemented in the breeder's service of many countries in the world [3].

Present review summarizes information on candidate gene, quantitative trait locus (QTL), causal mutations engaged in immunity control, and associated single nucleotide polymorphisms (SNPs) due to the genomic selection perspectives for disease resistance in animals. The studies on association of polymorphisms in several genome elements with total adaptive immune response in various species of agricultural animals allow creating the framework for realization of such plans. Identification of the potential genes and biological immune-reactivity mechanisms will help us understanding the formation of the disease tolerance/susceptibility in animals and detecting the markers of immune response traits for inclusion thereof in the genome selection criteria.

Present review compares molecular marker-based methods of animal immune response characterization as the tools for selection of individuals with high tolerance to diseases.

Innate and adaptive immunity are two categories of immune response. Studies of genetic background of immune response are based on identification of relevant QTL (quantitative trait loci) and single mutations in structural candidate genes involved in the immune response control. To search SNPs associations in particular QTL regions and gene candidates, such genes and SNPs found in databases (http://www.ncbi.nlm.nih.gov) are assessed for the relationship between SNPs and variation of qualitative traits. There is an aggregated linear model for evaluation of the relative effects of genes on tolerance/susceptibility to infectious diseases [4]. This model is applicable to study the marker and gene associations with incidence and distribution of diseases. However, traditional quantitative genetic analysis of certain pathology covers only part of the total genetic variation that affects the dynamics of infectious diseases in populations [5]. Although research data confirm applicability of linear model for a probabilistic estimate of susceptibility to the infection, characterization of the parameters assessed by this model is incomplete, and its infectious component is not always linear [6]. Another model is based on the equation for probability of the disease depending on genetically controlled specific susceptibility of the individual and the genotypes of the infected members of the group. These models are good tools to study the variability of quantitative traits, when all genes involved must be assessed simultaneously (e.g. in genomic prediction of breeding value), and to identify genes that facilitate the spread of the infection [7].

The high density SNP chips showed 45 main genes in bird genome, with localization in 209,296 bps region of major histo-compatibility complexes (MHC-B), which promote variability by recombination [8]. SNP genotyping allowed identifying 122 haplotypes by MHC-B, including new recombinant haplotypes due to crossing-over. Besides, evidences of gene duplications and deletion were obtained. It was shown that SNP panel is sufficient for identification of known and new recombinant haplotypes. Perceptions of recombinant contribution to variety of MHC-B haplotypes have been changed, including the opportunity for identification of hot recombination spots and estimation of recombination frequencies [8].

Immune responses refer to the complex quantitative traits and are controlled by a number of genes, manifestation of which depends on the environment. Search for the key mutations in charge for the genetically determined variability of a trait could be considered as an approach to disease tolerance diagno-

sis and as an approach to prevention and treatment of diseases. M. Siwek et al. [9] has studied the adaptive immunity under the effect of hemocyanin and genetic immune response to liposaccharides and lipoteichoic acid. Candidate genes and mutations in chicks were registered with identification of SNP associations in certain QTL regions. At genotyping by chips (Illumina, USA), the most significant SNPs associated by response to hemocyanin were found in gene encoding JMJD6 (Jumonji domain-containing 6 protein, arginine demethylase and lysine hystone) and located on chromosome 18. Four SNPs were located in candidate genes *FOXJ1* (transcription factor 1) on chromosome 18, *EPHB1* (B1 tyrosinase receptor) — on chromosome 9, *PTGER4* (prostangladin E receptor 4) — on Z-chromosome, *PRKCB* (protein kinase C β-isoform) — on chromosome 14. The association with antibody response to liposaccharides was found for all of them. One SNP in *ITGB4* gene (β4 integrin) located on chromosome 18 is also associated with genetic immunity response to liposaccharides. Characteristic of such gene product makes them the candidate for participation in immune response to liposaccharides, in control of T-cell functions and proliferation thereof. Thus, *FOXJ1* gene is involved in regulation of T-cell tolerance and inhibition of spontaneous autoimmune diseases; *PTGER4* gene modulates the immune response by intensification of the production of E2 prostaglandin in case of inflammation; *ITGB4* gene is associated with immune response to lipoteichoic acid which initiates such immune response through recognition of toll-like receptors 2 (TLR) interoperating with macrophages or antigen-presenting dendritic cells.

Therefore, SNPs associated with more significant incidences of immune response s to hemocyanin and lipoteichoic acids are located in QTL regions, which were primarily, based on linkage group analysis, proposed as the principal ones by their effect on the immune response. Similar analysis may merely serve as a preliminary search engine of the key mutations in gene candidates. Several universal genes may participate in formation of the genetic and adaptive immunity. It may be considered that this or other immunity mainly has an additive inheritance type.

QTL associated with immune response was found on chromosomes 9, 4, and 18 in chicks [10]. Additional statistical analysis of QTL, with narrowing of the confidence range, had shown that the selected areas on chromosomes 9, 4, 18 and Z have causal mutations associated with the main genetically determined variability of the innate and adaptive immune responses. Candidate genes associated with lipoteichoic acid antibody synthesis are located on chromosome 9 (genes *EPHB1*, *KLHL6*, *PROCR*) and on chromosomes 18 (genes *ITGB4, UNC13D*, *MAP2K4*, *FOXJ1*, *JMJD6*). The SNP polymorphism association was found of the area of *MAPK8IP3*, *IL9R*, *SOCS1* and *PRKCB* genes on chromosome 14 with the immune response to liposaccharides. The candidate genes for antibody response to lipoteichoic acid are on chromosomes 9 (*KLHL6*), 8 (*FOXJ1*, *ITGB4*, *JMJD6*), and Z (*PTGER4*).

Genome evaluation is a perspective tool for improvement of breeding for economically important qualitative traits in animals, i.e. milk and meat productivity and quality [3, 11, 12]. X. Lu et al. [13] had studied SNPs associated with immune response in 657 pigs. Piglets aged 21 days were vaccinated with a modified live vaccine against the classical swine fever. Blood samples were collected when the animals aged 20-35 days. Blood IFNγ and interleukin-10 (IL-10), their quantitative ratio, and virus-neutralization antibodies of IgG were assessed. Illumina porcine SNP60 BeadChip was used in genotyping. Following quality control, 46079 SNPs were selected for identification of associations based on regression model of each SNP. A total of 10000 iterations were performed for valid results. The 32 SNPs, which accounted for 3.23 to 13.81% of the total phenotype dispersion, were selected at statistically significant level. Phenotype dispersion by

IFNγ, IL-10, IFNγ/IL-10 and IgG comprised 37.52, 82.94, 26.74, and 24.16 %, respectively. It is possible that several significant SNPs are located in areas containing a number of known immunity genes. This study makes the basis for identification of mutations affecting the immune potential in pigs. Associations were found of SNPs in gene *PANE1* (Proliferation Associated Nuclear Element 1, minor histocompatibility antibody) with blood immunological parameters and body weight in young pigs at birth [14]. Further studies identified allele frequency of such gene in domestic pigs and wild boars and its association with reproduction values [15]. Wild pigs did not validly differ from the domestic ones in frequency of polymorphous variants of *PANE1*, however, litter size and weight decreased in sows with C→G replacement in intron 1 of gene *PANE1*.

Modern molecular methods can help to identify high associations of genes and genome areas with the response to vaccines and with tolerance to certain pathogens. This allows researchers to map tolerance-associated genes for further use in genomic selection. Special attention should be drawn to virus diseases. Their causative agents are constantly mutating and evolving that necessities molecular and genetic control of whether the associations involved in the disease tolerance have changed.

Genomic evaluation of the pigs of Korean and Yorkshire crosses in F_2 had shown 46865 SNPs [16]. Regression analysis showed 54 SNPs assumedly associated with neutrophil, lymphocyte, monocyte, eosinophil, basophil, immunoglobulin, insulin, and insulin-like growth factor 1 (IGF1) functions. Each set of SNPs had explained from 24 to 42 % of phenotype dispersion of the traits studied. Several pleiotropic SNPs were found on chromosomes 4, 13, 14, and 15. High density SNP microchips also revealed QTLs for blood components associated with immune response [17, 18].

Genetic factors impact susceptibility to and the course of porcine reproductive and respiratory syndrome (PRRS), a disease with significant economic damage to the livestock [19]. QTLs located on pig chromosome 4 explain most genetic variations in PRRS susceptibility. Genome-wide analysis of 200 pigs with Illumina porcine SNP60 BeadChip has revealed that specific haplotypes could associate with the desired phenotypes, and certain genomic regions were involved in a response to PRRS [19, 20]. The traits associated with the infection response were mostly controlled by the chromosome 4 region, however small effects were due to other chromosomes. These studies also assessed the predictive value of QTL-based genome estimates for pig breeding. Selection for SNP genotypes of QTLs located on chromosome 4 may reduce PRRS effects, including the economic ones. The key role of chromosome 4 mutation rs340943904 in the control of PRRS response is under consideration. The study results will help in development of breeding methods to combat PRRS.

Statistically valid data indicate wide-genome associations of SNPs with susceptibility to infectious diseases. Such associations are identified in cattle in tuberculosis caused by *Mycobacterium bovis*, the disease with significant economic damage and the risk of zoonosis [21-25]. Tuberculosis tolerance loci were revealed with Illumina BovineHD BeadChip. Identification of two new tolerance loci, the *PTPRT* (Receptor-type tyrosine-protein phosphatase T) genes and *MYO3B* (myosine IIIB), were due to use of linear and logistic mixed models, as well as regressions. Informative SNPs explain 21 % of phenotype tolerance to tuberculosis, including 6.2 % dispersion due to *PTPRT* gene and 3.6 % dispersion associated with the assumed *MYO3B* gene variant copies.

Be it repeat that modern methods of quantitative genetic analysis of pathology manifestation in the individual disclose only a part of the genetic variation [26], and selection for disease tolerance is seriously challenged by low heritability

of a trait. Selection for the tolerance by the estimates of direct and indirect selection traits is more effective than the traditional selection methods but necessitates the improved statistical models and the models of indirect genetic effect manifestation. Additionally, modern approach to selection requires relevant methods of data collection and test planning to reliably assess genetic parameters of susceptibility in the host and pathogenicity of the infectious agent [27]. Differences in the infection transfer may be due to inherited physiological and behavioral variations. It should be also noted that improper administration of antibiotics induces the tolerance of pathogens and requires additional measures to control diseases [28, 29].

Canadian researchers had shown that accounting for the immune response traits the animal breeding allows increasing the disease tolerance in dairy cattle. Recording of the cell-mediated reaction and response through antibodies allowed separating the animals into groups with strong, average, and weak immune response [30]. Inheritance ratio of 0.19 to 0.29 indicates perspectives of selection for immune response traits. In turn, higher immunity contributes to a decreased frequency of mastitis, hysteritis, and ketosis [31]. Cows with weak antibody-mediated immunity usually suffer from the most severe mastitis. Immunological parameters should be used in breeding for the improved immunity to reduce the frequency and severity of a number of diseases in agricultural animals. In cows, candidate genes and SNPs associated with antibody-mediated immunity, as well as biological mechanisms involved in control of immune response, were disclosed [32]. With $P < 0.05$ confidence, 4045 out of 54609 of the registered SNPs were associated with humorous immune response. After false alleles with low frequency were excluded, 402 SNPs were obtained. The SNPs, like the genes of major bovine histocompatibility complex (Bola), were mostly located on chromosome 23. So the study of dairy cattle shows numerous SNPs associated with varying capability to produce antibodies, which allows use of this trait in animal breeding.

Many chronic autoimmune diseases may be due to changes in the genes of immune response. Lab based technology was used to characterize in vitro the immune response as related to dairy cattle phenotypes including in vivo immune response phenotyping [33, 34]. Blood lymphocytes of cows different in the strength of immune response were stimulated with concanavalin A to study protein synthesis and gene expression. Production of interleukine 4 (IL-4), IFNγ and *IFNG* gene expression were higher in animals classified as high responders compared to those of low immune status. However the responders did not differ in a number of other traits studied. The authors concluded that the distinct cytokine profiles could be used to define disease resistance phenotypes. The laboratory tests are expected to select animals for immune reactivity in order to reduce incidence and severity of diseases.

Like immune-related QTLs, genes of effector proteins, e.g. cytokines, antiviral interferon, involved in the control of immune mechanisms against certain pathogen may be also mapped.

It was shown that tolerance of mice to infection caused by *Francisella tularensis* subsp. *holarctica* is due to emergence of CD69 molecules at surface of T-helpers and synthesis of IFNγ and IL-17 by splenocytes [35]. HLA-DR (human leukocyte antigen), the late activation marker, appears on the surface of T-helpers (CD69+ and CD45RO+) and cytotoxic lymphocytes under the effect of F1 capsular antigen of *Yersinia pestis* at immunization with a live pestiferous vaccine [36]. Specificities of activation of T and B lymphocytes, expression of their surface markers and synthesis of cytokines as influenced by specific *Y. pestis* and *F. tularensis* antigens are reported [37]. The effects of recombinant producers

of capsular F1 *Y. pestis* KM 277 antigen, the purified product (F1), chemical pestiferous vaccine and protective antigenic complexes of various tularemia agent sub-species on expression of Toll-like receptors 2 and 4 were compared [38]. Recombinant *Y. pestis* KM 277 strain, the capsular F1 antigen, and the chemical vaccine increased mRNA TLR2 expression during the first hours after injection with further enhanced cell proliferation in thymus and spleen resulting in high protective immunity.

Spontaneous production of interferon IFNγ (Th1 T-helper sub-population marker) and interleukin 4 (IL-4) (Th2 T-helper sub-population marker) in blood cell cultures and mixed population of lymphocytes, as well as blood levels of immunoglobulins IgG, IgM, IgA, IgE against capsular F1 antigen were compared to those induced with conconavalin A or antigen of inactivated pestiferous bacteria. The data showed functional activity of Th1 and Th2 cells (production of IFNγ and IL-4) after vaccination [38]. Receptors for IgM which in various periods of ontogenesis is present in cattle blood in soluble and bound forms are described. Qualitative changes in populations of animal cells bearing the receptor proteins IgSF [39], as well as functions of IgSF [40] are described.

TLRs are decisive in genetic immunity against many pathogens [41]. Each TLR identifies certain pathogen and participates in signal transfer to initiate the immune response. The mammals have 13 TLRs (from TLR1 to TLR13) specifically linking the ligands. Number of TLRs varies in different animal species. Toll-like receptors operate in many cell types, including macrophages, antigen-presenting dendritic cells, keratinocytes, and sperm cells. TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 on cell membrane recognize molecules specific for pathogens (except for the nucleic acids), while intracellular TLR3, TLR7, TLR8, and TLR9 identify nucleic acids. TLRs are relatively big proteins. Porcine surface and intracellular TLRs consist of 785-856 and 905-1050 amino acids, respectively. A system of TLRs on cell membranes is polymorphous that allows recognition of more pathogens. Pigs have 10 *TLR* genes which are mapped on chromosomes 1, 8, 10, 13, 15, and X. Genetic and functional tests revealed several missence-SNPs in porcine *TLR* genes. *TLR1*, *TLR5* and *TLR6* are involved in production of antibodies after vaccination against *Actinobacillus pleuropneumoniae* [42]. *TLR2* is associated with frequent pneumonias caused by *Mycoplasma hyopneumoniae* [43], *TLR5* is associated with expression of IL-2, IL-10 in mononuclear cells of peripheral blood [44]. SNPs in *TLR2* and *TLR5* cause the amino acid replacements related to differential response to *Salmonella enteric* [45]. Out of 10 of porcine TLS genes, *TLR4* is more frequent. SNPs in *TLR4* are reliably associated with changed transcriptional activity of interferon genes, tumor necrosis factor, interleukins IL-2, IL-4, IL-6, and with lung injuries [46]. In addition, SNPs in TLR4 correlate with the ability of pigs to become agents of infection because of the pathogen in feces [47]. Both humoral and cellular immune responses are effective in African swine fever [48].

Double intramuscular injections of the experimentally inactivated vaccines in chicks against the respiratory mycoplasmosis activate T-helper sub-populations soon after vaccination. Herewith, number of CD4+ T-helpers reaches the maximum values on day 21 [49]. Both histocompatibility gene clusters, MHC-B and MHC-Y, in chicks are located as separate haplotypes [50]. Although many genes of MHC-B are polymorphous, and the system itself is polygenous, the role of only some MHC-B loci is documented, and in most cases associations between MHC-B and disease tolerance are determined only at haplotype level [51]. *BG1* locus has quiet significant effect on development of Marek's disease [52]. Relationship between the genes of MHC-Y cluster discovered recently, and the disease tolerance is established [53]. Several poultry lines inbred for MHC-B, in-

cluding congenic White Leghorn lines, were produced to study the relationships between the MHC-B haplotypes and tolerance to infectious diseases. Haplotypes MHC-B were primarily identified by hemagglutination. Haplotypes including *BG* and *BF* loci were found among homozygotic families [54]. Recently, large-scale sequencing of MHC-B area of 59 kbps confirmed the differences between 14 standard haplotypes. It was proven that mutations, recombinations, and gene conversions have contributed to variation of MHC-B haplotypes [55]. For more accurate differentiation of MHC-B types in several chicken breeds and populations, 101 SNPs were revealed in the main area sequence (GenBank AB268588) containing 45 genes most part of which is involved in control of innate and adaptive immunity.

TLRs participate in activation of macrophages in mammals. *TLR15* expression in birds significantly increases at stimulation by both intact and heat- or formalin-inactivated *Salmonella enterica*, *Escherichia coli*, and *Enterococcus gallinarum*, but does not depend on known TLR agonists and *Rhodococcus equi* [56]. These observations show that several TLR agonists are not ligands of TRL15, which is responsible for recognition of specific gram-negative and gram-positive bacteria causing diseases in chickens.

Crosses of animals with different immune responses to detect QTLs defining such differences may serve an example of functional genomics methods in immune response studies. With the same purpose, the expression of thousands of genes before and after the infection is estimated with oligonucleotide chips via differentiation of the effects for specific antigens [57]. Interpretation of QTL effects is challenged since QTLs are big in size and may contain hundreds of potential candidate genes. Use of microchips allows identification of a large number of differentially manifesting genes, but, unfortunately, does not explain the specificity of their relationships. Cis- and trans-regulation of gene expression initiation still remains a challenge in studying genes operation in a QTL.

Recovery also depends on the effectiveness of immune response [58], and, thus, identification of genes affecting the immune functions may help to identify animals with different recovery speed. The inherited immune characteristics are related to immune-reactive QTL. Thus, the inherited traits, i.e. portion of immunity-related blood cell types and quantity of blood antibodies, are expressed.

T-regulatory cells (Treg), a small sub-population of T-lymphocytes, play an important role in the immune response modulation [59]. Suppressive activity of Treg may have adverse effects. At the same time, these cells are involved in tolerance to own antigens and suppression of autoimmunity in hemotransfusion. This phenomenon gives new perspectives for immune therapy of autoimmune diseases and better acceptance of homotransplants. Data on cellular and molecular mechanisms of immune processes in oncopathologies showed an important controlling and balancing effect of Treg family on the immune system [60]. Molecular and genetic specificities of peripheral Treg cells, micro environmental impact on their differentiation and activity, family self-regulation by nTregs, immune aspects of peripheral tolerance and immune therapy of oncological diseases are now key issues for experiments and clinical tests. Studying mechanisms of immune activation and regulation by naive T-cells, memory T-cells, MHC molecules, and signal proteins will contribute to a progress in anti-tumor vaccine therapy. Peripheral tolerance, i.e. suppression of potentially autoreactive T-and B-cells in peripheral tissues, and participation of Tregs in tolerance formation in malignant tumor are studied [61]. Seven Treg family members differing in immune phenotype and functional characteristics are described [62]. Flow cytometry was used to divide cytotoxic peripheral blood T-lymphocytes

into sub-populations (CD27+, CD28+, CD45RA+, and CD62L+) [64]. This method was also helpful at identification of CD3+CD8+ lymphocyte population during differentiation [63].

Thus, causative mutations and the candidate genes involved in animal immune function are associated with single nucleotide polymorphisms (SNPs) both in QTLs and the candidate genes themselves. Research results evidence on the presence of the key SNPs associated with strong and weak immune response. This data allows calculation of animal breeding value estimates for disease tolerance. Immune responses are usually under control of many genes with various phenotypic effects and under the significant effect of environment. Study of tolerance genes, causal mutations, and molecular markers gives the approach to disease diagnosis, prevention, and treatment at molecular and genetic level. The use of genetically determined characteristics of immune response together with other breeding value estimates will reduce disease incidence and severity in animals.

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