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Avian immunity and immunopathology of avian diseases

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Abstract
The immunosuppressive diseases in today's era has led to heavy burden of economic losses on the poultry farmers as these diseases lead to wiping out of the entire flocks at a stroke due to poor growth rate and heavy mortality. Avian immune response cannot be appreciated without knowing its basic structure. Thus, understanding of the immune system and the deleterious effects caused bacterial, viral, parasitic and neoplastic diseases on the immune system becomes necessary. Most infectious organisms stimulate immune responses within every compartment of the immune system. Resistance to infectious agents may depend upon innate mechanisms or acquired immune responses. Inflammation, phagocytosis, cell-mediated immunity and antibodies are components of a complex reaction which result either in resistance or in susceptibility. The innate and adaptive immune responses are owned by both mammals and avian and the avian adaptive immune response involving both cell-mediated and humoral immune responses, promoting immunological memory and helps fight against the pathogens.

Keywords: Avian, immunity, lymphoid organs, bacterial, viral, parasitic, neoplastic diseases

Introduction
Resistance to infectious agents may depend upon innate mechanisms or acquired immune responses. Most infectious organisms stimulate immune responses within every compartment of the immune system. In some situations, autoimmunity may contribute to the pathology associated with infections.

The Avian Immune System
Avian immune response can't be appreciated without knowing its basic structure. Lymphoid tissues are either of epithelial (e.g., thymus and bursa of Fabricius) or mesenchymal (e.g., spleen and bone marrow) origin and are colonized by hematopoietic cells via the blood. Primary lymphoid organs include the thymus and the bursa of Fabricius, that are colonized by stem cells of hematopoietic origin evolving respectively.
The immunologically mature cells then re-enter the circulation and colonize the peripheral lymphoid organs comprising of the spleen, ceacal tonsils, Peyer's patches, Meckel's diverticulum, the Harderian gland, and other gut, bronchus, skin, nasal and reproductive-associated lymphoid tissues. T and B-dependent zones are occupied primarily by T and B cells respectively, in the peripheral tissues [1].

Primary Lymphoid Organs
1. **Thymus:** It appears at the 5th day of the embryonic life and post-hatching; it continues to grow till 3-4 months of age then regresses with onset of sexual maturity. Its peak level of activity occurs in the young age [2]. It is responsible for the maturation and differentiation of stem cells into thymus-dependent or thymus derived lymphocytes or T-cells which have the major role in cell-mediated immunity.
2. **Bursa of Fabricius/ cloacal bursa:** It a lymphoepithelial hollow, round or oval sac-like extension of the hindgut located in the caudal body cavity and connected by short duct with the dorsal region of the cloaca. The bursal mucosa has 11-13 longitudinal folds [3]. It is responsible for maturation and differentiation of the stem cells into bursal-dependent or bursal derived lymphocytes or B-lymphocytes. B-cell has the major role in antibody-mediated immunity.

Secondary Lymphoid Organs

The matured B and T-cells are migrated to these sites from the primary or maturation lymphoid organs in a process known as immune migration or immune peripheralization. They include**:**

I. **Gut associated lymphoid tissue (GALT):** GALT is one of the most important components of secondary lymphoid organs which represent all the lymphoid structures and cell aggregation which present in the digestive tracts [4]. In association with the secretory IgA, it is responsible the presence of the digestive local or mucosal immunity which is one of the most important immune mechanisms. GALT includes:

- The massive sub-mucosal lymphoid cell aggregation in the digestive tracts.
- Esophageal tonsil is a novel member of the mucosal associated lymphoid tissue (MALT), which is located around the entrance of the proventriculus, containing 6 to 8 single units, which are surrounded by a thin fibrous capsule and serves as 'tonsillar crypt'. Stratified squamous epithelium is infiltrated by lymphoid cells, i.e. T cells, plasma cells, macrophages, and dendritic cells, but not B cells, to form lymphoepithelium (LE) [5]. T- and B-dependent regions are present in the subepithelial lymphoid tissue is organized into which are the interfollicular areas and the germinal centers, respectively.
- Gastric tubular glands embedded in submucosa of proventriculus are classified as branched tubular glands and open into the mucosal surface. The glands contain numerous secretory tubules which are lined by cuboidal cells and each tubule continued by one duct opened into the main collecting duct which opened into luminal surface [6].
- Meckel's diverticulum which is a pouch at the connection site between the intestine and the umbilical cord [7].
- Lymphoid or annular rings which are present at the end of the jejunum and the beginning of the ileum, well developed in the waterfowls [8].
- Caecal tonsils are the largest collection of GALT located at ileocecal junctions but not present at the time of hatching and develop shortly afterwards. It is easily identified by 10 days old and its size increases up to 12 weeks [9]. It contains both T- lymphocytes (50%) and B-lymphocytes (50%) and large numbers of immature and mature plasma cells and with age, the number of B-lymphocytes and plasma cells increases. It involved in the antibody production and cell-mediated immune response.
- Peyer's patches located in the intestinal mucosa [10] and structurally similar to the caecal tonsils. Subjacent to the epithelium, there is heavy B- dependent lymphocyte infiltration. Peyer's patches in chickens share several characteristics with mammalian ones [11].
- Lymphoid aggregates which present in the urodeum and proctodeum of the cloaca are also part of the GALT [4].

II. **Head-associated lymphoid tissue (HALT):** HALT is one of the most important components of secondary lymphoid organs which represent all the lymphoid structures and the massive lymphoid cell aggregation which present in the head region. HALT includes:

- **Harderian/Harder's/paraocular gland:** The Harderian gland (HG) is an immune-endocrine organ located in the orbit behind the eye. It appears and develop after hatching. It contains numerous plasma cells which produce and secrete primarily IgA and other immunoglobulins. It is the major secondary lymphoid organ of HALT. B-cells comprise 80% of lymphoid cell population while T-cells comprise 20% of lymphoid cell population [12].
- **Conjunctival-associated lymphoid tissue "CALT":** a massive lymphoid cell aggregation located under the mucosa of the conjunctiva [13]. In SPF birds, it is not prominent but it is prominent in poultry especially turkeys.
- Paranasal glands, lachrymal duct and lateral nasal ducts.

III. **Bronchial-associated lymphoid tissues (BALT):** BALT has a role for initiation of respiratory humoral immune responses in chickens and turkeys [14]. It is one of the most important components of secondary, peripheral or seeding lymphoid organs which represent all the lymphoid structures which present in the respiratory tract. BALT in association with the secretory IgA are responsible the presence of the respiratory local or mucosal immunity which is one of the most important immune mechanisms. BALT [15] includes:

- Sub-mucosal lymphoid cell aggregation in the respiratory tracts.
- Bronchial epithelium whose cells are primarily non-ciliated squamous and then become more columnar ciliated with age.
- Lymphoid nodules found in the lung associated with the primary bronchi.

IV. **Skin-associated lymphoid tissues (SALT):** Lymphocytes were also found scattered in a wide range of tissues including intestinal epithelium and lamina propria, skin, liver, gonads and pancreas. SALT represents all the lymphoid structures and the massive lymphoid cell aggregation which is located under the skin.

V. **Spleen:** It is the largest secondary lymphoid organ that is composed of white and red pulps which comprises about 80% of splenic tissue. The white pulp surrounds the blood vessels in the spleen and has morphologically distinct areas. Periarteriolar lymphoid sheaths (PALS) surround the central arteries. Peri-ellipsoid lymphoid sheaths (or PELS) analogous to the mammalian marginal zone, surround the penicillary capillaries. Germinal centres are found at the bifurcation of arteries, at the origin of the PALS [1].

VI. **Mural lymphoid nodules:** These are organized accumulations of lymphoid tissue which are circular, elongated, or oval, non-capsulated and contain diffuse lymphoid tissue within which, are usually found three or four germinal centers either within or closely applied to the lymphatic vessels, especially those of the limbs and neck [16].

VII. **Pineal gland:** It is located between the cerebral hemispheres and the cerebellum. Avian pineal glands maintain rhythmic activity for days under *in vitro* conditions. Several physical (light, temperature, and magnetic field) and biochemical [Vasoactive intestinal polypeptide (VIP), norepinephrine, PACAP, etc.] input channels, influencing release of melatonin are also functional *in vitro*, rendering the explanted avian pineal an excellent model to study the circadian biological clock [17].

VIII. **Bone marrow:** It is essentially a primitive lymphoid

organ but after the immune migration, it also acts as a secondary immune organ. As a secondary lymphoid organ, it contains B- lymphocytes, mononuclear cells and T- lymphocytes [18].

IX. **Bursa of Fabricius:** As both a primary and secondary lymphoid organ, it is responsible for the diversification and maturation of avian B cells, which respond to alimentary and environmental antigens present in its lumen [19]. As a secondary lymphoid organ, it contains B-lymphocytes, mononuclear cells and T- lymphocytes.

There are no lymph nodes in birds except for the primitive lymph nodes in the aquatic birds such as cervico-thoracic nodes at the thoracic inlets. Their structure is fairly simple and the flow of lymph relatively fast due to the presence of a main or central sinus which probably constitutes an intranodal lymphatic vessel [16].

Immunity in Birds

Fowls, like all animals, have very strong, built-in defenses (immunity) against diseases. The air, feed, housing system and diseased or carrier animals are responsible for the commencement of most of the pathogens into the environment. The innate and adaptive immune systems work together in the birds to protect and maintain their health. Together they create an effective defense to the invading pathogens. The immune responses have been discussed briefly as follows:

1. Innate Immunity

Immunity may result from incompatibility between the host and the pathogenic organism. Exceptions like genetic resistance to avian leukosis viruses where resistance to particular subgroups of the virus depends upon the absence of virus receptors [20]. A totally different mechanism is involved in microbial antagonism associated with the normal bacterial flora of the chicken [21].

- **Non-Specific Defense Mechanisms**

Innate immunity also involves various primitive non-specific defense mechanisms, which prevent the entry of organisms into the body. To cause disease, pathogens have to penetrate through the skin or the mucosa of the airways, genital tract, and digestive tract into the host animal [22]. The major line of defense is the skin, which when intact, is impermeable to most infectious agents and resistant to the growth of most bacteria. Although, *Staphylococcus aureus* appears to be able to overcome the local immune response [23].

The respiratory mucosa is susceptible to all kinds of inhaled harmful factors. Immunoglobulin A (IgA)-dependent mucosal immune and non-specific natural immune factors (such as mucous cilia clearance system) act as the first line of defense and IgA plays an important role in the immune exclusion to infection pathogen in mucosal epithelium [24].

(i) Humoral factors: - Lysozyme is an abundant and widespread bactericidal substance which is a muramidase which splits the mucopeptide wall of susceptible bacteria. Other plasma components, which are collectively known as "acute phase proteins" increase in concentration in response to infection or tissue damage. For example, ceruloplasmin is released from liver after intravenous injection of *E. coli* endotoxin [25] or administration of heat-killed *Mycoplasma gallisepticumor M. meleagridis* [26].

The nature of the anti-viral effect is not clear but is probably multifactorial. Binding to ganglioside receptors on cells may trigger the synthesis of ribosomal binding proteins which blocks translation of viral but not host RNA. Interferon has anti-viral activity by acting on certain accessory cells of the immune system and enhances the activity of non-specific natural killer (NK) cells.

The activation of complement via the alternative pathway may be triggered by extrinsic agents; in particular, microbial polysaccharides such as endotoxin acting independently of antibody may generate C3 convertase which splits C3 into two active fragments, C3a and C3b [27].

C3b not only amplifies the complement response via convertase formation but also acts as an effector itself that mediated functions in innate and adaptive immunity and is essential for the induction of the terminal pathway of complement effector generation by leading to the generation of C5a and MAC [28].C3b binds to the bacteria and leukocytes, because of their receptors for C3b, engulf them. C3a causes the degranulation of mast cells leading to histamine release and an increase in the permeability of blood vessels this in turn results in more C3 leaking to the site, as well as facilitating the chemotaxis of leukocytes.

(ii) Cellular mechanisms: Phagocytosis and intracellular killing by hydrolytic and other enzymes is a primitive defense mechanism. Metchnikoff recognized two major cell types responsible for the engulfment and digestion of microorganisms, termed macrophages and microphages.

- **Macrophages**

Macrophages are cells of bone marrow origin descended from monocytes or a similar cell. Monocytes circulating in the blood are immature macrophages and are continually released from the bone marrow. Cells of bone marrow origin, probably monocyte-like, can also differentiate into cells like Kupffer cells of liver, osteoclasts of bone and Langerhans cells of the epidermis [29].

Macrophages also have receptors for one of the activated components (C3b) of the complement system which may be generated by components of the cell wall of bacteria such as *Salmonella* [30] and coliforms as they possess OMPs (Outer Membrane Proteins) and some tumor cells. The inactivation and subsequent degradation of phagocytosed material results from the fusion of phagocytic vacuoles with lysosomes. Non-digested residues may sometimes be discharged extracellularly but more often persist and may cause chronic inflammation such as in case of *Mycobacterium*. The responses are characterized by expression levels of pro-inflammatory cytokines and nitric oxide production [31].

- **Heterophils**

The heterophil of the chicken provides protection against invading microorganisms[27]. They contain acid phosphatase and β-glucuronidase but lack the enzymes peroxidase and alkaline phosphatase, which are found in mammalian neutrophils. Heterophils appear to be the dominant phagocytic cell involved in acute inflammatory reactions [32].

- **Eosinophils, Basophils and Mast cells**

Avian eosinophils do not respond to inflammatory stimuli in the same way as mammalian eosinophils. Mast cells are involved in the initiation of inflammation by releasing active mediators which facilitate the migration of heterophils and

monocytes to the site of injury. Basophils may have some part in the early acute inflammatory response and the induction of immediate hypersensitivity reactions in chickens. Mast cells have been found in tumors of the fowl and are increased in nerves affected with Marek's disease [33].

- **Thrombocytes**

Thrombocytes are mononuclear cells which function similarly as the platelets of mammals causing blood coagulation by clotting and subsequently disintegrating [34]. However, in addition, they are phagocytic and they have lysosome- like cytoplasmic inclusions and acid phosphatase-positive granules [35].

- **Natural killer (NK) cells**

NK cells are capable of recognizing carbohydrate determinants on the target cells and eliminating cells with incompatible or incomplete glycoproteins. Avian NK-cells have been described as a population of cells in the chicken embryonic spleen at a developmental stage where T-cells have not yet migrated to the periphery [36]. NK cells probably play a role in natural and vaccine-induced resistance to Marek's disease [37].

2. Acquired Immunity

- **Antibodies and cell-mediated immunity**

Phagocytic cells have considerable antimicrobial potential but this can only be realized if the phagocytes interact with invading microorganisms through receptors [38]. When the antibody molecule attaches to an organism, the Fc region is exposed and then can bind to the Fc receptors on macrophages and other phagocytes. Similarly, antibody binding to antigen will fix complement by the classical pathway which can then bind to complement receptors.

Antibodies are produced by B lymphocytes but in the case of most antigens, T lymphocytes (T helper cells) and antigen-presenting dendritic (macrophage related) cells are also involved [39]. Antibodies may be mediators of cell-mediated immunity, on exposure to specific antigen into cytotoxic T cells or delayed hypersensitivity T cells. The former act by killing cells or organisms bearing the exciting antigen; the latter act by producing soluble mediators (lymphokines) that cause the recruitment and activation of macrophages.

Immunity against Bacterial Infections

Bactericidal function develops steadily in the chicken during embryonic life and in the immediate post-hatching period [40]. Antibodies to bacteria begin to be transferred from the yolk to the embryonic circulation at about 11 days of incubation [41] and passively transferred antibody levels reach a maximum at hatching.

The increasing level of immunoglobulins may accelerate bacterial clearance and increase intracellular killing. Blood clearance only relates to the attachment and ingestive phases of phagocytosis. The development of macrophage-mediated bactericidal activity may be due to the increasing competence of lymphocytes as the transfer of spleen cells to susceptible day-old chicks can protect them against otherwise lethal doses of bacteria.

Innate immunity is important in controlling bacterial infections, particularly at mucosal surfaces such as the gastrointestinal tract. Recognition by the host, or evasion of detection and subversion of innate immunity by the pathogen are key to the disease process [42]. Simple physical barriers may prevent many bacterial infections including antimicrobial secretions such as lysozyme, muco-ciliary clearance, the acidic environment of the gizzard and proventriculus and tight cellular junctions at epithelial layers. Like mammals, pattern recognition of pathogens through receptors such as Toll-like receptors (TLR) are important in innate immune activation in the chicken [43].

In spite of developing phagocytic function, the newly hatched chick is poorly immunologically reactive and relies heavily upon passively acquired maternal immunoglobulins. IgG is transferred from the yolk [44] but unlike calves and piglets, there is no transfer of IgM or IgA to the chick, and the presence of these two immunoglobulin classes in serum results from active synthesis. Chicks are therefore, relatively poorly equipped to deal with early mucosal colonization by bacterial pathogens.

In *Salmonella* infection in the gut, early host responses include a localized inflammatory response with an associated influx of heterophils. Despite greater uptake, the non-flagellate salmonellae induce much less IL-1β and IL-6 in the gut and a reduced heterophil infiltrate [45]. Live salmonellae readily invade cultured heterophils and macrophages but are then killed by these cells, a response enhanced by prior exposure of cells to proinflammatory cytokines such as IFN-γ or IL-2 [46]. Evidence for an effective host response includes the age-dependent ability to clear the *Salmonella* from the gut and the more rapid clearance after secondary challenge.

In colibacillosis in chickens, host immune cells sense the type of pathogen that may be encountered through receptors such as the Toll-like receptors (TLRs), which distinguish different classes of pathogen-associated molecular patterns (PAMPs) [47]. Microbial product-induced activation of immune cells leads to the activation of intracellular signaling pathways related to microbial killing mechanisms and production of pro- and/or anti-inflammatory cytokines [48].

Four main TLRs are involved in the recognition of bacterial motifs in chickens. TLR-2, which recognizes peptidoglycan; TLR4, which binds lipopolysaccharide (LPS); TLR-5, which recognizes flagellin; and TLR-21, which recognizes unmethylated CpG DNA commonly found in bacteria [49]. Bird's lungs possess parabronchi which are in close contact with blood capillaries, an important area for gas exchange. At any given moment, air may be flowing into and out of the lung, but also staying in the air sacs during the whole process. These peculiar anatomical features may strongly favor bacterial colonization of bird's lower airways [15].

The pathogenic mechanism for avian Mycoplasmas include adherence to host target cells, mediation of apoptosis, innocent bystander damage to host cell due to intimate membrane contact, molecular (antigen) mimicry that may lead to tolerance and mitotic effect for B and/or T lymphocytes, which could lead to suppressed T-cell function and/or production of cytotoxic T cell, besides Mycoplasma by-products, such as hydrogen peroxide and superoxide radicals. Moreover, Mycoplasma ability to stimulate macrophages, monocytes, T-helper cells and NK cells, results in the production of substances, such as tumor necrosing factor (TNF-α), interleukin (IL-1, 2, 6) and interferon (α, β, γ) [50].

Immunity against Viral Infection

Owing to potential economic loss due to viral infections, commercial chicken and turkey flocks are routinely vaccinated with antiviral vaccines. The vaccines are not always effective and viral diseases may occur in vaccinated

poultry flocks. Thus, there has been much interest in studies on antiviral resistance mechanisms and the role of viral immunity in protection against disease.

Antibodies are very effective in preventing reinfection with many viruses, serum antibody being important when the virus has to pass through the blood stream before reaching its target organ (e.g. infectious bursal disease virus) and local antibody being essential when the target organ is the same as the portal of entry (e.g. respiratory viruses).

There are a number of ways in which antibody may protect against virus infections. These include neutralization, which may depend upon antibody blocking the attachment to or penetration of cells by virus or upon the lysis of virus particles. Antibody and complement may also cause the lysis of infected cells and antibody to fusion protein can prevent the spread of avian Paramyxoviruses by cell fusion [39].

Chicken Anemia Virus (CAV) infection causes a disease in young chicks which is characterized by generalized lymphoid atrophy, increased mortality and severe anemia. The virus appears to target erythroid and lymphoid progenitor cells in the bone marrow and thymus respectively. Destruction of erythroid progenitors in bone marrow results in severe anemia, and depletion of granulocytes and thrombocytes. Destruction of precursor T cells results in depletion of mature cytotoxic and helper T cells and sub-optimal antibody responses. Apoptosis appears to be a feature of the lymphocyte depletion in the thymic cortex, which may be mediated by one of the non-structural viral proteins, VP3 (apoptin) [51].

An example of a virus disease where immunity appears to depend solely upon antibodies is infectious avian encephalomyelitis. Birds infected after 2-3 weeks of age do not develop clinical signs probably because of the development of immune competence. Chicks bursectomized after hatching were found to develop severe encephalitis when inoculated with the virus at 28 days old. Maternally derived antibodies are protective. Similarly, passively administered antibodies protect immunosuppressed (bursectomized) chickens even when given 48 hours after infection [52].

Antibodies are also probably responsible for protection against Infectious Bursal Disease (IBD) virus. Destruction of the immunoglobulin-producing cells is the principal cause of IBDV-induced immunosuppression, which leads to significant impairment of the primary antibody responses. Innate immunity is the primary barrier against pathogens and intestinal mucosa is the first barrier that prevents the invasion of the IBDV. IBDV uses its one of four structural proteins (pep 46) to disturb the cell membrane and enter the target cells. This structural protein deforms membrane, its destabilization starts and pores are formed subsequently translocation. This system has the ability to distinguish self from the foreign particles and their destructive response should be only targeted towards foreign particles. IBDV damage the B cells, leading to lower antibody production and T cells, resulting in impaired virus killing ability [53].

In the egg drop syndrome 1976 (EDS 76) and other adenoviruses the main method of transmission is through the embryonated egg and virus is usually unmasked following a decline in antibody titer. Reactivation of adenoviruses may also occur around peak egg production, possibly associated with stress-induced immunosuppression. Several reports have shown the coexistence of infectious bursal disease (IBD) and CIA viruses in areas where HPS occurs frequently [54]. Systemic antibodies may control the reactivation of vertically transmitted virus and reinfection can occur in the face of relatively high titers of neutralizing antibody.

Immunity at the respiratory mucosa has been implicated in resistance to many respiratory viruses such as Newcastle disease virus, infectious bronchitis virus and influenza viruses. This local immunity is nevertheless dependent on the bursa for its development [55], [56] e.g. bursectomy was found to increase deaths following challenge with an avian influenza virus. Chicks with high serum antibody titers to Newcastle disease virus and infectious bronchitis virus may be susceptible to respiratory infection.

In the case of infectious bronchitis virus, there is considerable strain variation in the capacity to induce interferon and no strain was found to be susceptible to the inhibitory effects of chicken interferon. The local production of an IgA-like antibody is produced by plasma cells underlying mucosal tissues and is actively transported onto the epithelial surface in association with secretory component which is synthesized in the Golgi apparatus of epithelial cells. The paraocular lymphoid tissue of the chicken, also make a major contribution to the production of local antibodies on the mucosal surface [57].

Immunity is derived from neutralizing antibodies formed against the viral hemagglutinin and fusion glycoproteins, which are responsible for attachment and spread of the virus [58]. The innate immune response to NDV infection is an immediate reaction designed to control and inhibit virus growth and spread and aid in developing pathogen-specific protection through the adaptive immune response. The early reactions of the innate immune system use germ-line encoded receptors, known as pattern recognition receptors (PRR's), which recognize evolutionarily conserved molecular markers of infectious microbes, known as PAMP's (pathogen-associated molecular patterns). Recognition of PAMPs by PRRs, either alone or in heterodimerization with other PRRs induces intracellular signals responsible for the activation of genes that encode for pro-inflammatory cytokines, anti-apoptotic factors, and antimicrobial peptides.

Cell-mediated immunity (CMI) is specific adaptive immunity mediated by T lymphocytes and has been suggested to be an important factor to the development of protection in chickens vaccinated against NDV and contribute to viral clearance. The subsets of T lymphocytes, including cytokine-secreting CD4+ T helper cells, and CD8+ cytotoxic T lymphocytes (CTL), constitute the principal cells of the CMI response. Cell-mediated stimulation following NDV infection is detected as early as 2–3 days post infection [58].

In the case of some avian viruses, neither systemic nor locally produced antibodies appear to play a significant role in protection. Thus, with the herpesvirus responsible for infectious laryngotracheitis - experimental bursectomy did not increase susceptibility and no correlation was found between neutralizing antibody titers and protection [59]. Infectious laryngotracheitis virus seems to be particularly refractory to the effects of antibody and resistance may rely solely upon a cell-mediated thymus-dependent mechanism.

Immunity against Neoplastic Diseases

Neoplastic diseases of poultry comprise a variety of conditions possessing a single common denominator: neoplasia involving one or more of the cell types. Neoplastic diseases of poultry fall into two broad classes, namely: those with an infectious etiology and those which are non-infectious.

I. Marek's disease

Maternal antibodies against Marek's disease virus also ameliorate the disease indicating some functional significance of antibody in resistance [60]. Despite this, cell-mediated immunity probably has a dominant role in resistance to Marek's disease and is responsible for the suppression of virus replication and the elimination of transformed tumor cells. T lymphocytes are involved not only in mounting a cell-mediated immune response but also, with B lymphocytes and antigen-presenting dendritic cells, in the production of antibodies.

Four phases of infection *in vivo* can be delineated: (1) Early productive-restrictive virus infection causing primarily degenerative changes. The infection is productive–restrictive because the virus remains cell-associated and is only transferred by cell-to-cell contact, (2) Latent infection, (3) A second productive restrictive infection phase coincident with permanent immunosuppression and (4) The proliferative phase involving nonproductively infected lymphoid cells that may or may not progress to the point of lymphoma formation [61].

MDV infection of naive host occurs via inhalation of dust or skin dander encapsulated viral particles into the respiratory tract. Primary infection occurs when virus particle breaks mucosal tolerance in the lungs, site of entry into the epithelial cells. Local viral replication establishes infection and initiates viral immediate-early gene, viral Interleukin-8 (vIL-8), transcription and translation [62]. Inflammatory responses in the underlying tissue recruit innate immune system cells which result in uptake of infectious virus particle by macrophages. Infiltration of lymphocytes via action of vIL-8 follows resulting in MDV infection of B-cells. Viral replication in B cells initiates semi production lytic viral infection and disease progression. MDV infected B cells secret vIL-8 that acts as a chemotactic factor for and gains access to T-cells. This specific lymphotropism (B cells and T cells) enables systemic disseminated viremia [63]. Viral replication causes apoptosis of B and T lymphocytes in a hallmark of immunosuppression.

MDV integrates specifically into the genome of CD4+ T cells enabling escape from immune detection and initiates latent Viral Infection [64]. Early latently infected and activated CD4+ T cells have not been phenotypically characterized by cell surface markers. Early latently infected and activated CD4+ T cells migrate to cutaneous sites of replication namely feather follicle. Infection of feather follicle epithelium enables fully productive viral replication. Viral replication results in syncytia formation. Infection of feather epithelium leads to secretion of mature virion in skin danders and dust that act as the major source of infectious materials. Horizontal transmission is the only recognized form for environmental persistence and infection in field conditions [62].

II. Avian leukosis

Avian leukosis viruses, induce neoplasms by one of two main types of mechanisms [65] as follows:

- Viruses that do not carry a viral oncogene induce neoplasms by activation of a cellular proto-oncogene. Thus, lymphoid leukosis is initiated by activation of the c-myc oncogene by the LTR promoter, a mechanism termed 'promoter insertion' or 'insertional mutagenesis'. Erythroid leukosis is caused by activation of the *c-erbB* oncogene. Initiation of neoplasms by this mechanism is slow, occurring after weeks or months. Such ALVs are termed 'slowly transforming' and the tumors are called 'slow onset tumors'.
- Viruses that have a viral oncogene induce neoplasms by insertion of the oncogene into the genome of the target cell. Such ALVs are termed 'acutely transforming', and neoplastic cells are induced within a few days. Depending on the oncogene possessed by the virus, acutely transforming ALVs induce different types of neoplasm, for example: v-myc: myeloid leukosis (myelocytoma); v-myb: myeloid leukosis (myeloblastosis); *v-erbB:* erythroid leukosis; v-src: sarcoma.

- **Reticuloendotheliosis**

Reticuloendotheliosis virus causes a number of disease syndromes in poultry and game birds and subclinical infections are not uncommon such as:

- **Runting disease syndrome**

Non-defective REV can induce in chickens and ducks a variety of non-neoplastic lesions that are collectively designated as the runting disease syndrome. The lesions include runting, bursal and thymic atrophy, enlarged peripheral nerves, abnormal feather development, proventriculitis, enteritis, anemia, and liver and spleen necrosis. Cellular and humoral immunosuppression also occurs. The abnormal feathering, in which the barbules of wing feathers are adhered to the feather shaft, is termed 'nakanuke' in Japanese, and has been observed in chicken flocks vaccinated with REV-contaminated vaccines [66]. The peripheral nerve lesions occasionally reported are histologically similar to those induced by MDV.

- **Chronic lymphoid neoplasms**

Non-defective REV can induce two types of lymphoid neoplasms in chickens. Bursal lymphomas may occur after along latent period involving the bursa and other organs that are indistinguishable from lymphoid leukosis induced by ALV. The tumor is of B-cell origin, arising in the bursa, and is caused similarly by REV proviral insertional activation of the cellular *myc* oncogene. Non-bursal lymphomas of T-cell origin have also been induced experimentally. These have latent periods as short as six weeks, and involve the thymus, liver, heart and spleen. Whether these lymphomas originate from B- or T-cells has not been determined. Histologically, the lymphomas appear more similar to T-cell tumors [65].

- **Acute reticulum cell neoplasia (reticuloendotheliosis)**

The genetically defective T strain of REV carries the v-rel oncogene, probably derived from the cellular oncogene, c-rel and requires a non-defective REV as a helper virus for replication. The T strain REV is highly oncogenic, inducing a widespread proliferation of primitive mesenchymal or reticuloendothelial cells and death within one to three weeks when injected into young chicks. More than one type of cell is probably targeted, including both immature B- and T-cells [67].

Immunity against Parasitic Infections

Chickens are challenged by seven species of *Emeria* parasites with the most important being *E. tenella, E. maxima, E. necatrix and E. acervulina*. The most important features of the lifecycle, with reference to immunity, are the phases of intracellular development (avoiding the action of antibody), the short duration of the infection cycle and the level of

immunity generated by primary exposure to small numbers of parasites. The specificity of protection induced by prior exposure is restricted to the *Eimeria* spp. used to prime the birds [68] and can be strain-specific with some species, such as *E. maxima*. With the most immunogenic *Eimeria* spp. (e.g., *E. maxima* in the chicken), a very small priming infection leads rapidly to the establishment of, essentially, complete immunity (i.e., no oocysts produced). Priming with similar numbers of less immunogenic *Eimeria* spp. (e.g., *E. tenella*) induces substantial immunity to re-challenge infection but some oocysts are produced. Complete immunity to the less immunogenic *Eimeria* spp. can be established by multiple priming infections. In the case of the fully immune host, the majority of parasites are killed very rapidly with essentially no parasites remaining after 48-72 h post-challenge.

The mechanisms of resistance to primary infection may differ between the avian *Eimeria* spp. Depletion of CD81T cells led to a decreased oocysts output with both *E. tenella* and *E. acervulina* [69] and this was attributed to depletion of cells involved in transport of sporozoites. Primary infection with all *Eimeria* spp. leads to substantial immunity to secondary challenge and the fully immune host terminates infection very rapidly. In the immune animal the intracellular sporozoite represents the main target for immunity [70].

Most descriptions of responses induced by non-eimerian intestinal parasites are with the protozoan *Cryptosporidium baileyi* and the nematode *Ascardidia galli*. Infection with either of these organisms induces a variety of responses including antigen-specific antibodies, lymphocyte proliferation and cytokines [71]. Infection with *A. galli* induced increased levels of IL-4 and IL-13 mRNA in the intestine of chickens at 14 days post-infection [72]. The ability to resolve primary infection and immunity to secondary infection with the intracellular protozoan *C. baileyi* is dependent upon T cells rather than B cells as evident by studies with partially thymectomized and bursectomized chickens. However, maternally derived antibody appears to confer partial protection against infection of the progeny of hens immunized by three large doses of parasites [73] probably by interfering with zoite invasion.

The course of infection with *Histomonas meleagridis* differs considerably between chickens and turkeys with the former being relatively resistant to the devastating pathological consequences of infection in the liver that typify the disease process in turkeys. Antigen-specific IgM, IgY and IgA antibody response can be detected in chickens or turkeys exposed to infection with *H. meleagridis* [74]. The lack of an early intestinal response in turkeys may allow the *H. meleagridis* to replicate and migrate to the liver tissue.

Conclusion

In nutshell, the immune systems and responses of mammals and birds are quite similar. The innate and adaptive immune responses are owned by both and the avian adaptive immune response involving both cell-mediated and humoral immune responses, promoting immunological memory. However, when one looks at the organs, cells, and molecules of the immune response in birds, one begins to understand that mammals and birds achieve the same overall responses often in quite different ways and in many facets (but not all), the avian immune response is discrete.The chronicle of avian immunology is fascinating and deficient, as there is still the need for explanations of a number of unique features and the different strategies adopted by the avian system.

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