家禽誌 26(2) : 131~144(1999) K.J. Poult. Sci. 26(2) : 131~144(1999)

# Avian Gut Immune System and Local Responses to *Eimeria* Parasites

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# 조류의 장내 면역체계와 콕시듐 (*Eimeria*) 기생충들에 대한 국소면역 반응

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## ABSTRACT

Coccidiosis, an intestinal infection caused by intracellular protozoan parasites belonging to several different species of *Eimeria* seriously impairs the growth and feed utilization of livestock and poultry. Due to complex life cycle of organism and intricate host immune responses to *Eimeria*, coccidia vaccine development has been difficult. Understanding of basic immunobiology of pertinent host-parasite interactions is necessary for the development of novel control strategy. Although chickens infected with *Eimeria* spp. produce parasite-specific antibodies in both the circulation and mucosal secretions, antibody mediated responses play a minor role in protection against coccidiosis. Rather, increasing evidence show that cell-mediated immunity plays a major role in resistance to coccidiosis. T-lymphocytes appear to respond to coccidiosis both through cytokine production and a direct cytotoxic attack on infected cells. The exact mechanisms by which T-cells eliminate the parasites, however, remain to be investigated. Since it is crucial to understand the intestinal immune system in order to develop an immunological control strategy against any intestinal diseases, this presentation will summarize our current understanding of the avian intestinal immune system and mucosal immune responses to *Eimeria*, to provide a conceptual overview of the complex molecular and cellular events involved in intestinal immune responses to enteric pathogens.

## INTRODUCTION

Many intestinal infections in poultry such as coccidiosis, salmonellosis, and cryptosporidiosis represent economically important diseases for

the poultry industry(reviewed in 1). Host responses to parasitic infections are complex and involve many facets of cellular as well as humoral immune mechanisms(reviewed in 2, 3). The Eimeriid coccidia exhibit a complex life cycle comprised of stages both inside and outside of the host. During the in-host stage, there are both intracellular and extracellular stages and both asexual and sexual reproduction. In view of the complex life cycle of the coccidia, it should not be surprising that host immune responses to these parasites are also complex. Following coccidial infection, both antibody and cell-mediated immune responses are activated although cell-mediated immunity plays a major role in disease resistance(reviewed in 3). Unlike many protozoan parasites, the primary target tissue for coccidia is the intestinal epithelium. Thus, understanding the immune system-parasite interactions in the gut leading to parasite elimination is crucial for the design of new approaches to coccidiosis control.

## THE GUT-ASSOCIATED IMMUNE SYSTEM

### 1. Component of intestinal immune system

In chickens as in mammalian system, there exists a separate mucosal immune system that exhibits a number of unique features(reviewed in 2). The GALT have evolved with specialized features that reflect their role as the first line of defense in mucosal surfaces. These include antigen presenting cells, immunoregulatory cells, and effector cell types distinct from their counterparts in the systemic immune system(4). It is now widely accepted that the common mucosal immune system consists of two separate but interconnected compartments: mucosal inductive sites which include the nasal-associated and gut-associated lymphoreticular tissues (NALT and GALT) strategically located where they encounter environmental antigens and mucosal effector sites which include the LP of the intestine and the upper respiratory tract (reviewed in 2). These mucosal effector tissues consist mainly of T cells, predominantly CD4+ memory/effector T cells, but also contain a high numbers of B cells and plasma cells, mainly of the IgA isotype.

Within the gastrointestinal mucosa, intestinal lymphocytes are present in two anatomic compartments: the epithelium(termed intraepithelial lymphocytes, IEL) and the lamina propria, morphologically separated by a basement membrane from the epithelium(termed lamina propria lymphocytes, LPL)(5). The intestinal leukocytes from chickens contain 80% lymphocytes, 10-15% monocytes, approximately 5% mononuclear cells and, less than 1% polymorphonuclear leukocytes and plasma cells (5, 6). The cells isolated from mechanical scraping of the muscularis mucosa revealed that small intestinal LP leukocytes contain 80% lymphocytes, 20% monocytes and less than 1% polymorphonuclear leukocytes. Mononuclear cells isolated from the epithelium and lamina propria were reported to contain immunoglobulin positive cells but the percentage was higher in the LPL(29.5%) than in IEL(7.9%) or spleen cells(19.4%). In chickens as in mammals, T cells can also be separated into CD4 and CD8 expressing subpopulations on the basis of their function(7). The phenotypes of intestinal intraepithelial T cells have been examined in chickens using flow cytometry. Molecular complexes similar to human and murine CD3, CD4 and CD8 antigens have been identified(7, 8, 9). The predominant subset of IEL T lymphocytes expresses the CD3 polypeptides(gamma,

delta, epsilon, and zeta) noncovalently associated with the ab chain receptor heterodimer of the antigen specific T cell receptor(TCR)(10). Another subset of T lymphocytes expresses the CD3 polypeptide chains in association with the gd chain receptor. The ontogeny of T cells which bear different TCR has been recently studied(8, 10, 11).

A third type of cell mediating intestinal immunity is the natural killer(NK) cell. NK cells represent a class of lymphocytes which are cytotoxic to hemopoietic tumor cells and cells infected by virus or other intracellular parasites in the absence of prior sensitization(12, 13, 14). NK cells constitute a population of non-T, non-B, non-macrophage mononuclear cells with characteristic morphology that are capable of spontaneous cytotoxicity against a wide variety of syngeneic, allogenic, and xenogeneic target cells. NK-cells lack immunological memory and the MHC restriction and thus their cellular lineage is debatable(12). A recent study described a unique IEL subpopulation, termed TCR0 cells, showing cytoplasmic CD3 and lacking surface TCR /CD3 complex, which was detected mainly in the intraepithelium where most express CD8 antigen(15). TCR0 cells, obtained at day 14 of embryonic development, from the spleen, before the T cell appearance, can be enriched in the presence of conditioned medium from concanavalin A-stimulated spleen cells, and show cytotoxicity against NK-susceptible target cells (reviewed in 16). NK-cell activity has been reported to be present in the intestinal IEL population of mice(17, 18), rats(19) and guinea-pigs(20). In chickens, NK cell activity has been demonstrated in the spleen(21) and peripheral blood(22, 23), thymus(14), bursa(14) and intestine(14,24). Great variability in cytotoxic potential was observed among NK cells of different lymphoid organs. Furthermore, a substantial strain variation in NK-cell activity was also demonstrated. NK cell activity increased with their age and their cytotoxic potential was not fully developed until 6 weeks after hatching(25).

**2. Effector cells associated with gut-associated immune system**

The roles of various components of GALT in host defense against microbial infections has been studied extensively(26). Three general functions of gut-associated immune system include: 1) processing and presentation of antigen, 2) production of local antibodies, and 3) activation of cell-mediated immunity.

In chickens, IgA and IgM are the predominant immunoglobulins in the external intestinal secretions. Although IgG is found in the gut, it is believed to be derived from the circulation or leaked from the lymphatics following permeability changes which occur during infection. Secretory IgM which is pentameric is effective in elimination of microbes. However, several distinctive features are important for IgA to function as a secretory antibody. One is the ability of IgA monomer to polymerize. Other properties of secretory IgA are its ability to associate with a 15-Kda peptide joining(J) chain and a 70-Kda protein, the secretory component (SC) produced by epithelial cells. The IgA-SC complex is internalized in endocytic vesicles, transported across the cytoplasm and exocytozed on to the external surface of the epithelium. A functional homologue of mammalian SC has been described in chickens(27). A minor source of IgA in secretions is derived from blood via the hepatobiliary IgA transport system.

The major functions of sIgA include prevention of environmental antigen influx into

internal body compartments, neutralization of viruses and microbial toxins and prevention of adherence and colonization of mucosal surfaces by microbial pathogens. Secretory antibodies may bind to the pathogen's surface and prevent binding to the epithelium by direct blocking, by steric hindrance, by induction of conformational changes, or by reduction of motility. In this manner, microorganisms would be susceptible to the natural cleaning functions of the mucosae. The role of secretory immunoglobulins has been documented in agammaglobulinemic patients. However, the role of secretory immunoglobulins is less clear in some poultry infections. Despite the absence of immunoglobulins, agammaglobulinemic chickens are resistant to reinfection with coccidia(28). Therefore although the primary role of sIgA is to prevent invasion of microbes in the intestine, it is less certain whether sIgA limits the course of major infections once it is established.

Cell-mediated immune responses include both antigen-specific as well as antigen non-specific activation of various cell populations including T lymphocytes, NK cells and macrophages. T lymphocytes are comprised of functionally two distinct subpopulations distinguishable by their surface phenotypes. Cytotoxic T lymphocytes (CTL) recognize foreign antigens in the context of MHC class I molecules whereas T helper cells recognize antigens in association with MHC class II molecules. Although CTL activity has been demonstrated in the intestine of mammals, MHC-restricted IEL CTL activity has yet to be shown in chickens. Recently, there has been increased interest in the selective homing of TCRgd+ cells to the intestinal epithelium in mice(29) and in chickens(10). A considerable interest in gut mucosal lymphoid populations, particularly IEL NK cells, has developed in recent years(26). It has been suggested that IEL NK cells are active in the first line of host defense because of their close proximity to the gut where a variety of antigenic substances are introduced. The observation that chicken intestinal IEL contain NK cells that mediate spontaneous cytotoxicity(24) suggests that NK cells may play an important role in local defense. Intestinal IEL NK activity depends not only upon the type of target cell but also upon the incubation time and the host genetic background. Kinetic studies revealed that cytotoxicity was detectable from 2 hr after incubation and progressively increased up to 16 to 18 hr. Furthermore, NK cell activity was higher in the jejunum or ileum than in the duodenum or caecum.

**3. Cytokine production in the intestine**

It has been shown that intestinal mucosal lymphoid populations including intra-epithelial lymphocytes are active in the first line of host defense because of their close proximity to the intestinal lumen where a variety of antigenic substances including the coccidian parasite are introduced to the host. Recent studies have indicated that intestinal intra-epithelial lymphocytes mediate effector function via secretion of biologically active cytokines(30). Although many different kinds of cytokines which are produced in the intestine have been identified in the mammals, limited information exists in chickens. Presence and secretion of IFN-gamma, IL-15 and TGF-b in chickens in response to coccidia has been described(31). Three different isoforms of transforming growth factor-beta(TGF-a) have been identified in the chicken intestine and include TGF-as 2, 3 and 4 (32). Expression and localization of TGF-as 2, 3 and 4 proteins and their corresponding mRNAs

has been examined during development of the embryonic chicken intestine, a tissue that may potentially be in close proximity to the coccidiosis parasite and thus may become infected by this organism. Growth stimulatory and growth inhibitory autocrine growth factors are potential candidates as modulators of intestinal epithelial cell growth. TGF-a may be such a growth factor that may be able to function in the intestine and has been shown to potently inhibit normal epithelial cell growth and modulate differentiation in several cell types including bronchial epithelial cells, osteoblasts, adrenocortical cells and myoblasts, among others(reviewed in 33). Using the techniques of RNA Northern blot analysis and immunohistochemical staining analysis with specific cDNA probes and antibodies for TGF-as 2, 3 and 4, our results indicate that TGF-as 2, 3 and 4 proteins and their corresponding mRNAs are expressed in the intestinal epithelium by 4 days of incubation and continue to be expressed in a spatial as well as temporal manner throughout development of the intestine in the embryo. At the same time, expression of TGF-a4 protein detected by immunohistochemical staining also increases with development of the embryonic intestine, with expression of TGF-a4 protein prominent in the tips of the villus by 19 days of incubation. Since expression of TGF-a4 mRNA increases with development of the embryonic chicken intestine and expression of TGF-a4 is high in the tips of the intestinal villus later in embryonic development, it may be that TGF-a4 may play a role in modulating growth of the intestinal villus. Additional studies will be needed to determine whether the localization of TGF-as 2, 3 and 4 in specific cells of the intestine has biological relevance for embryonic development in the chicken. IFN-gamma is an important cytokine which activates macrophages and is produced following coccidiosis(31) in the intestine. IFN-g, one of the important soluble factors produced by activated lymphocytes, is involved in the differentiation, maturation and proliferation of hematopoietic cells and enhances nonspecific immunity to tumors, as well as to microbial, viral and parasitic pathogens. Chicken IFN-g regulates the host immune response including activation of lymphocytes and the enhancement of immunity through expression of major histocompatibility complex(MHC) class II antigens. Recently, chicken IL-15 has been identified(34) and its presence in the chicken intestine reported(34). Although the biological function of intestinal IL-15 remains to be studied, high level of expression in the intestinal tissues indicate its role in local immune response to pathogens.

## INTESTINAL IMMUNE RESPONSES TO COCCIDIA

### 1. Role of intestinal lymphocytes in sporozoite transport

The details of the sporozoite invasion and their subsequent translocation are not entirely defined. That *Eimeria* species tend to be very site selective suggests that sporozoites from different species recognize different host cell structures during the invasion process. Shortly following infection, *E. tenella* sporozoites can be seen invading cells of the intestinal(or cecal) surface epithelium(35). Some species complete their development in the surface epithelium, while, other species develop in endothelial cells of villus lacteals, the LP, or the epithelium of the crypts. Possible translocation mechanisms are discussed later. A number of factors influence the ability of sporozoites to invade epithelial cells, including whether or not the host

was previously exposed to the parasite and therefore has developed an immunity. Monoclonal antibodies(Mabs) have been used to study structures associated with sporozoite invasion. Mabs that recognize surface or surface/internal antigens of the *E. tenella* sporozoite, were able to inhibit invasion by *E. tenella in vitro*(36). Recently, a chicken hybridoma that secretes a Mab capable of inhibiting sporozoite invasion of lymphocytes *in vitro* has been developed(37). This monoclonal antibody recognizes the conoid, an apical complex structure known to be involved in host cell invasion by *Toxoplasma gondii* (38). Furthermore, this monoclonal antibody recognizes a common antigen shared between sporozoites and merozoites from several *Eimeria* species(39).

The role of antibodies in inhibiting sporozoite invasion of host cells is debatable. Some studies indicate antibody-mediated inhibition of sporozoite invasion(40, 41) while other studies do not (18). When chickens immune to *E. tenella* were challenged, 50% fewer intracellular sporozoites were observed 6 hr post inoculation as compared with challenged non-immune birds(40, 41). This inhibition of invasion may be related to specific antibodies present in the mucosa of immune birds which act by directly blocking invasion or by enhancing intraluminal destruction of sporozoites. However, bursectomized chickens, which produce few or no antibodies, do development protective immunity following primary infection with *E. tenella*(28). Furthermore, *E. tenella* has been observed capping and shedding immune complexes(18), and sporozoites collected from the ceca of the immune birds exhibit normal development when transferred to naive chickens(41). In *E. tenella*-immune chickens, sporozoites penetrated the surface epithelium and migrated through the LP in numbers equal to those seen in naive chickens. However, only a few sporozoites entered the crypt epithelium and developed into trophozoites; no further development was detected. Conversely, *E. acervulina* immune birds had 11% more intracellular sporozoites(40, 41) than controls, indicating that immunity does not necessarily depend on blocking invasion of sporozoites. Since *E. acervulina* immune birds passed no oocysts, however, development was arrested at some point.

Not all *Eimeria* spp. develop at the site of invasion. Some species are transported, by host cells, from the site of invasion to the site of development. Early reports suggested that macrophages(42, 43) or IEL(44, 45) were responsible for sporozoite transport, although the identity of the cells was not confirmed. Although large numbers of macrophages were observed in the intraepithelial region, they only rarely contained sporozoites(46). Extracellular sporozoites were rarely seen in tissue spaces and no developmental stages(trophozoites or meronts) were observed in IEL. Because IEL are a heterogeneous population consisting of B cells, T cells, and NK cells(25), the nature of the IEL responsible for *E. acervulina* sporozoite transport was identified using a panel of Mabs detecting chicken leukocyte subpopulations(47). Following primary infection, most sporozoites were seen inside CD8+ lymphocytes, indicating that these cells are responsible for sporozoite transport. A significant number of sporozoites were also detected inside macrophages. However, macrophages are phagocytic in nature and it is possible that different mechanisms exist for sporozoite invasion of CD8+ cells. Following secondary infection, there was an accumulation of sporozoites in CD8+ cells, suggesting that sporozoites were unable to exit these cells to com-

plete their journey to crypt epithelial cells. Furthermore, when CD8+ cell-depleted chickens were infected with *E. acervulina* or *E. tenella*, there was, on average, a 55% decrease in oocyst production during a primary infection(48). These data further suggest a role for CD8+ lymphocytes in sporozoite transport and are in agreement with observations that in birds immune to *E. maxima* or *E. tenella* sporozoite transport and/or transfer from IEL to crypt enterocytes is inhibited. This inhibition of sporozoite transfer to crypt epithelial cells during secondary infection could indicate that sporozoites are unable to exit once inside activated CD8+ T cells.

**2. Host immune responses to coccidia**

Animals infected with *Eimeria* spp. produce parasite-specific antibodies in both the circulation and mucosal secretions(49). Circulating antibodies consist of IgM, IgG, and IgA whereas secretory IgA was detected in bile and gut washings of infected animals(50, 51). Serum IgM response peaked at 17 days post infection(dpi) of *E. tenella*. Biliary sIgA was detected as early as 7 dpi *E. tenella* or *E. acervulina*. Challenge infection with *E. tenella* or *E. acervulina* did not elicit an anamnestic sIgA response. Although antibodies are produced, *in vivo* studies using hormonal and chemical bursectomy(28) clearly indicated that antibodies play a minor role in protection against coccidiosis.

The importance of T cells in immune responses to coccidia has been well documented (reviewed in 2, 3). The role of T cells in coccidiosis resistance was investigated with agents that suppress cellmediated immune responses such as cyclosporin A(Cs-A), betamethasone and dexamethasone. When Cs-A was given concurrently with oocysts, resistance to primary infection was enhanced(28). Cs-A given prior to oocyst inoculation increased susceptibility, and if given prior to secondary infection, protective immunity was eliminated(28). Dexamethasone treated chickens showed reduced T-cell proliferation, reduced interleukin-2 and g-interferon production, and increased susceptibility to *Eimeria* infection(52) even though coccidia specific IgA and IgG responses were at times enhanced.

The changes in intestinal T cell subpopulations in duodenum following primary and secondary *E. acervulina* infections were investigated(53). The number of duodenal IEL expressing the CD8 antigen increased in SC and TK chickens following primary infection. Following secondary infection, a significantly higher numbers of CD8+ IEL were observed in the SC chickens which manifested a lower level of oocyst production as compared to TK chickens. The CD4+ IEL numbers increased 7 days after primary infection in SC and TK chickens and in TK chickens, seven days after challenge infection. Two color immunofluorescence analysis of duodenum IEL at 10 days following challenge infection revealed that the majority of CD8+ IEL coexpressed TCRab. Furthermore, SC chickens showed increased TCRab+CD8+ cells shortly following challenge infection with *E. acervulina*. These results suggest that variations in T-cell subpopulations may reflect eimeria-infection related changes in the gut-associated lymphoid tissues and that a significant increase in TCRabCD8+ IEL in SC chickens may reflect enhanced acquired immune status in SC chickens compared to TK chickens.

The growing evidence that T cells might be the primary mediators of immunity to *Eimeria* spp., led to investigations of T helper cells. A recent study shows that depletion of CD4+ cells had no effect on primary *E. acervulina* infection,

but resulted in a significant increase in oocyst production following primary *E. tenella* infection (48). This difference could be related to nature of host-parasite interaction or cell changes that occur during these infections. These findings provide evidence that suggest a protective role for CD8+ IEL in *E. acervulina* infection. Depletion of either CD8+ cells or TCRab+ cells resulted in substantial increases in oocyst production following challenge *E. acervulina* infection in chickens. This suggests that cells coexpressing CD8+ and TCRab may be critical for protection against reinfection with *E. acervulina*. As opposed to primary infection, a challenge infection usually results in the reduction in numbers of oocysts produced and amelioration of clinical symptoms. These results provide strong evidence that CD8+ T cells mediate host immunity to coccidian parasites. Thus, new strategies to control coccidiosis may need to focus on manipulating the activities of CD8+ lymphocytes.

### 3. Cytokines/lymphokines involved in host response to coccidia

Previous investigations of the molecular and cellular aspects of host immunity to parasitic infections suggest that an intricate and complex interplay of different cell populations and cytokines are involved not only in the pathogenesis of disease, but also the development of protective immunity(reviewed in 2 & 3). In *Leishimania* major infection of mice, for example, the difference between resistance and susceptibility to disease was attributed to different patterns of cytokine production by T cell helper-1(Th1) and Th2 cells. In murine coccidiosis, IFN-g has been implicated in primary immunity to *E. vermiformis* infection(54). IFN-g production has been used in chickens as a measure of T cell responses to coccidial antigens (55, 56). Lymphocytes from Eimeriainfected chickens produced higher level of IFN-g when induced with Con A as compared to lymphocytes from uninfected chickens(55, 56). Strain differences in *Eimeria*-induced g-IFN production was observed(55, 56). Recently, recombinant chicken IFN-g(57), and led us to investigate its role in avian coccidiosis. The results showed for the first time that administration of exogenous recombinant chicken IFN-g into live chickens significantly hinders intracellular development of *Eimeria* parasites and reduces body weight loss(58). After infection with *E. acervulina*, expression of TGF-b4 mRNAs increased 5~8 fold in intraepithelial lymphocytes and 2.5 fold in spleen cells whereas the mRNAs for TGF-b2 and 3 remained constant in these cells suggesting a role for TGF-b4(59). This increase in expression of TGF-a4 in response to infection with the coccidian parasite is similar to the induction of TGF-a1 in the mouse following infection with the protozoan parasites *Leishmania braziliensis* and *Trypanosoma cruzi*. In both these cases, TGF-a1 has been shown to influence the replication of *Leishmania* and *Trypanosoma* in macrophages and acts to increase the intracellular replication of these parasites, thus providing a mechanism for these parasites to escape the immune protection system(60, 61). Whether TGF-a plays a similar role in coccidiosis remains to be determined in future studies.

Macrophages produce various cytokines following coccidiosis. Sporozoites and merozoites of *E. tenella* induced *in vitro* TNF-like factor production by normal peripheral blood derived macrophages(62). Treatment of chickens with anti-TNF antibody resulted in a partial abrogation of *E. tenella*-induced body weight loss in SC chickens but not in TK chickens(63).

Although the exact role of TNF in coccidiosis needs to be further characterized, this result may explain the severity of clinical signs associated with coccidial infection.

Although the exact mechanisms by which these cytokines mediate host immune response against coccidia remains to be investigated, significantly higher numbers of CD8+ IELs(64) in *Eimeria*-immune chickens indicate that intestinal T lymphocytes are involved. Many of these were in direct contact with parasitized epithelial cells(35) suggesting that a soluble cytokine such as IFN- g may be produced. Our recent studies showed that IFN-g mRNA expression in caecal tonsils and splenic lymphocytes was generally higher in SC compared to TK chickens following *E. acervulina* infection, while intraepithelial lymphocytes from the duodenum demonstrated reduced levels of this cytokine in both strains, particularly following primary infection(31). IL-15 mRNA expression in the caecal tonsils was significantly decreased in SC and TK chickens, whereas in the spleen and duodenum IL-15 transiently increased in SC chickens but decreased in TK chickens. TGF-b4 mRNA levels generally increased in lymphocytes from the caecal tonsils, spleen and duodenum from both strains. These differences in lymphocyte subpopulations and cytokine mRNA expression between SC and TK chickens following *E. acervulina* infection indicate a complex genetic control of the native immune response to coccidiosis.

**4. Role of NK cells in coccidiosis**

Positive correlations between NK cell activity and genetically determined disease resistance to coccidia(65) have been noted. Increased NK cell activity occurs in the early stages of coccidia infection, suggesting a role for NK cells in the control of parasite proliferation and the outcome of infection. The levels of NK cell activity in splenic and intraepithelial lymphocytes are higher than normal, coinciding with parasite elimination. Thus, these cells may be involved in immunosurveillance against eimerian parasites. Enhancement of intestinal intraepithelial NK cell activity is observed during the post-patent period following Eimeria infection. Following the infection of chickens with *Eimeria*, there is a increase in asialo GM1 bearing cells and cells with NK markers suggesting that IEL NK cells may be involved in defense against invasion of the gut mucosa by coccidia. Further characterization of chicken NK cells will increase our understanding their roles in mucosal and systemic immunosurveillance against infectious agents.

## CONCLUSIONS

Intestinal immune responses to coccidia parasites that lead to protective immunity involve the complex interplay of soluble factors, leukocytes, epithelial cells, endothelial cells, and other physiological factors of the gut-associated lymphoid tissues(GALT). The research on immunity to coccidiosis demonstrates that immune responses to coccidia are extremely complex and different effector mechanisms may be involved depending on the stage of parasite development and on whether a primary or secondary response is occurring. It will undoubtedly be some time before a detailed description of immune mechanisms involved in protection against coccidiosis becomes clear. It is likely that these complex interactions have contributed to the difficulties in developing an effective vaccine against Eimeria spp. However research into the avian common mucosal immune system assumes a

high priority, as the development of vaccines against intestinal infections such as coccidiosis, colibacillosis, salmonellosis and intestinal viruses becomes an industry priority. The advent of new molecular techniques to manipulate the genomes of various pathogens and an enhanced understanding of interaction of the GALT with peripheral lymphoid organs will soon enable new approaches to vaccination against enteric pathogens.

## ACKNOWLEDGMENTS

This work was supported by the Cooperative State Research Service, U. S. Department of Agriculture, NRI grant under agreement number 98-35204-6471.

## 적 요

다양한 *Eimeria* 종에 속하는 세포내 원생동물 기생에 의한 장내 감염증인 콕시듐증은 가축과 가금의 성장과 사료이용에 심각한 손상을 준다. *Eimeria*의 대한 유기체의 복잡한 생활주기와 숙주의 복잡한 면역반응 때문에 콕시듐백신의 개발은 그동안 쉽지 않았었다. 숙주와 기생체에 관련된 상호반응의 면역생화학적인 기초에 대한 이해는 새로운 제어 대책의 개발에 필수적이다. *Eimeria* spp.에 감염된 병아리는 순환계와 점막분비계통에서 기생체 특이항체를 생산하나, 항체반응을 통한 콕시듐증 방어에는 큰 역할을 하지 못한다. 오히려 세포성 면역이 콕시듐증에 대한 저항에 중요한 역할을 한다는 증거가 증가하고 있다. T-임파구는 사이토카인 (Cytokine) 생산과, 감염된 세포에 대한 직접적인 세포독성공격으로 콕시듐증에 반응하는 것 같다. 그러나 T-세포가 기생체를 제거하는 정확한 메카니즘은 더 연구되어야 한다. 여러 가지 장내 질병에 대한 면역학적 조절대책을 수립하기 위한 장내 면역계를 이해하는 것은 쉽지 않으나, 이 보고서는 *Eimeria*에 대한 장내 면역계와 점막 면역반응에 대한 최근 연구성적을 요약 하므로서, 장내 병원체에 대한 장내면역 반응과 관련된 복잡한 분자적 세포적 반응 결과에 대한 전체적인 개요를 설명 할려고 하였다.

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