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Genetics of Disease Resistance in Chicken

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Abstract

Although poultry industry has gained momentum during the last few decades, there are still various impediments like improper infrastructure, unscientific management and above all various deadly infectious diseases which incur huge economic losses on poultry industry. These diseases include viral diseases like Avian Influenza, Marek's Disease, New Castle disease and bacterial diseases like Colibacillosis, Pasteurellosis and Salmonellosis, etc. Development of disease resistant poultry has been found successful practice over the use of drugs or vaccines for disease control. Studies involving genome wide associations to figure out certain candidate genes that are involved in disease resistance have also been carried out. Single nucleotide polymorphism studies to unveil the mechanisms underlying disease resistance in chicken show that SNPs and other candidate gene approaches play a vital role in providing disease resistance. Also, understanding the genes and biological pathways that confer genetic resistance to various infections will lead towards the development of more resistant commercial poultry flocks or improved vaccines against various diseases. This chapter shall focus on various factors involved in disease resistance in chicken that interact with the pathogen and provide resistance against the pathogen.

Keywords: chicken, genetics, pathogen, disease resistance

1. Introduction

Poultry is a principal component in the global agricultural economy by serving as one of the primary sources of proteins for humans. Worldwide egg and poultry meat production is close

to 73 million tons and 100 million tons respectively [1]. Despite such an increase in the growth of poultry industry, this industry is consistently threatened by various diseases, including those caused by viral, bacterial and parasitic infections. These diseases can lead to substantial economic losses in two ways, firstly there is a reduction in the production of poultry related products, and also the input costs like labour and feed get increased. The impact of these losses in poultry industry is more worse on the livelihood of poor people in the developing countries where up to 25% of monthly income may be lost due to poultry disease [2]. Chickens have developed different responses to counter these diseases. These responses include immunological and genetic responses of the poultry. The genetic interaction between the host and the pathogen is a key factor in deciding the disease resistance. The chicken karyotype includes 38 autosomes, many of which are relatively small and uniform in size, often termed microchromosomes. Current knowledge of chicken immunogenomics such as the quantitative trait locus (QTL) mapping of the combination of DNA variations, immune response by the host and the transcriptome can be used to identify disease resistant genes. Disease resistant genes are those encoding antibodies, microRNA and other materials that help the host resist the damage caused by pathogens. Recent advances in the field of molecular biology have led to the discovery of many disease resistant genes. In poultry, genes such as MHC (major histocompatibility complex) genes, the *Nramp1* (Natural resistance-associated macrophage protein 1) gene, IFN (Interferon) genes, *Mx* (Myxovirus-resistance) genes, anti-ALV (Avian leucosis virus) genes and the *Zyxin* gene have been linked to disease resistance [3]. In most of the multicellular organisms single-nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variations (CNVs) are the major sources of genetic and genomic structural variations [4]. These genetic variations may be exploited to study the disease resistance levels in different organisms. Recent advances in the technology and cost effectiveness of genotyping, genomic selection approach has been followed extensively for animal breeding. The discovery of chicken genome and development of chicken transcriptome and proteome analysis has led to a better understanding of the mechanisms underlying the genetic susceptibility and resistance against different diseases. Genetic enhancement of the immune response can increase vaccine efficacy and disease resistance, thereby reducing drug residues in food. In order to reduce the drug residues in the food and introduce the genetic breeding programs for improving the disease resistance in the chicken we need to have a better understanding of the disease resistant genes. Also, breeding for disease resistance requires tools such as indicator traits or genetic markers that can be used for selection. Some diseases that have been found to cause serious economic losses to poultry industry in terms of morbidity and mortality are discussed below.

2. Salmonellosis

Among the different diseases occurring in poultry, those caused by the genus *Salmonella* is the most common, causing serious economic losses to the poultry industry in terms of mortality, reduced growth and loss of egg production. Two species are currently recognised in the genus *Salmonella*, *S. enterica* and *S. bongori*. These two species further comprise of about 2500 serovars. Chickens can get infected with *S. enterica* at any time during their life. However,

infections within the first hours and days of their life are epidemiologically the most important, as newly hatched chickens are highly sensitive to *Salmonella* [5]. Infection with most of the *Salmonella* serovars remains unnoticed as the birds do not show clinical signs, however infection with *S. gallinarum* and *S. pullorum* leads to clinical manifestations. Clinical signs that include lack of appetite, depression, respiratory distress, caseous core diarrhoea and early death are predominantly observed in young chicks. In laying hens symptoms include reduced egg production, fertility and hatchability [6]. The level of bacterial invasiveness depends upon the serovar that has caused the infection and host's immune status. Prophylactic measures, vaccination and use of antibiotics are insufficient to eradicate salmonellosis in poultry stocks, whatever the serotype involved. The major problems associated with the widespread use of antibiotics are the development of bacteria resistant to antibiotics, and the accumulation of antibiotic residues in food for human consumption [7]. In this context, selection of more resistant chickens can be considered as an alternative solution to decrease occurrence of the disease. In recent years, advances in molecular technology have created a new horizon for the genetic improvement of quantitative traits, particularly disease-resistant traits. The identification of direct or indirect molecular markers for these traits would facilitate the use of marker-assisted selection or gene introgression [8].

2.1. Genes involved in resistance to Salmonellosis

Many genes have been found to contribute towards resistance against bacterial infections. Some of the main genes involved are Major histocompatibility complex (MHC) genes, Caspase1 genes, NRAMP Family encoding genes, inducible nitric oxide synthase (iNOS) gene, genes encoding complement proteins and Toll-like Receptor 4 (TLR4) genes. Major histocompatibility complex studies have shown that different MHC-B haplotypes contribute differently towards the genetic resistance against salmonellosis. Also microsatellite analysis has shown that MHC-1 class has been linked to *Salmonella* colonisation [9]. Single-strand conformational polymorphisms (SSCP) and sequence polymorphisms have linked MHC I and MHC II to resistance against *salmonella* [10], and to antibody response kinetics [11]. The indigenous and commercial breeds of chickens in Vietnam also linked *Salmonella*-specific antibody responses to MHC-B haplotype [12]. Interleukins and chemokines also play a vital role in *Salmonella* infections. While comparing the interleukin mRNA expression in the heterophils of resistant and susceptible chickens, it was shown that the mRNA level of different interleukins like IL-6, IL-8 and IL-18 increased significantly in resistant chicken as compared to the susceptible chicken. The mRNA levels of transforming growth factor (TGF β 4) were found to decrease in heterophils of resistant chicken. Also the mRNA levels of interferon gamma (IFN γ) were found to be lower in susceptible chicken when compared to resistant chicken [13, 14]. Resistance to *Salmonella* has been linked to different genes like ILs, IFN γ , TLRs, iNOS and genes involved in apoptosis. Resistant chicken lines showed a higher expression of the interleukins like IL-2, IL-6, IL-8 and IFN γ in the small intestines as compared to susceptible chicken lines [15]. Interferon gamma gene expression was significantly lower in susceptible chicks as compared to resistant ones. Interferon γ expression level represents a valuable indication of immunodeficiency associated with persistence of *Salmonella* in the chicken digestive tract, and IFN γ thus represents a factor to consider in the development of prophylactic measures for the

reduction of *Salmonella* carrier state [16]. The natural resistance-associated macrophage protein 1 (NRAMP1) is a candidate gene associated with *Salmonella enteritidis* (SE) mediated immune response, and is related to the phagocytosis of SE. Studies have shown that the enhancement of host immunity mediated by the up-regulation of NRAMP1 mRNA in heterophil granulocytes and spleen might be more obvious and earlier in the SE infection resistant chicks as compared to susceptible chicks [17]. Different variations in the Nramp-1 gene have been associated with resistance to salmonellosis [18]. Natural resistance-associated macrophage protein 1 and 2 encoding genes (Nramp1 and Nramp2) are related to many diseases. Association analysis indicated that A24101991G is significantly associated with chicken salmonellosis resistance [19]. Certain genes like NRAMP1, TGF β 3, TGF β 4, and TRAIL have been found to be potent candidates for disease resistance against *salmonella* [20]. The candidate gene approach is a useful method to investigate genes that are involved in genetic resistance. Earlier studies showed that there is an involvement of 12 candidate genes in the pathogenesis of *Salmonella* in meat-type chicken [21]. These genes include NRAMP1, prosaposin (PSAP), inhibitor of apoptosis protein 1 (IAP1), inducible nitric oxide production (iNOS), Caspase-1 (CASP1), interferon-gamma (IFN γ), immunoglobulin light chain (IGL), interleukin-2 (IL2), transforming growth factors B2, B3 and B4 (TGFB2, B3 and B4) and ZOV3. *Salmonella enteritidis* infection was given to birds at 3 weeks post hatch. At day 7 post infection SE load was quantified in caecum, spleen and liver contents. In caecum nine out of 12 genes were found to be associated with bacterial load. These genes include CASP1, SLC11A1, IAP1, PSAP, iNOS, IL-2, TGFB2, TGFB4 and IGL. Five genes (SLC11A1, IL2, CASP1, IGL and TGFB4) were found to be significantly associated with bacterial load in liver. Only one gene i.e. TGFB3 was found to show association with bacterial load in spleen. The above study confirmed polygenic nature of SE resistance. A quantitative trait locus (QTL) on chromosome 5 was identified that was involved in controlling bacterial load in spleen and was named as SAL1. This QTL was found to be involved in bacterial clearance by macrophages. Single nucleotide polymorphism studies have shown three SNPs in an exon of chTLR15. One of the SNPs was found to be associated with *Salmonella* infection. The 'T' allele in SNP C726T might be linked to resistance of *Salmonella* infection. The mRNA expression of TLR15 in heterophils of chickens infected with SE was lower than that of the control group at day 3 pi. However, TLR15 was up-regulated in the spleen of chickens infected by SE at day 3 pi [22]. The above discussed genes are potential candidates that can be used for selection programmes for increasing genetic resistance against *Salmonella* Enteritidis in chickens. A number of factors which include Nramp1, MHC, TLR4 and a novel genetic locus SAL1 determine the genetic resistance of chicken against SE. After analysing and comparing studies of Myeloid differentiation primary response gene 88 (MyD88), novel mutation G4810372T was found that was thought to have an effect on immune response of the individual. Further studies are needed to elucidate the molecular mechanisms that occur due to MyD88 gene polymorphisms. After correlating susceptibility towards *Salmonella* Pullorum and MyD88 polymorphisms, it was found that alleles in SNP1 locus and SNP1 and SNP3 genotypes show a significant effect against *Salmonella*. Also the advantaged haploid type (TTC) combined by SNP1, SNP3 and SNP4 loci played a very significant role in genetic resistance to *Salmonella* Pullorum infection. Myeloid differentiation primary response gene 88 polymorphisms or advantaged haploid type in a particular region had a positive effect against susceptibility to *Salmonella* Pullorum infection. From the above observations it can be concluded that MyD88 can be used as a candidate

gene which could provide a conceptual reference for marker assisted selected for poultry [23]. In a study that was based on the biological function and SE response of various genes, five candidate genes were selected that were found to have a role in *Salmonella enteritidis* infection. These genes include toll like receptor 4 (TLR4), macrophage migration inhibitory factor (MIF), T cell specific protein (CD28), tumour necrosis factor (TNF)- α factor (LITAF) and MD-2. In TLR4, CD28 and MD-2 single nucleotide polymorphisms were found. The SNPs were tested for associations between sire SNP and *Salmonella enteritidis* response. The association of sire SNP with cecum bacterial load and vaccine antibody response was found to be statistically significant. Association of MD2 SNP was statistically significant with bacterial load in spleen. The use of the above studied SNPs can be used in marker assisted selection and may result in improvement in diseases resistance in poultry [24].

3. Avian influenza virus

Avian/Bird flu, caused by avian influenza virus (AIV) belonging to Orthomyxoviridae family, is the most fearful viral disease of birds and has a potential to cause a detrimental effect on poultry flocks. This disease is of great economic, zoonotic importance and may also lead to pandemic threats. This virus can lead to disease that may range from subclinical symptoms to highly virulent pathogenicity in poultry birds. The frequent disease outbreaks caused by avian influenza virus (AIV) not only affect the poultry industry but also pose a threat to human safety. Based on the level of pathogenicity the disease has been categorised into two groups. The first group is highly pathogenicity avian virus (HPAI) which is highly contagious, and can affect multiple organs. This disease has a potential to spread across national boundaries and is a listed disease of World Organisation for Animal Health (OIE). The second group is low pathogenicity avian virus (LPAI) which is mild disease in poultry that causes mild clinical symptoms like depression and anorexia. Avian influenza virus (AIV) has caused a great economic loss across the globe [25]. The AIV mostly gets amplified in poultry at live poultry markets and finally disseminates to humans [26]. While replication of LPAI occurs in epithelial cells of respiratory and gastrointestinal tract, HPAI replicates in multiple tissues [27]. World Health Organisation has emphasised on the preventive measures to be taken in order to minimise the risk of pandemic influenza and also have highlighted the importance of elucidating the host factors that are related to infection [28]. Currently live or inactivated viral vaccines are used to reduce the incidence of AIV, but these measures are not promising as the efficacy of these vaccines is complicated by different factors which include age/ health status of bird and also the antigenic variant of the virus. So there is an urgent need to develop promising and long lasting strategies to combat these viral diseases. To complement current approaches against AIV, development of poultry flocks that are AIV resistant can be used as a proactive measure to control epidemics and pandemics of influenza in both avian and human populations.

3.1. Genes involved in avian influenza virus

Many studies have been carried out to figure out different disease resistant mechanisms and genes in AIV. Previous studies on Beijing-You chicken have revealed 39 SNPs associated with

different immunological traits against avian influenza virus. An important QTL was found on chromosome 16 that was related to total $I_g\gamma$ concentration. Also five candidate genes that were related to $I_g\gamma$ levels were found that might play a role in immune modulation of birds infected with AIV. Different candidate SNPs for marker assisted selection for disease resistance have been identified. The candidate genes play a vital role in regulating immunological response in chicken [29]. Approaches like RNA interference (RNAi) technology can be used to develop transgenic poultry that are resistant to AIV. Synthetic RNA duplexes (siRNA) can be used to trigger RNAi [30]. Also RNAi can be triggered by expression of RNA duplexes in hairpin structures (shRNA) [31] which by RNA endonucleases can be processed into siRNA. While working on cell lines, chicken embryos, synthetic RNA duplexes specific for conserved domains of the influenza virus genes have been found to inhibit replication of various influenza viruses. [32, 33]. Stable expression of influenza-specific shRNA via a lentiviral vector in a cell line renders the cells refractory to influenza virus infection [33]. After introduction of the above mentioned lentiviral vector into mouse lung, an inhibition in virus production was observed *in vivo*. From these studies we can conclude that there is a possibility to develop influenza resistant poultry flocks by transgenic expression of influenza-specific shRNA. Current proposals to develop influenza resistant chicken include using combination of transgenic and RNAi that can be used for AIV gene expression inhibition. Screening of siRNAs as candidate genes *in vitro* is the key step for transgenic breeding. A combination of bioinformatics and other online search tools to design siRNAs that target different mRNA sites of AIV H5N1 subtype. Five rational siRNAs were chosen, five U6 promoter driven shRNA expression plasmids that contained the siRNA genes were constructed that were used to develop stably transfected Madin-Darby Canine Kidney cells. Data obtained from Indirect Immunofluorescent Antibody (IFA), virus titration, PUI stained flow cytometry, Real time PCR and DAS ELISA revealed that all the five stably transfected cell lines when exposed to CCID₅₀ of AIV were resistant to viral replication. Finally transgenic chicken were developed from the plasmids (pSi604i and pSi1597i). These findings provide baseline information for breeding transgenic chickens resistant to AIV in combination with RNAi [34].

4. Marek's disease

Marek's disease (MD) is a neoplastic disease in chickens, caused by the Marek's disease virus (MDV). Marek's disease virus (MDV) is an alpha herpes virus that targets avian species and establishes chronic infection. It is a highly contagious lymphotropic disease that remains an important source of economic losses to the world poultry industry since it was first reported by Joseph Marek [35]. Marek's disease signs include depression, wasting, loose watery stool, paralysis, lymphomas and severe immunosuppression. Although vaccination programs have been used to control onset of the disease, MDV still replicates in vaccinated chicks. These highly contagious cell free virions are continuously shed in the environment. This makes MDV environmentally persistent as well as a highly infectious [36]. Continuously more virulent MDV strains evolve that makes the current vaccination programs ineffective and urge for a need to develop strategies that will augment existing MDV control strategies [37].

4.1. Genes involved in resistance to Marek's disease

The genetics of the host response to the MDV have been studied for many years. Many loci have been known to be involved in disease resistance but only few genes have been identified to have an actual role. Major histocompatibility complex plays a vital role in resistance against MD [38]. Being a polygenic trait, many genes and gene loci have been reported to be involved in MD resistance. Major histocompatibility complex is one among gene/loci to be involved in genetic resistance against MD. Other genes that are non MHC in origin have also been linked to play a role in genetic resistance/susceptibility to MD. These genes include growth hormone gene, cytokines (IL 6 and IL 18) and the stem lymphocyte antigen 6 complex, LY6E gene. Loci rs14527240 and GGaluGA156129 have been reported to play a role in host resistance/susceptibility to MD. Also expression studies suggest a possible role of SMOC1 gene in MD susceptibility [39]. Nitric oxide which apart from being a promising antiviral agent, also plays a role in modulating immunological responses. While working on Marek's disease it was found that chickens resistant to MD have the ability to produce more nitric oxide than susceptible chicken lines. The above observation was made by measuring nitric oxide levels from the chicken fibroblasts that were taken from these chicken lines after treatment with LPS and recombinant Chicken IFN- γ . Further plasma nitric oxide levels were measured in chicken lines (N2a, P2a) inoculated with JM-16 strain of MDV. The levels of NO were found to be increased in N2a chickens in majority of the experiments carried out (four out of five). In comparison, in only one experiment the levels of NO were found to be elevated in P2a chickens that too at 10th day post infection. The level of the NO production was found to be associated with the range of virulence of the MDV strain. Inoculation with more virulent strains induced highest NO level which suggests the possible role of NO during the disease progression. Quantitative real time PCR studies show that IFN γ does not primarily induce iNOS gene expression during MDV infection. Nitric acid production and inducible nitric oxide gene expression are mediated during cytolytic phase of infection. These findings suggest that NO may play a role in increasing MDV virulence by suppressing immune system [40]. In order to breed chicken which are genetically resistant to the Marek's disease, we need to have an ample knowledge about markers that play a role in the resistance to MD. A study was carried to find out the MD resistant markers in chicken lines, copy number variation (CVN) were studied in inbred MD resistant and susceptible chicken lines. In four chicken lines 45 copy number variations were found, out of which 28 CVNs were involved in cellular proliferation and immunological responses. Also two CVNs that were found to be associated with resistance to MD were transmitted to the descendent recombinant congenic lines that differ in MD susceptibility. These observations may be useful for designing better and reliable strategies to improve genetic disease resistance in poultry.

5. Newcastle disease

The causative agent of Newcastle Disease is Newcastle Disease virus (NDV) which belongs to paramyxovirus and is a negative sense RNA consisting of about 15×10^3 nucleotides [41]. This is an enormous destructive and contagious disease that causes serious problems in poultry

industry across the globe. Among different poultry diseases NDV was reported to be the fourth most destructive disease that led to heavy losses to poultry industry [42]. Newcastle Disease was considered to be most widespread disease in animals along with rabies and bovine tuberculosis [43]. After infection with NDV the host comes up with non-specific symptoms which include ruffled feathers, depression, breathing problems, anorexia, hyperthermia and listlessness followed by death. Affected chicken show respiratory and neurological complications and also reduction in egg production. Chicken infected with NDV are able to raise an antibody and gene response. The antibody response varies in different chicken breeds, hence understanding the genetics of the immune response may help in improving disease resistance in chicken [44].

5.1. Genes involved in resistance to Newcastle disease

A study was conducted to elucidate the host antibody response towards NDV. A novel QTL locus that was found to be associated with antibody response was found. From the proximal end of GGA1 this QTL region was located approximately 100 Mb away. This region was proposed to play an important role in immune response of the chicken. Two genes namely ROBO1 and ROBO2 were thought to be promising candidate genes that might have a role in modulating antibody response in chicken infected with NDV. For further confirmation of the role of these genes, studies that include silencing and over expression of ROBO 1 & ROBO2 need to be carried out both *in vivo* and *in vitro* [44]. Host response towards NDV infection is poorly understood. In order to have a better understanding of the host pathogen interactions during NDV infection a transcriptional profiling study of chicken embryo cells that were infected with NDV strain D58 was carried out by quantitative real time PCR. Some of the genes under study were upregulated and some were down regulated. Genes such as IFN- α , IFN- γ , DDX-1 and MHC-1 were upregulated IL-6 gene was down regulated. The expression levels of the M and F genes of the virus were also measured. The genes that encode for pro inflammatory response, cellular responses and other genes that regulate interferons were found to be affected during the infection. These findings suggest the involvement of different signalling pathways that are involved in host response towards infection [41].

6. Conclusion

For effective control of different infectious diseases in chicken, the best and most reliable approach is the improvement of the genetics of disease resistance. Enhancement of immune responses may lead to improved efficacy of vaccines and disease resistance, hence reduction in drug residues in the food products. Introducing new technologies that will help us to unveil the underlying transcriptional and other molecular mechanisms for disease resistance in chicken is a promising tool to improve genetic resistance for diseases. Technologies that aid in identification of disease resistant genes include next generation sequencing, microarray analysis, RNA sequencing and high density SNP genotyping. The development and distribution of disease resistant poultry flocks represents a proactive strategy for controlling diseases in chicken and complements current approaches for disease control by drugs and vaccination.

Conflict of interest

The authors declare that they have no competing interests.

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