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Alloantigen Systems and Genetic Resistance of Chickens to Coccidiosis

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ABSTRACT: Genetic resistance of chickens to coccidiosis has been investigated for several decades. Many authors have paid attention to relationship between the resistance and alloantigen systems. Among 12 alloantigen systems of chicken blood types, the contribution of *A*, *B*, *C*, *E*, and *I* systems to susceptibility or resistance to coccidiosis have been studied. The *B* system, which is the major histocompatibility complex (MHC) of chickens, has been identified as contributing largely to susceptibility to coccidiosis of chickens, partially in collaboration with background genes, but several authors claimed that its contribution was less than background genes. Differences extent in the contributions of *B* system to resistance in embryos and that in chickens was observed. Possibility of contribution of alloantigen genes, *e.g. A, E, C* and *I*, other than *B* genes to the resistance of chickens to coccidiosis was also suggested. Alloantigen genes may work in collaboration with background genes in expressing susceptibility or resistance to coccidiosis in chickens.

INTRODUCTION

Host resistance to diseases is an important issue in chicken genetics. Coccidiosis, Marek's disease, Sarcoma tumors, infectious bursal disease etc. have been investigated (reviewed by Gavora, 1990). Coccidiosis is one of the most important diseases whose host resistance in chickens has been studied by many authors (e.g., Champion, 1954; Rosenberg et al., 1954; Challey, 1966; Jeffers and Shirley, 1982; Jeffers and Wagenbach, 1970; Long, 1970, 1973; Siegel, 1976; Gross, 1976, Johnson and Edgar, 1982; Mathis et at., 1984).

Chicken blood types were allotted to 12 alloantigen systems, i.e., *A, B, C, D, E, H, I, J, K,*

L, P, R (Briles et al., 1950, 1962; Gilmour, 1960; Crittenden et al., 1970). Each system has 2 (at *J, L, R*), 3 (at *H, K*), 5 (at *I*) and many alleles (at *A* – *E, P*). The *B* system, consisting of more than 30 alleles, is the major histocompatibility complex (MHC) in chickens, and is analogous to H–2 of mice and HL–A of humans (Schierman and Nordskog, 1961, 1963; Jaffe and McDermid, 1962; Pazderka et al., 1975). The *C* system is detected on leucocytes and weakly related to histocompatibility (Schierman and Nordskog, 1965), while the *A, D, E* and *L* systems do not appear to be related to histocompatibility. The *K* and *R* systems are related to agglutination to vaccinia virus (Brown et al., 1973) and susceptibility to Rous sarcoma (Crittenden et al., 1970). Not well characterized are the *H, I, J, L*, and *P* systems. Relationship between resistance to diseases and *B* haplotypes have been investigated by many authors, especially to Marek's disease, Sarcoma tumors, erythroblastosis, lymphoid leukosis, spontaneous autoimmune thyroiditis, infectious bursal disease, fowl cholera and coccidiosis (reviewed by Gavora, 1990, Matsuda, 1990).

History of breeding of chickens resistant to coccidiosis was reviewed by Long (1973) and Jeffers and Shirley (1982). In this paper I review the relationship between alloantigen systems and genetic variation of resistance to coccidiosis in chickens.

A. Genetic Aspects of the Host Response *in vivo*

Mathis et al. (1984) revealed that resistance to coccidiosis in chickens was moderately heritable by examining weight gain, packed red blood cell volume, mortality and coccidial lesions in random bred chicken population infected with *E. tenella* and *E. acervulina*. Two approaches have been used to study the effects of alloantigen systems to host responses to coccidiosis. One approach involved comparisons between alloantigen systems of chicken from lines varing in resistance to coccidiosis. The other approach was performed by comparing resistance of stocks with different haplotypes of alloantigens. Of the alloantigen systems, those investigated in terms of host responses to coccidiosis are *A, B, C, E, I*.

a. *B* system

The *B* system is the MHC of chickens. It is known knowledge from mice that MHC antigens are widely related to immunological recognition, e.g., cytotoxic T cells recognize viral or tumor antigens in association with MHC antigens on target cells to kill the cells, helper T cells recognize foreign antigens with MHC antigens on antigen–presenting cells (APC) and after recognition of antigens with MHC antigens on B cells and macrophages, helper T cells cooperate with B cells to induce antibody production and with macrophages to kill intracellular microorganisms. Therefore, contributions of the *B* system to susceptibility to coccidiosis has been the focus of research by many investigators. I will mention details of these experimental designs, because they used variety of lines of chickens, parasites, methods of infection and immunization. This will be informative in order to compare the results of these experiments.

Johnson and Edgar (1986) compared *B* genotypes in lines R and S which were selected respectively for resistance and susceptibility to acute cecal coccidiosis. The R line originated from selection that began in 1948 in Single Comb White Leghorns (Edgar et al., 1951) at Auburn

University in Alabama in the U.S. Both lines had B^2; R had B^5 and a recombinant of B^2 and B^5 (possibly F^2G^{2-5}) and S had B^1, B^3, B^4 and B^6. In the last stages of selection, B^4 in R line and B^5 in S line, which were possessed at low frequency in the early stages, had become extinct, and there was an increase frequency of B^5 in the R line as a result of intensification of selection pressure.

Bumstead and Millard (1987) compared susceptibility of 7 inbred and partially inbred lines of chickens to *E. tenella* and *E. maxima*. They showed that there were large differences between these lines in the effects of challenge on weight gain and mortality for both species of parasite. However, correlations between 3 criteria (weight gain, mortality and oocyst production) were low, suggesting different mechanisms in which parasites affect chickens or that chickens affect parasites. In these lines, there was no indication of association of resistance to coccidiosis with resistance to Marek's disease. They compared mortality of progeny from B^4B^{12}xB^4B^{12} matings of White Leghorn line C after challenge with *E. tenella*. The mortality was greatest for $B^{12}B^{12}$ homozygotes (6 death/6 investigated), intermediate for heterozygotes (7/10) and least for B^4B^4 homozygotes (4/9). This small numbers of chickenbs in this experiment allows only the suggestion that B^4 or B^{12} are associated with susceptibility to *E. tenella*. They (1992) also compared oocyst production of 8 inbred lines of chickens to 7 species of chicken Eimeria. Each inbred lines had different pattern of oocyst production and lines which discharged larger number of oocysts of E. tenella discharged smaller number of oocysts of the other species and vice-versa, indicating that inverse relationship between susceptibility to E. tenella and susceptibility to the other species. These results suggest existence of common genetic factors affecting susceptibility to the 6 eimerian species other than E. tenella.

Clare et al. (1985) compared susceptibility of the F_4 cross of line 6_1 (B^2B^2) and line 15_1 (B^5B^5) which were two highly inbred Single Comb White Leghorns lines from USDA Regional Poultry Research Laboratory (RPRL), East Lansing in Michigan, U.S. At 6 weeks of age, chickens were immunized with 500 oocysts of *E. tenella* daily for 5 days, and then challenged with 10,000 oocysts 2 weeks after the last primary exposure. B^2B^2 had significantly higher lesion scores than of B^2B^5 and B^5B^5 genotypes 6 days following challenge. There were no significant differences among the 3 groups in body weight gain. When nonimmunized chickens were challenged, although there were no differences in lesion scores, B^2B^2 chickens had significantly lower weight gains than B^2B^5 or B^5B^5 chickens, indicating that B^2B^2 chickens were more susceptible to *E. tenella* infection under conditions of both immunization and nonimmunization. They (1985) also compared susceptibility of noninbred lines (UNH105) of New Hampshires having different *B* alloantigens under the same experimental schedule as mentioned above. When immunized, $B^{23}B^{23}$ chickens had significantly lower lesion scores than $B^{23}B^{24}$ chickens, while $B^{24}B^{24}$ were intermediate. Nonimmunized $B^{23}B^{24}$ chickens had significantly lower weight gains than $B^{23}B^{23}$ or $B^{24}B^{24}$ ones. Effects of *B* haplotypes were not clarified in B^{23} and B^{24}. The contribution of background genes and the overall level of genetic heterogeneity of the New Hampshire stock may have influenced the responsiveness.

The *B* complex consists of three chromosomal regions which encode cell surface antigens, *B-L*, *B-F* and *B-G* (Pink et al., 1977). *B-F* and *B-L* antigens are homologues of mammalian class I and class II antigens, respectively. *B-G* codes for a unique avian erythrocytic antigen, and is named class IV because it does not correspond with any regions in H-2 or HLA. Clare et al. (1989) observed resistance and immunity to *E. tenella* among *B-F/B-G* recombinant

chickens. They used six B–F/B–G recombinant haplotypes on a $B^{17}B^{17}$ background. When chickens were infected with 25,000 or 2,500 oocysts of *E. tenella* at 5 weeks of age, $B^{17}/B(F^2$–$G^{23})$ chickens, which were an F1 between $B^{17}B^{17}$ chickens and B–F/B–G recombinant chickens that have recombinant genes of B^2 at B–F region and B^{23} at B–G region but express B^{17} haplotype, had greater weight gains and lower lesion scores. When chickens were challenged 21 days after immunization with 500 oocysts for each of 5 consecutive days beginning at 5 weeks of age, $B(F^{21}$–$G^{19})$ and $B(F^{21}$–$G^{23})$ homozygous chickens had lower lesion scores than $B(F^2$–$G^{23})$. In heterozygous chickens, $B^{17}/B(F^{21}$–$G^{19})$ chickens had lower lesion scores than $B^{17}/B(F^2$–$G^{23})$ or $B^{17}/B(F^{21}$–$G^{23})$ ones. These results suggest an association between B–F^2 and resistance of naive chickens and between B–F^{21} and resistance to challenge after immunization. Resistance to chicken coccidiosis in naive chickens and that in immunized chickens should be considered separately. These results indicate that susceptibility to *E. tenella* vary in chickens possessing different recombinant MHC haplotypes.

Ruff and Bacon (1984, 1989) studied the role of *B* systems in susceptibility and immunity to *E. tenella* and *E. acervulina*, using six *B*–congenic lines of chickens. Congenic lines were developed after four or five generations of backcross matings in RPRL White Leghorn inbred line $15I_5$ (homozygous for B^{15}), i.e., each line was homozygous for B^2, B^5, B^{12}, B^{13}, B^{19}, or B^{15}, while background genes were common. B^{15} chickens had significantly greater weight gains, higher plasma pigments and somewhat lower lesion scores, dropping scores and oocyst production after *E. tenella* infection, than B^2 chickens. When challenged with 1,000 oocyst at 35 or 38 days of age after immunized with 100 oocysts once or 4 times beginning at 21 days of age, there were no significant differences between B^2 and B^{15} in susceptibility. B^{15} chickens were more resistant than B^2 and B^{19} lines to a heavy infection ($1x10^6$) with *E. acervulina* based on weight gain. With a lighter infection ($1x10^5$) lision scores were higher for B^2 than B^5 or B^{15}. They concluded that the *B* complex has a detectable influence on resistance and susceptibility to avian coccidiosis, but that it may play only a minor role in the development of immunity to a challenge infection.

Lillehoj and her colleagues (1988, 1989, 1990, 1991) observed immunological responses of RPRL $15I_5$–*B* congenic lines to *Eimeria* infection. Lillehoj et al. (1989) compared susceptibility among $15I_5$–*B* congenic lines (B^2, B^5, B^{12}, B^{13}, B^{15}, B^{19}, and B^{21}) and other inbred lines possessing B^6B^6, $B^{13}B^{13}$, B^2B^2 and $B^{15}B^{21}$. The *B* congenic lines varied in oocyst production, lesion scores and packed cell volumes after primary or secondary *E. tenella* infection, suggesting an association between the *B* complex and susceptibility to *E. tenella*. However, when susceptibility of $15I_5$–*B* congenic line with B^2B^2 was compared to a commercially obtained inbred line possessing B^2B^2, difference was observed in oocyst production after primary and secondary infection, suggesting an interaction of *B* genes and genetic background for the outcome of host responses to *E. tenella* infection. By using *B*–congenic or inbred lines of chickens mentioned above, Lillehoj et al. (1988, 1990) observed differences among lines in cellular and antibody responses to recombinant coccidial antigens and oocyst production of the immunized chickens after *E. acervulina* challenge. Lillehoj and Bacon (1991) also investigated difference of chicken lines in T cell subpopulation in intestinal intraepithelial lymphocytes of *B*–congenic lines (B^2B^2 and B^5B^5) which were progeny of RPRL $15I_5$ after *E. acervulina* infection.

Dunnington et al. (1992) investigated the contribution of *B* complex to susceptibility to *E.*

tenella by using their own lines of chickens. From sublines of chickens selected for high antibody (HA) or low antibody (LA) response to sheep erythrocytes (Siegel and Gross, 1980), they developed sublines having all possible combination of haplotypes at the *B* complex ($B^{13}B^{13}$, $B^{13}B^{21}$, $B^{21}B^{13}$, and $B^{21}B^{21}$; the first designation is contribution of the sire, the second that of the dam) in each of the two genetic backgrounds (HA and LA). They measured weight changes and cecal scores after challenge infection to naive and to immunized chickens. Between chickens having background genomes of HA and LA (each line consisted of four *B* haplotypes above mentioned), there were significant differences. However, there were no differences among chickens having different *B* haplotypes (results were analyzed after data of chickens of HA and LA with the same *B* haplotype were pooled). They concluded that the background genome (HA vs. LA), rather than *B* haplotype (B^{13} vs. B^{21}), imparted greater resistance or susceptibility to *E. tenella*.

From these articles, the *B* system is considered to contribute largely to susceptibility to coccidiosis of chickens (Bumstead and Millard 1987, Clare et al. 1985, 1989, Ruff and Bacon 1989), partially in collaboration with background genes (Clare et al. 1985, Lillehoj et al. 1988, 1989, 1990, 1991), or less than background genes (Dunnington et al. 1992, Johnson and Edgar 1986).

b. Other systems

Johnson and Edgar (1984, 1986) investigated the diversity of *A, E* and *C* alloantigens in chickens from lines genetically resistant (line R) and susceptible (line S) to *E. tenella*. Line R had a high frequency of haplotypes A^7E^5 and A^9E^1, and line S had a range from high to low frequency of A^9E^3, A^9E^5, A^9E^2 and $A^{11}E^1$. Frequencies of *C* genes in line R were 59% of C^1 and 41% of C^4, and those in line S were 12% of C^1, 19% of C^2 and 69% of C^3. They concluded that genes other than *B* gene have measurable effects on *E. tenella* infection.

Martin et al. (1986) produced specific segregants at loci *I* with homozygosity for B^{21}, H^2, and L^1 by mating in a line selected for high antibody response to sheep erythrocyte antigens (Siegel and Gross, 1980). These chickens were immunized at 20 days of age and challenged at 31 days of age by *E. tenella*. Lesion scores of chickens from I^4I^4 homozygous parents were significantly lower than those from I^2I^4 x I^4I^4 or I^2I^4 x I^2I^4 matings. This suggests that *I* gene correlates with acquired immunity to *E. tenella* infection.

These results suggest possibility of contribution of alloantigen genes, *e.g. A, E, C* and *I*, other than *B* genes to resistance to chicken coccidiosis.

B. Genetic Aspects of the Host Response *in ovo*

Complete life cycle of development of *E. tenella* is obtained in chicken embryos after inoculation of sporozoites (Ishii and Onaga, 1971; Itagaki et al., 1972; Long, 1965, 1970, 1973; Nakai et al., 1982). Mortality of the embryos and oocyst production are dose dependent (Nakai et al., 1982).

Jeffers and Wagenbach (1970) observed differences in mortality after *E. tenella* infection among chicken embryos from 8 lines of chickens. Long (1970) also obtained different

susceptibility in chicken embryos of two lines by observing mortality after *E. tenella* infection. These authors, however, did not state the alloantigen systems of these lines.

Nakai et al. (1993) compared susceptibility of chicken embryos of H-B2 and H-B15 lines to *E. tenella* infection. These two lines originated in Turku University, Finland, and are partly inbred lines possessing homozygous *B* haplotypes (B^2B^2 and $B^{15}B^{15}$, respectively). H-B2 had lower mortality and higher oocyst production than H-B15. Embryos of H-B2 were considered to be more resistant to *E. tenella*. However, when 10-day-old chickens of these lines were inoculated with *E.tenella*, there were no significant differences between the two lines in the body weight gain, cecal length, cecal lesion score, oocyst production, except for cecal shrinkage 7 days after infection. This indicates that there was almost no difference in susceptibility between the two lines in chickens and suggest that *B* haplotypes of embryos and chickens may have different roles in resistance to *E. tenella*. It may be postulated that the role of the *B* system in resistance to eimerian infection varies at different stages of immunological maturation of embryos and chickens. The relationship between the *B* system and immunological maturation should be investigated further.

C. Concluding Remarks

It seems exceedingly difficult to reveal the relationship between alloantigen systems and resistance to chicken coccidiosis. There are several reasons as following:

(i) Limited numbers of inbred or congenic chicken lines exist, and almost all of them are available only in a few institutes. Accordingly, direct comparison of results among different researchers is almost impossible.

(ii) Mechanisms of pathogenicity of chicken coccidium are complicated. Then criteria, e.g., mortality, weight gain, packed cell volume, cecal lesion score, oocyst production etc., are difficult to be chosen to express resistance or susceptibility. Results obtained through one criterion may contradict those using other criterion. Mortality and weight gain express the systemic response of the host to coccidiosis, and the cecal lesion scores and oocyst production express mainly local response of the host.

(iii) Immunological responses have not been well understood in coccidiosis. It is important to see the susceptibility of chickens after immunization. The chicken industry may prefer chickens that easily acquire resistance after immunization rather than those that show severe protection in the naive condition. Immunological properties of chickens are much more complicated. If one chicken does not allow development of coccidia, the chicken may acquire low level of immunity because of low immunological stimulation by small number of parasites grown. On the other hand, such a chicken may survive at exposure of high dose of parasites and may acquire high level of immunity.

It is not easy to provide a definitive conclusion at the present time; however, alloantigen genes, especially *B* genes, could contribute to susceptibility to coccidiosis of chickens to a certain extent. These genes may work in collaboration with background genes in expressing susceptibility or resistance to chicken coccidiosis. The relationship between the alloantigen genes and resistance to coccidiosis should be investigated further.

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