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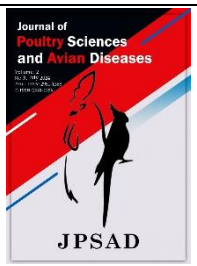

Avian Innate and Adaptive Immune Components: A Comprehensive Review

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A B S T R A C T

This article provides a comprehensive classical overview of the avian immune system, highlighting its unique components and functions. Although fundamentally similar to mammals, the avian immune system possesses distinct features in its tissues, cells, molecules, and genes. The study elaborates on the innate and adaptive immune components and critical functions in birds, detailing and artistically drawing the various organs such as the Bursa of Fabricius, thymus, spleen, and Harderian gland and cells involved in immunity. It discusses the role of innate immune cells and molecules along with the significance of B-and T lymphocytes immunoglobulins, antigen-presenting cells (APCs), especially macrophages and dendritic cells (DCs) and their related cytokines, including interleukins (ILs), emphasizing their crucial role in adaptive immunity especially activating various T lymphocytes. The article also underscores the complexity and efficiency of the avian immune system in combating pathogens and highlights the evolutionary adaptations that distinguish those from mammalian immune systems. This knowledge contributes to a better understanding of avian immunology and should go beyond this classical immune system, which is vital for improving disease management and vaccination strategies in birds.

Keywords: *Avian Immunity, Bursa of Fabricius, Dendritic cells, Harderian gland, Heterophils, Lymphocytes, Toll-like receptors.*

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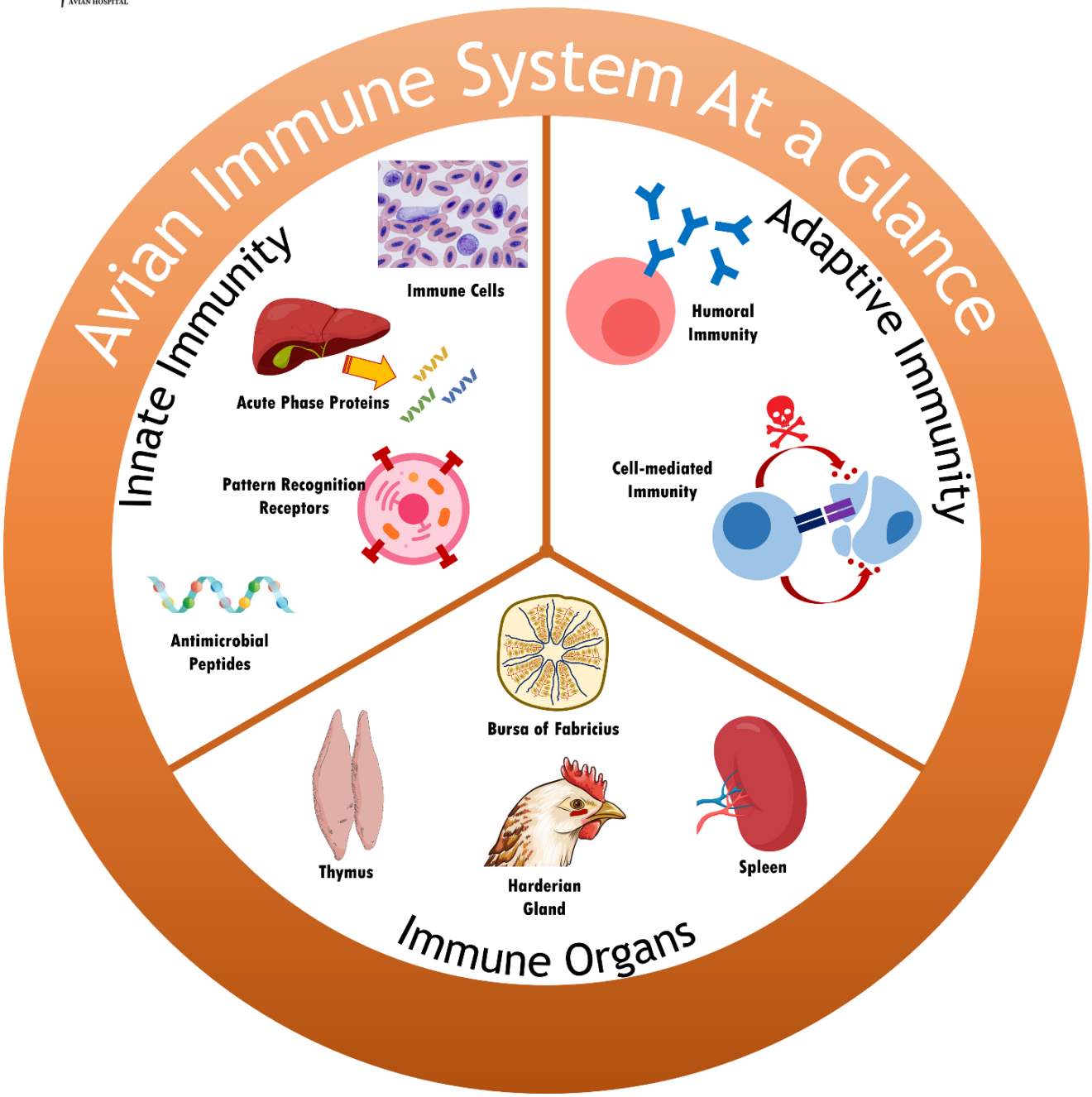

Schematic overview of the study on the avian immune system, highlighting some of its unique components and functions, which is dynamically comparable to that of mammals and urgently needed for detailed research and development.

1 Avian's immune system

Domestic birds, such as chickens, turkeys, and ducks, are crucial human protein sources. They contract infectious diseases from bacteria, viruses, fungi, and parasites. Birds are armed with sophisticated immune systems comprising different organs, cells, and molecules to combat pathogenic microbes (1-3). The avian immune system comprises two functional aspects: the humoral and cell-mediated immune systems, which collaborate to ward off harmful microorganisms/pathogens and prevent disease. While the fundamental principles of the immune response and habitats remain consistent among all vertebrate species, birds possess a distinct set of immune organs/tissues, cells, and molecules compared to mammals. In birds, bone marrow, thymus, and bursa of Fabricius are primary lymphoid organs.

In contrast, all other lymphoid organs are secondary, and all immune cells arise from undifferentiated mesenchyme elements in the yolk sac during the embryonic period. Those

undifferentiated immune cells migrate to other organs before hatching and during the first three days of life. After hatching, the lymphoid organs are classified as primary and secondary (1-3), and other than bone marrow and thymus, they are secondary. Here, we address those protective or immune arms of defense against invading microbes in birds.

1.1 Bursa of Fabricius

The Bursa of Fabricius (BF) is a pouch-like extension located above the rectum and connected to the cloaca by a short duct in birds (Figure 1). The BF's inner surface has many folds filled with lymphoid follicles. It is covered by epithelium and filled with B-lymphocytes that are modulated within the bursa and become terminally differentiated plasmatic cells capable of producing specific local and circulating antibodies (1, 4). The BF is a primary lymphoid organ that amplifies and differentiates B-lymphoid progenitors within its microenvironment. Discovering the dual function of the immunologic response with thymus-dependent and humoral (bursal-dependent) arms has been increasingly encouraging. For example, removing the bursa during early embryonic development impairs humoral immunity.

In contrast, bursectomy during late embryonic stage or neonate chicks reduces the number and functions of circulating B-lymphocytes (4), further underscoring the importance of the bursa in providing a vitally unique microenvironment necessary for the proliferation and differentiation of B-lymphocytes. The bursa contains ~12,000 follicles, particularly B-lymphocytes, dendritic cells, macrophages, and epithelial cells. Developmentally, interactions between different parts of the embryo lead to bursal follicles forming into which dendritic cells and B-cell precursors migrate (4, 5). This complex developmental process is carefully controlled both chronologically and spatially. Morphologically, it involves distinct stages: firstly, the creation of a vesicle-like structure in the mesenchyme of the tail-bud, resembling the epithelial foundation of the bursa; secondly, the colonization of the bursal mesenchyme by specific cells, known as hematopoietic stem cells (HCs), and the migration of blood-borne cells into the bursal epithelium, initiating the formation of follicles; and finally, the development of the follicular cortex around the time of hatching (5).

The mucosa of the BF features 11-13 longitudinal folds covered by specialized follicular epithelium, forming the elevated follicular pad. It also consists of columnar or pseudostratified interfollicular epithelium. The underlying connective tissue houses 8000-12000 lymphoid/bursal follicles, each comprising the outer cortex and inner medulla predominantly containing densely and loosely packed lymphocytes. The cortex and medulla are separated by a single layer of cuboidal epithelial cells resting on a basement lamina, which seamlessly connects with the basal cell layer of the interfollicular epithelium (5, 6). Small blood vessels can be found only in the cortex. A scattered assembly of lymphocytes located just above the opening of the bursal duct includes numerous T cells, suggesting that the BF serves as a secondary lymphoid organ, like gut-associated lymphoid tissue (6, 7).

Primary function of the BF is to serve for the development of the antigen-specific B-cell repertoire crucially. It is vital in transforming pre-bursal stem cells into bursal ones within the bursa until the 5th week of life. B-cells possess the ability to restore both the bursal morphology and the production of specific antibodies, of which process marks a distinct stage in the progressive maturation of avian cells responsible for antibody production (8) and formation of fully developed antigen-specific post-bursal B cells population along with self-renewing post-bursal stem cells. Unlike pre-bursal or bursal stem cells, these post-bursal B cells have permanently completed their bursal development (8, 9).

The BF also plays a key role in boosting the diversity of antibodies by extensively facilitating high-rate gene conversion. This process involves explicitly one functional V gene (either VH1 or VL1) engaging in gene conversion with a cluster of V pseudogenes. Within the bursal microenvironment, stem cells from the bursa undergo productive gene conversions, leading to further differentiation. Of course, those (>90%) undergo unproductive conversions are eliminated within the BF. Outside the BF, only minor gene conversion events and somatic point mutations may occur, underscoring the central function of the BF in shaping molecular events during avian B cell development (9, 10).

1.2 Thymus

The thymus is a paired organ situated on either side of the trachea in the neck (Figure 1) and consists of five lobules. Within the thymus, T cells, crucially cellular part of specific immunity, undergo multiplication. In birds, the thymus is distinctive, comprising numerous separate lobes of oval tissue in the neck adjacent to the vagus nerve and jugular

vein. Its maximal activity occurs during very young stages; the thymus is also closely associated with birds' erythropoietic function and breeding cycle, and its removal thymus linked to the rejection of allogeneic grafts and delayed skin reactions (11). Structurally, the thymus can be categorized into cortical and medulla regions, with cellular composition, especially lymphocytes in various maturational stages and stromal cells such as epithelial cells, dendritic cells, macrophages, and fibroblasts, creating an optimal environment for the differentiation and maturation of lymphocytes, thereby suggests a comparable mechanism of lymphocyte development in thymuses of both avian and mammalian (12, 13).

1.3 Spleen

Like other vertebrates, in birds, the spleen (Figure 1) is the largest lymphoid organ and serves as a crucial immune response, although there are some physiological and anatomical differences. It also serves as the primary site for the differentiation and proliferation of lymphocytes and actively participates in hormonal and cell-mediated responses. Moreover, in birds, the spleen is instrumental in orchestrating innate and adaptive immune reactions, highlighting its significance in immune regulation. Although the immune responses to systemic antigens are similar in avian and mammals, the absence of lymph nodes in birds makes the spleen the primary location for various immune responses. Notably, the red pulp of the avian spleen, particularly around major arteries and veins, harbors abundant-antibodies producing plasma cells that are distributed throughout the body via the bloodstream, rendering researchers to preferably assess antibody titers in peripheral blood/serum (14, 15).

1.4 Harderian gland

The dominant eye-associated lymphoid tissue/ paraocular/ orbital gland in birds is the Harder's gland, which, in addition to its lubricating and cleaning functions, plays a crucial role in the local immunity of the eyes and upper respiratory tract. The position of the Harderian gland shows minimal variation in birds, remaining ventromedial to the eyeball (see Figure 1). While some glands may be slightly more anterior, the overall consistency is observed across various bird species, including sparrows and fowls, as well as over 80 other bird types (16, 17). The innervation and blood supply to the Harderian gland are similar in all studied birds, with the blood supply originating from the ophthalmotemporal branch of the external ophthalmic artery and innervation provided by the inferior branch of the oculomotor nerve(18).

1.5 Lymphatic system

The lymphatic system in poultry is a complex network comprising lymph nodes [Though birds lack encapsulated lymph nodes like those of mammals but substantially develop diffuse lymphoid tissue with many lymphoid follicles], lymphatic vessels, and the spleen, collaborating to combat infections. Its primary function involves filtering lymphatic fluid to eliminate pathogens. Subsequently, the diffuse lymphoid tissue and spleen generate/proliferate white blood cells, such as B-and T-lymphocytes, crucial for the immune response against various (non)infectious pathogens (18, 19). Many other non-well-known immune organoids in birds, like heart lymphatic organs (Figure 1) etc., exist, and their structural and functional roles remain to be further investigated.

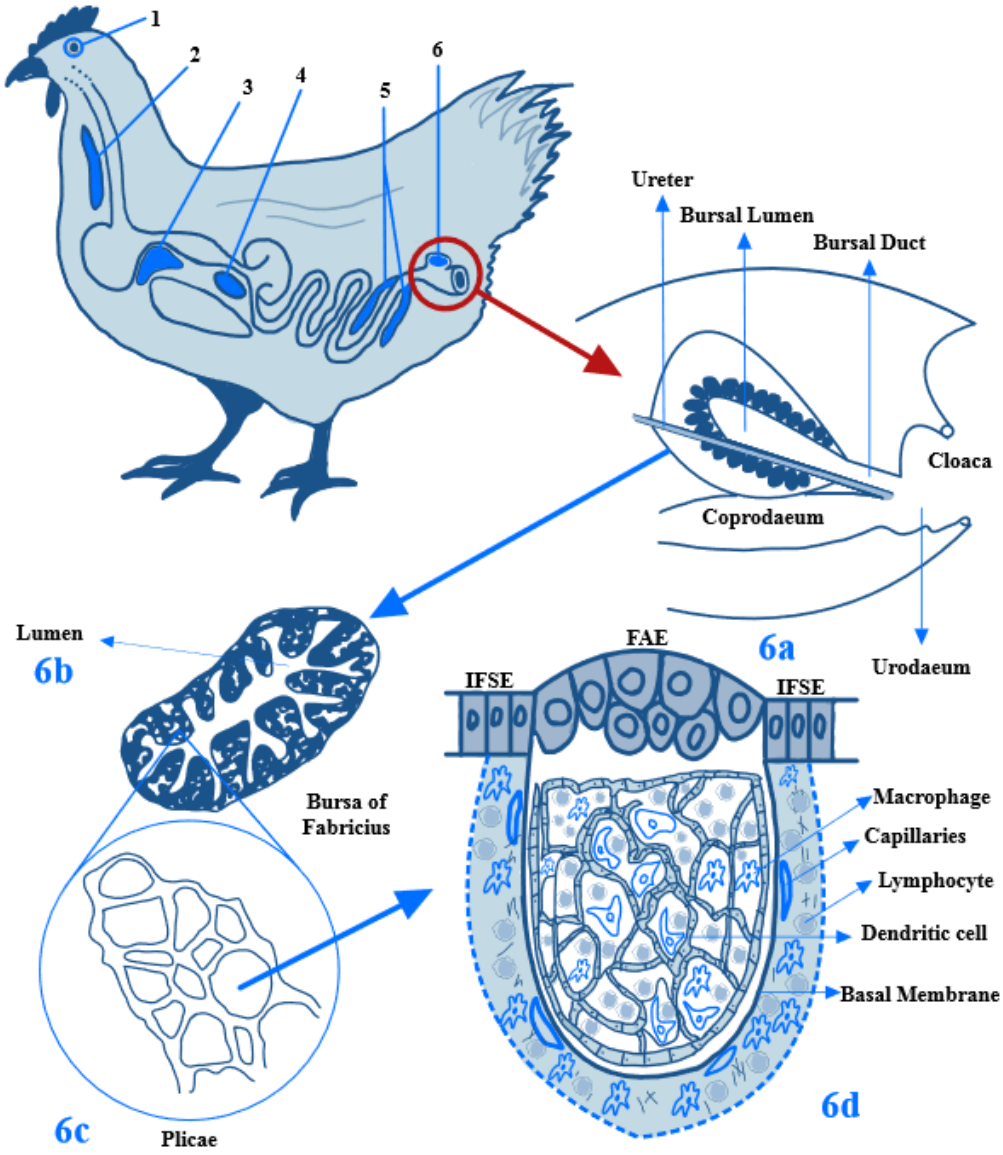

Figure 1. Schematic view with some details of avian lymphoid organs with their approximate locations 1, 2, 3, 4, 5, and 6 are the Harderian gland, thymus, Heart lymphatic glands, spleen, cecal tonsil, and Bursa of Fabricius (BF) are located directly behind and around the eyes, in the chest region near the heart, around the heart tissue, in the abdomen situated dorsally at the angle between proventriculus-gizzard-and liver, in the large intestinal region and near the cloaca, respectively. 6a). the Bursa of Fabricius. 6b) The histological view of BF with lumen and numerous follicles covered by visible pseudostratified epithelial cells. 6c) Portions of the long mucosal folds (plicae) project into the lumen of the bursa with numerous follicles, each composed of a cortex and medulla filled with the lamina propria of each fold. 6d) overall and in-depth schematic view of a single follicle and the paler medulla composed of mainly small lymphocytes in various sizes and some dendritic cells (DCs), macrophages, and non-immune cells. The cortex primarily contains lymphocytes. Layers of undifferentiated epithelial cells [Interfollicular surface epithelium (IFSE) and follicle-associated epithelium (FAE)], which are cuboidal, occupy the periphery of the medulla. A capillary network separates the cortex and the medulla.

2 Avian innate immune system

Functionally, immune systems are divided into an early-responding innate immune system and a slow-reacting adaptive immune system. Host cells are exposed to a large number of pathogens daily. Despite this exposure, birds are not seriously affected by these pathogens. The primary reason for this is the highly efficient early defense response produced by the birds' innate immune arms. Innate immunity is the first line of defense against infections. It comprises physical and chemical barriers at the epithelial layer, such as the skin, gastrointestinal, and respiratory tracts, that prevent the entry of microbes.

Additionally, innate immunity helps to remove damaged cells and initiates tissue repair. Another critical role of innate immunity is to activate adaptive immune responses. Cells and molecules of the innate immune system (with a largely myeloid lineage of immune cells (especially heterophils and monocytes and related molecules) develop earlier than those of the adaptive immune system (especially T and B cells and their related molecules). During the first two weeks after hatch, there are further increases in polymorphonuclear cells in all parts of the body, especially in the intestine. Innate immunity provides immediate protection by recognizing conserved microbe patterns and indicators of host cellular damage known as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (20). Innate immune responses are mainly non-specific to pathogens; their functions to various pathogens are almost similar (21-23). The innate immune system combats microorganisms using antimicrobial peptides, bacteriolytic enzymes, phagocytes, non-phagocytic innate immune cells, and the complement system (24-26). It can eventually guide the adaptive immune system to produce the most effective response against various microbes (27). Below, some key components of the avian innate immune system are presented.

2.1 Defensins

Defensins are a group of small cystine-rich peptides with antimicrobial properties and can fight bacteria, fungi, protozoa, and enveloped viruses. They are found in both animals and plants. Although they have many similarities, they also differ in their structure. These cystine-rich peptides range in length from 18 to around 45 amino acids. They comprise hydrophobic and cationic amino acid residues (28, 29). There are about 14 types of defensins in chickens and three in turkeys (30). The skin of chickens shows moderate expression of AvBD3, AvBD9, and AvBD11 (31). Chicken β-defensins AvBD1 and AvBD2, were initially discovered in peripheral blood leukocytes, and AvBD4–7 are highly expressed in bone marrow, while AvBD4–7 show weak or no mRNA expression in heterophils (30). In the respiratory tract, high expression of β-defensins is observed in the trachea for AvBD3 and AvBD9 (31, 32).

2.2 Toll-like receptors

With a huge evolutionary concept, the transmembrane toll-like receptors (TLRs) are a subfamily of pattern recognition receptors (PRRs) (33). They were first discovered in drosophila. Mutation of TLR gens caused abnormality in establishing the dorsoventral (DV) axis of the Drosophila embryo. Also, the drosophila TLR mutant was susceptible to fungal infections (34, 35). Both immune and non-immune cells expressed TLRs, such as dendritic cells, macrophages, lymphocytes, and epithelial cells. Like other PRRs, TLRs recognize PAMPs [e.g., bacterial LPS, peptidoglycan, pathogen nucleic acid (DNA or RNA), lipoteichoic acid, fungal glucans, etc.] and DAMPs [e.g., heat shock protein (HSP), extracellular ATP, high-mobility group box 1 (HMGB1), histones, and other molecules that indicate abnormal conditions in the host cells, indicating injury to the cells (33, 36, 37). When PAMPs or DAMPs bind to TLRs, they activate and mature antigen-presenting cells (APCs) such as macrophages and dendritic cells. These cells are positioned differently to monitor the entry of pathogens (38, 39). Once developed, these cells secrete cytokines that stimulate pro-inflammatory responses, increasing the gene expression of TNF-α, IL-1, and IL-6. Additionally, APCs present antigens to naive T lymphocytes, which prompts their differentiation into effector T cells (40, 41). So far, most studies on TLRs have focused on humans, zebrafish, fugu, and mice. However, few studies have thoroughly explored chickens' (ch)TLR-mediated immune response and their role in disease resistance (42-45).

Structurally and functionally, the avian TLR family consists of ten TLRs designed to recognize different ligands. These include TLR1A and B, TLR2A and B, TLR3, TLR4, TLR5, TLR7, TLR15, and TLR21. Two chTLRs, named chTLR15 and chTLR21, have been identified with no counterparts in mammalian TLRs (39). However, despite extensive analysis, no orthologues of mammalian TLR9, TLR11, TLR12, or TLR13 can be found in any of the

available avian genomic databases/resources. Some TLRs face extracellular space, like TLR1-2-4-5-15; others are endosomal, like TLR3-7-21 (39). TLR1A and B, TLR2A and B recognized bacterial cell wall, TLR3 recognized dsRNA, TLR4 bacterial LPS, TLR5 recognized bacterial flagellin, TLR7 recognized ssRNA, TLR15 recognized pathogens protease, and TLR21 recognized CpG DNA motifs (39).

TLR15 is a unique type of Toll-like receptor found in birds (46, 47) but not in mammals and fish. It is expressed in various chicken organs, including the spleen, BF, bone marrow, and intestine (48). chTLR15 is activated by fungal and bacterial proteases (49) and responds to proteases at different tissues with high proteolytic capacity. It recognizes bacterial components and triggers the immune response to *Escherichia coli*, *Salmonella*, and *Enterococcus* (50).

ChTLR21 is a protein similar to TLR9, a receptor present in mammals (51). It is believed that chTLR21 has evolved independently to recognize microbial DNA as a signal of danger and initiate an immune response. CpG oligodeoxynucleotides (ODN) are known to stimulate TLRs and have been studied extensively. Research has shown that chTLR21 is involved in recognizing CpG ODN and triggers an immune response similar to that observed in mammals (51). Studies have also shown that CpG-ODN can enhance immune responses and stimulate the production of antibodies and immune cells in chickens. Combined with the avian influenza virus vaccine, it can improve the effectiveness of the vaccine (52, 53). ChTLR21 has been detected in several cells, including avian macrophages and B lymphocytes (54).

Whether chTLRs can affect phagocytosis, particularly in critically important innate immune cells in birds, monocytes, macrophages, DCs, and heterophils (55). TLRs are a type of PRR that can trigger signals to promote immune responses and indirectly eradicate pathogens (56). Phagocytosis is one of the most vital components of the non-specific immune responses, where microbes are trapped, processed, and eventually degraded/killed. It is essential in initiating adaptive immune responses (56, 57). TLRs can modulate phagocytosis through four primary factors. Firstly, TLRs signaling may function as phagocytic receptors. Secondly, TLRs can affect the activation of other phagosome formation. Thirdly, TLRs may influence the maturation process of phagosomes into phagolysosomes. Finally, TLRs signaling may affect the production of proteins involved in all steps of phagocytosis (58). Therefore, it is essential to understand the relationship between TLRs and phagocytosis. Studies show that in the absence of TLRs signaling, phagocytosis of bacteria such as Salmonella typhimurium, Staphylococcus aureus, and Escherichia coli is impaired due mainly to reduced phagosome maturation and formation (53, 57). Other studies have shown that TLRs regulate the MyD88-dependent initiation of p38, which is essential for the maturation of phagosomes (53, 56, 57). So, it is unequivocally accepted that TLRs are involved mainly in the phagocytosis of microbial pathogens. Many authors have also reported that TLRs recognize PAMPs through a Toll-interleukin 1 receptor (TIR) domain. This domain contains MyD88 adaptor molecules and TIR domain-containing TRIF (adaptors inducing IFN protein), which initiate an intracellular signaling cascade and inflammatory mediators such as IL-6 and TNF-α (57, 59-61). The details of PRRs, especially TLRs, along with their ligands, are shown in Table 1.

On the other hand, chTLR activation results in a different gene expression profile. For instance, chTLR3/4 signaling pathways induce type I interferons (IFNs), except chTLR2 and chTLR5 (57, 59, 62, 63). Meanwhile, chTLR7-mediated pathways activate the IFNs through mechanisms different from chTLR3/4 pathways (46, 57). Therefore, the individual signaling pathways of TLRs are different. At the same time, MyD88 is common to almost all chTLRs, clearly indicating the potential role of MyD88-dependent and MyD88-independent pathways in activating immune responses (59), especially initiating "appropriate inflammatory responses" (mother of immune responses).

Table 1. Comparison of the major PRRs between avian and human and their principal ligands; "-" means not yet determined/unknown.

PRR	Human/avian	Ligand	Reference
TLR-1	human	Bacterial tri-acyl lipopeptide	(64)
	avian	Lipoprotein	(65)
TLR-2	human	Peptidoglycan from Gram-positive bacteria	(64)
	avian	Lipoprotein and peptidoglycan	(66)
TLR-3	human	Single-stranded viral RNA (ssRNA) and double-strand-RNA (dsRNA)	(64)
	avian	dsRNA	(67)
TLR-4	human	LPS, lipoteichoic acid, fibronectin, heparin sulfate	(64)

	avian	LPS	(68)
TLR-5	human	Flagellin	(64)
	avian	Flagellin	(66)
TLR-6	human	Lipopeptides, a peptidoglycan from Gram-positive bacteria and Zymosan from fungal cell wall	(64)
	avian	-	-
TLR-7	human	Single-strand RNA (ssRNA) compounds	(64)
	avian	ssRNA	(69)
TLR-8	human	ssRNA	(64)
	avian	-	-
TLR-9	human	Unmethylated CpG motifs found in microbial DNA	(64)
	avian	-	-
TLR-15	human	-	-
	avian	Lipoprotein (from yeast)	(66)
TLR-21	human	-	-
	avian	CpG oligodeoxynucleotides (from Bacteria and viruses)	(68)
RIG-I	human	Viral RNA	(70)
	avian	-	-
MDA5	human	Viral dsRNA	(71)
	avian	Viral dsRNA	(48)
CRP	human	Microbial phosphorylcholine and phosphatidylethanolamine	(72)
	avian	phosphocholine on microorganisms and lysophosphatidylcholine	(73)
NOD-1	human	Diaminopimelic acid (DAP)	(74, 75)
	avian	γ-glutamyl diaminopimelic acid (DAP), a PGN-breakdown product of all Gram negative	(76)
NOD-2	human	muramyl dipeptide (MDP)	(77, 78)
	avian	muramyl-dipeptide, a PGN motif common to most bacteria	(79)

2.3 Antigen-presenting cells

Antigen presentation is a process in which the immune system collects information about the antigenic environment. Classically, pivotally important B-and T lymphocytes sense the environmental antigens through this process. Depending on the context, antigen presentation can lead to either lymphocyte activation or tolerance. For example, antigen presentation can activate lymphocytes to respond to a pathogen challenge or induce tolerance to self-antigens. An antigen is processed either endogenously or exogenously, and the resulting peptides are expressed on the surface of APCs bound to either major histocompatibility complex (MHC) class I or class II molecules (80). Like mammals, almost all cells in birds express MHC-I heterodimer molecules on their outer surface. They use the specialized MHC peptide binding cleft to express peptides derived from endogenous antigens sampled from the cytoplasm or nucleus (80). Figure 2 schematically shows branches of avian's various immune cells' lineage in the lymphoid organs and bloodstream blood, originating from key stem cells/progenitors.

2.3.1 Dendritic cells (DCs)

In the early 1970s, Ralph Steinman and Zanvil Cohn discovered a rare cell type in murine spleen cell preparations that could be distinguished from macrophages and other leukocytes (81). They proposed the name "dendritic cells" based on cellular morphology (In Greek, it means tree-like); in that decade, Steinman et al. reported that these DCs were necessary for activating T cells in mixed lymphocyte reactions (MLRs) (82). Recently, it has been acknowledged that the original DCs discovered by Steinman are a distinct cell lineage that can be differentiated from related mononuclear phagocyte system (MPS) cells based on their ontogeny (83). These cells are now called "classical" or "conventional" (c)DCs to distinguish them from other cell lineages like monocyte-derived DCs or bone marrow-derived DCs. The cytokine Flt3L, which works through the Flt3 receptor, drives the generation of cDCs. However, macrophages and monocytes lack Flt3 expression (80). There are two subsets of mammalian cDCs: cDC1 and cDC2 (84-86). Each subset has its specific functions. The cDC1 subset is responsible for cross-presenting antigens and induction of Th1 responses. On the other hand, the cDC2 subset is specialized in inducing Th2 and Th17 immune responses (87-89).

Of the three types of mammalian professional APCs (DCs, B lymphocytes, and macrophages), B cells can be excluded as being necessary for antigen presentation. This is because bursectomized birds, which lack B cells, can still mount normal T-cell responses, so avian macrophages may be sufficient to mount classical immune responses (90).

Professional Antigen-presenting cells, DCs, and macrophages are highly adaptable and versatile. They carry out a range of functions, such as endocytosis and exocytosis, breaking down foreign substances, producing cytokines, and presenting antigens to naive T- lymphocytes. These functions occur in both healthy and pathological conditions (91). It is known that both DCs and macrophages come from a shared hematopoietic stem cell precursor expressing CD45+ (92). Recent experiments conducted using transgenic mice have provided evidence that most of the Langerhans cells (LC, a type of DCs that is located in the stratified squamous epithelium) originate from erythro-myeloid progenitors in the yolk sac rather than from fetal liver or bone marrow-derived HSCs (93). They constitutively express MHC-II glycoproteins during antigen presentation. Thymic (T)DCs are found in the thymic medulla and are crucial in central tolerance. Interdigitating (I)DCs are found in T cell-dependent lymph nodes and spleen areas, where they stimulate naïve T-lymphocytes. Lastly, follicular (F)DCs are non-phagocytic cells found in the germinal centers of the B-lymphocytes area of the follicles, and they are responsible for germinal center responses and B –lymphocyte selection (94).

2.3.2 Macrophages

Macrophages play central roles in innate immune responses and mounting adaptive immunity by functioning particularly as APCs; as such, they are critical in protecting birds from microbial infections. They can engulf bacteria and produce broad antimicrobial molecules such as reactive oxygen species (ROS), nitric oxide (NO), and cytokines to eliminate the invading pathogens and signal to other immune cells to establish an appropriate response to the infection (95-97). IFN-γ is produced by natural killer cells (NK) and T-lymphocytes and stimulates macrophages to secrete NO, which forms peroxynitrite, a potent antimicrobial oxidant (98).

As the embryo develops, macrophages with phagocytic activity have been observed in the liver as early as embryonic incubation day (EID) 12 and in the spleen at EID 16 (99). Elicited macrophages can be obtained from day-old chicks and turkey poults, indicating that this aspect of the innate immune system is remarkably functional even at hatching (100).

Receptor-mediated recognition is necessary for the binding of microorganisms before phagocytosis by macrophages. Macrophages possess various receptor systems, such as scavenger receptors, complement receptors, Fc receptors, C-type lectins, and mannose receptors that facilitate opsonic and nonopsonic recognition (101). During phagocytosis, particles are internalized into phagosomes that later fuse with lysosomes to create a phagolysosome. Lysosomes have a range of antimicrobial proteins and enzymes, including acid phosphatase and β-glucuronidase (102). Myeloblasts express low levels of enzymes, while mature macrophages express them at high levels constitutively (103).

Although macrophages phagocytize most bacteria, some, like *Staphylococcus aureus*, can escape via caspase-3 activation and macrophage cell death (104). Macrophages are known to play an essential role in the pathogenesis of specific avian Marek's disease virus (105), feline coronavirus (106), and human immunodeficiency virus (HIV) (107). Studies have shown that coronaviruses such as the severe acute respiratory syndrome coronavirus (SARS-CoV) can replicate within human macrophages (108), causing severe pathology by interfering with macrophage functions (109). However, a single in vitro study has indicated that IBV, particularly nonpathogenic Beaudette and Massachusetts type 82822 strains, do not replicate in avian macrophages (110).

The process of efferocytosis, which is the clearance of dying cells by macrophages, is crucial for maintaining tissue health, resolving inflammation, and restoring the function of damaged and infected tissues. This process has significant immunomodulatory effects and helps limit the release of intracellular DAMPs that drive inflammation. During development, programmed cell death is vital in forming various embryo organs and structures. In the CSF1R-transgenic chickens, macrophages were present in areas of programmed cell death, such as the interdigit regions of embryo leg buds, where they express lysosomes, indicating their phagocytic function (111). In post-hatch animals, TIM4 Kupffer cells and TIM4 bursal cells also aid in detecting and removing apoptotic cells in the steady state (89).

2.3.3 Heterophils

Heterophils are a type of granulocyte. They have eosinophilic granules in their cytoplasm and a lobed nucleus when they are mature. Heterophils are responsible for killing bacteria. They can be classified as immature, mature, and toxic heterophils. Toxic heterophils show changes in response to the severity of an illness (112). Wharton-Jones first described heterophils in 1846 (113). In chickens, heterophils are similar to neutrophils found in mammals/humans and play a crucial role in defending the body against pathological and inflammatory conditions. Immediately after hatching, during which the innate immune system has not yet fully developed, many heterophils are released from the spleen, but their numbers decline after days seven of hatch. As a result, the function of heterophils is also limited compared to older chickens (114-117). Therefore, young chickens are more vulnerable to infections during the early post-hatch period.

Studies on the function of heterophils and cytokine gene expression have demonstrated the resistance of birds to Salmonella infection (118, 119). When stimulated, heterophils in chickens release granules and chromatin-like molecules, which form extracellular traps. These traps contain DNA, histone-DNA complexes, and elastase from heterophil cytoplasmic granules (120). Microbial molecules are responsible for stimulating degranulation. When exposed to harmful pathogens, the avian's body releases cytokines such as interleukin (IL)-6, IL-8, and IL-18 to fight against pathogens (121, 122). This increased production of cytokine RNAs and proteins can lead to a high population of heterophils, which are primed and effective in responding to pathogens (118). The number of heterophils recruited to the site of infection depends on local chemoattractant production (123). The initial response of heterophils to pathogens involves activation and transportation, which is determined by the chemotactic nature of the response. Antigen presentation is a process in which the immune system collects information about the antigenic environment. Classically, pivotally important B-and T lymphocytes sense the environmental antigens through this process. Depending on the context, antigen presentation can lead to either lymphocyte activation or tolerance. For example, antigen presentation can activate lymphocytes to respond to a pathogen challenge or induce tolerance to self-antigens. An antigen is processed either endogenously or exogenously, and the resulting peptides are expressed on the surface of APCs bound to either major histocompatibility complex (MHC) class I or class II molecules (80). Like mammals, almost all cells in birds express MHC-I heterodimer molecules on their outer surface. They use the specialized MHC peptide binding cleft to express peptides derived from endogenous antigens sampled from the cytoplasm or nucleus (80). Figure 2 schematically shows branches of avian's various immune cells' lineage in the lymphoid organs and bloodstream blood, originating from key stem cells/progenitors.

Granulocytes are associated with a process called oxidative burst. However, heterophils lack the myeloperoxidase (MPO) enzyme necessary to produce enough peroxide anion to kill pathogens. As a result, chickens depend on non-oxidative antimicrobial reactions such as β-defensins and cathelicidins (30, 124). Although some reports suggest the presence of the MPO in chicken heterophils, there is still some contradiction (125).

Bacteria stimulating TLRs on heterophils activate their bactericidal functions (126). TLR2 and TLR4 ligands activate heterophils to produce different cytokines and interferons, usually produced in response to bacteria and viruses. Heterophils also possess Fc and complement receptors, which act through signaling pathways. These signaling pathways are mediated through G proteins, Ca, and Protein Kinase C-dependent pathways. TLR activation also leads to the production of cytokines through the activation of the NF-κB pathway in chicken heterophils (126, 127).

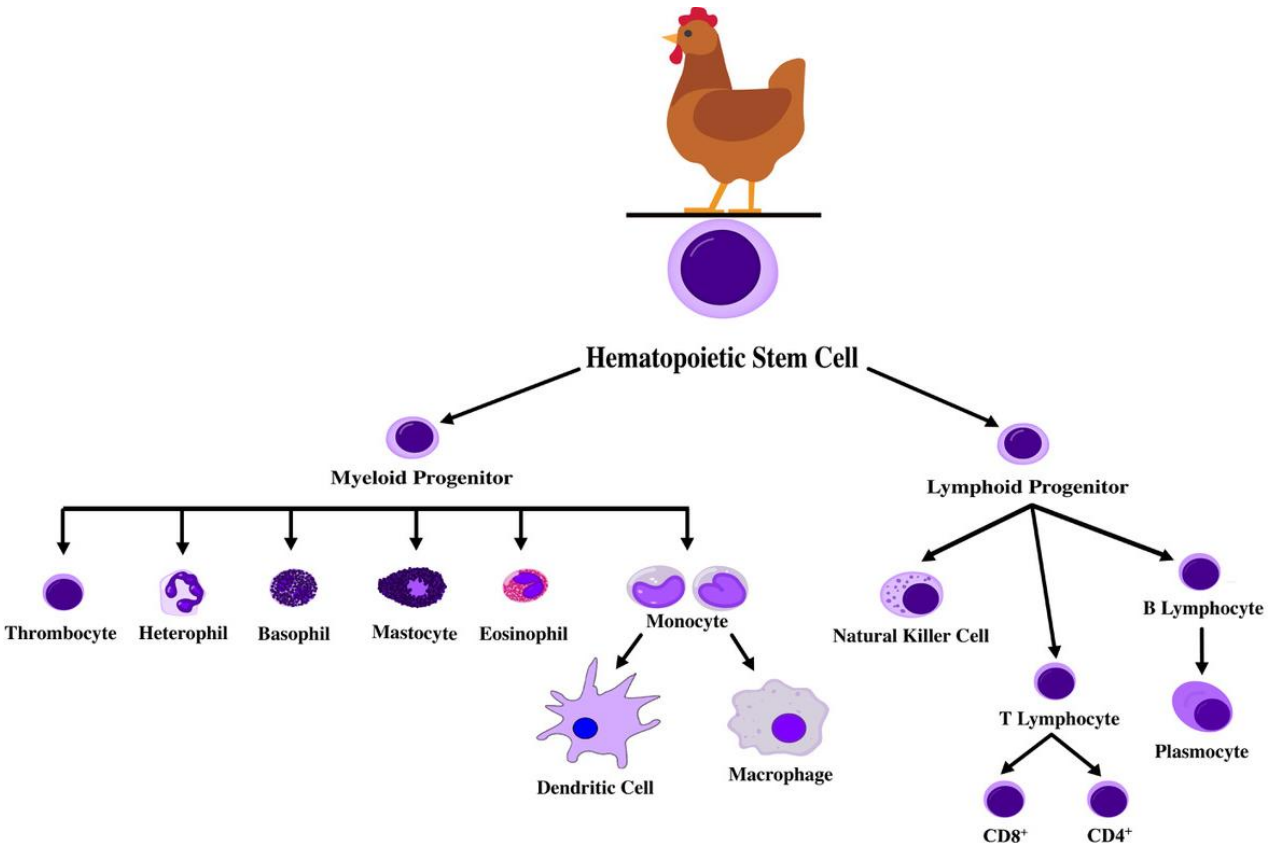

Figure 2. Schematic drawing of avian's various key immune cells. Originated from pleuripotential/hematopoietic stem cells and are branched to lymphoid and myeloid progenitors primary immune organs and then releases in blood stream for appropriate immune responses.

2.4 Chicken acute-phase proteins

As one of the most crucial branches of innate immunity, acute-phase proteins (APP) are typically identified as proteins that undergo a 25% or more significant change in plasma concentrations during an acute-phase response (APR). This response is classified as either positive or negative APP, depending on whether the protein levels increase or decrease. Additionally, positive APP can be further categorized into three groups based on the degree of increase: group I for proteins that increase by one-fold, group II for those that increase between two- to five-fold, and group III for those that increase up to 1000-fold (128). Chicken APPs are primarily synthesized in the liver, but APP mRNA has also been identified in other healthy chicken tissues. In 55-day-old broilers, extrahepatic Serum Amyloid A (SAA) mRNA was observed in significant levels in the lungs (70%) and cecal tonsils (72%), which were comparable to the liver and to a lesser extent in the spleen (26%). Furthermore, extrahepatic expression of Ovotransferrin (OVT) was discovered in the lungs (20% of liver expression). Although CRP, PIT54, and mRNA were detectable in various tissues, they were present in very low concentrations compared to the liver (129).

2.4.1 Chicken C-reactive proteins (CRPs)

CRPs are another key component of the innate immune system; they are cyclic oligomer that binds to phosphocholine in a Ca2+-dependent manner. It plays a crucial role in protecting against infection, clearing damaged tissue, preventing autoimmunity, and regulating the inflammatory response (130). CRPs are proteins found in primitive arthropods, where they are expressed constitutively and not as part of an APR and are evolutionarily very well-conserved (131). In mammals, CRPs are major acute-phase proteins used in diagnostic medicine for humans and animals (132). Constitutive hepatic expression of CRPs has been reported in chickens fed with aflatoxin, resulting in slightly increased mRNA levels (133). It was reported that chickens infected with *Ascaridia galli* exhibited a slight increase in CRPs at the mRNA level in their spleen (134).

2.4.2 *Fibrinogen*

Fibrinogen (FB) plays a significant role in physioimmunological hemostasis, providing a substrate for fibrin formation. It also contributes to tissue repair by providing a matrix for migrating inflammatory-related cells. The pro-inflammatory functions of FB are linked with its ability to bind to various immune cells. In mammals, the production of FB by the liver is associated with acute-phase responses (APRs) (135, 136). In chickens, during a turpentine-induced APR, the plasma levels of FB increased more than two-fold (137, 138). Similarly, infection with *E. coli* or *E. tenella* also increased plasma FB levels is apparent; this non-specific broad action of immunity may help limit the spread of infection/invading pathogen.

2.4.3 *PIT54*

In mammals, free hemoglobin (Hb) from lysed erythrocytes is bound by haptoglobin (Hp). Hp inhibits the toxic, pro-inflammatory, and oxidative activity of Hb. Phagocytes recognize the Hp-Hb complex and scavenge it. Although no Hp gene has been identified in the chicken genome, a functional homolog regarding Hb binding was identified as PIT54. PIT54 is a soluble member of the family of scavenger receptor cysteine-rich proteins that also contain CD163 (139). The antioxidative properties of PIT54 have been established, and it is a single-chain polypeptide bound to a carbohydrate component. Unlike mammalian Hp, PIT54 has a different Hb binding capacity. It binds with lower affinity to chicken Hb than mammalian Hp binds to mammalian HB(140). After being challenged with LPS from S. typhimurium or E. coli infection, increased plasma PIT54 levels were observed significantly (141, 142) to activate other parts of innate immunity and eventual pathogen removal.

2.4.4 *Chicken serum amyloid A (SAA)*

Generally, SAA is a protein associated with high-density lipoproteins in mammals. It is produced in the liver in response to stress, trauma, or infection. SAA is responsible for regulating lipoprotein transport and metabolism, and it also aids in preventing tissue damage (143, 144). Only one SAA gene has been identified in chickens, mainly expressed in the liver (145). Studies have shown that the hepatic SAA mRNA expression increases 33-fold in response to infection with *S. gallinarum* (146). Moreover, increased expression of SAA mRNA has been reported in the spleen of chickens infected with *S.enteritidis* (55-fold) (147) or H5N1 influenza (40-fold) (148). In mammals, SAA is the precursor of amyloid A, responsible for tissue deposits leading to secondary amyloidosis (149).

2.4.5 *Ovotransferrin (OVT)*

Mammals have two distinct soluble glycoproteins belonging to the transferrin family. One of them is transferrin, which is found in plasma and is responsible for binding and transporting iron. The other one is lactoferrin, which is present in extracellular fluids and has antibacterial and immunomodulatory properties (150). In chickens, the only soluble glycoprotein of the transferrin family is OVT. This protein can be found in plasma and eggs but differs in glycosylation (151). Unlike mammals, transferrin is a positive APP in chickens, and its expression at mRNA and protein levels is up-regulated under an APR (152, 153), more so is the simultaneous overexpression of OVT and APR in the oviduct. In chickens, OVT and APP plasma levels increased seven days after the challenge with ILTV, E. coli, FPV, ARV, IBDV, and IBV (154). Recently, it has been discovered that the presence of OVT content in feces has the potential to be a valuable indicator of gut barrier failure caused by enteric pathogens. It was found that there is a significant correlation between the severity of gut barrier failure caused by coccidiosis or necrotic enteritis and the levels of OVT present in feces (155).

2.5 *Inflammation*

As a pivotally main component of innate immunity, inflammation is necessary for appropriate classical immunity. The inflammatory response refers to a complex series of local and systemic changes in various cellular processes, circulation, metabolism, endocrine profiles, and neurologic and vasculature parameters that occur immediately upon introducing immunogenic material into an animal. In experiments involving chickens, immunogens are typically introduced subcutaneously or intraperitoneally. Regardless of the immunogen type or injection site, the acute phase response remains relatively similar, with differences mainly in the degree and temporal characteristics of the response (156-158).

The initial stage of the inflammatory response involves the recognition of the immunogen, triggering the production of various local inflammatory mediators. Phagocytic cells then adhere to endothelial cells in the venules and migrate from the bloodstream in response to chemotactic stimuli.

Stimulated by local inflammatory mediators and the recognition of the immunogen, phagocytes are fully activated. They ingest and destroy the invading pathogen, releasing hydrolytic enzymes and ROS into the inflammatory site (158).

Cytokines released from phagocytic cells, particularly macrophages, play a crucial role in recruiting and activating specific components of the classically acquired immune responses, such as lymphocytes, and coordinate the systemic acute phase response. In addition, chicken peripheral blood adherent cells present antigens to T-cells in the context of MHC II-encoded molecules, initiating cellular and humoral immune responses (158, 159).

2.5.1 Dynamic changes in immune cell numbers and functions

Timely recruitment of effector immune cells to the sites of injuries is crucial for the host's defense mechanism. Cells derived from the myeloid lineage (e.g., monocytes, macrophages, and DCs) are widely distributed across epidermal and mucosal surfaces, allowing for the recognition of pathogens/immunogens entering the body and the release of initial inflammatory mediators. Recent research acknowledges the involvement of non-immune cells in this process (160, 161). Unlike mammals, the specific inflammatory mediators, such as complement, IL-1, tumor necrosis factor (TNF), IL-6, interferons, platelet-activating factor, heparin, histamine, leukotrienes, and other arachidonic acid metabolites, and their sources in birds are not fully characterized. These mediators attract and activate inflammatory cells from the circulation (160-162).

Dynamically, the emigration of inflammatory cells in response to subcutaneously introduced immunogens has been well-documented in chickens. Heterophils and monocytes emigrate concurrently, predominantly heterophils immigrating in the early inflammatory process followed by high monocytes. After migrating from venules, these cells move to the immunogen site, where monocytes transform into macrophage-like cells (161-163). Lymphocytes start immigrating into the inflammatory site around 12 hours, and macrophages may fuse to form giant cells. Heterophils disintegrate after phagocytizing the pathogens/immunogens, and macrophages become the predominant exudate cell. Over time, macrophages, fibroblasts, and fibrin form a granuloma, walling off the site of inflammation (163, 164). Monocyte-originated monokines at the inflammatory site contribute to vascular and cellular changes, immunogen removal, specific immune response stimulation, walling off the site, and eventual tissue repair orchestration. These monokines could also enter the bloodstream, leading to a systemic acute phase response (165).

Although avian monokines are not fully understood, activities corresponding to mammalian BL-1, IL-6, TNF, and colony-stimulating factors have been identified. Macrophages release various monokine activities, and the myelomonocytic growth factor (cMGF) is a well-characterized avian monokine. Other activities include induction of hepatic metallothionein accretion, fibrinogen synthesis, granulocyte colony stimulation, skeletal muscle protein degradation, and related reactions (166). This will be more apparent in any stress conditions in birds. Environmental factors such as diet and density can lead to stress in birds, known as physiological stress. If the stress worsens, it can lead to inappropriate inflammatory and oxidative reactions/stress. Oxidative stress is a significant risk factor for tissue damage and organ dysfunction, and it can be caused by various factors (as shown in Figure 2). It is widely recognized that oxidative stress can activate several signaling pathways, leading to the activation of transcription factors, gene expression, and induction of apoptosis and cell death in immune and non-immune cells (167). Overall, the inflammatory response in chickens involves a complex interplay of different cell types and mediators, with monokines playing a crucial role in regulating both local and systemic immune responses (165, 166).

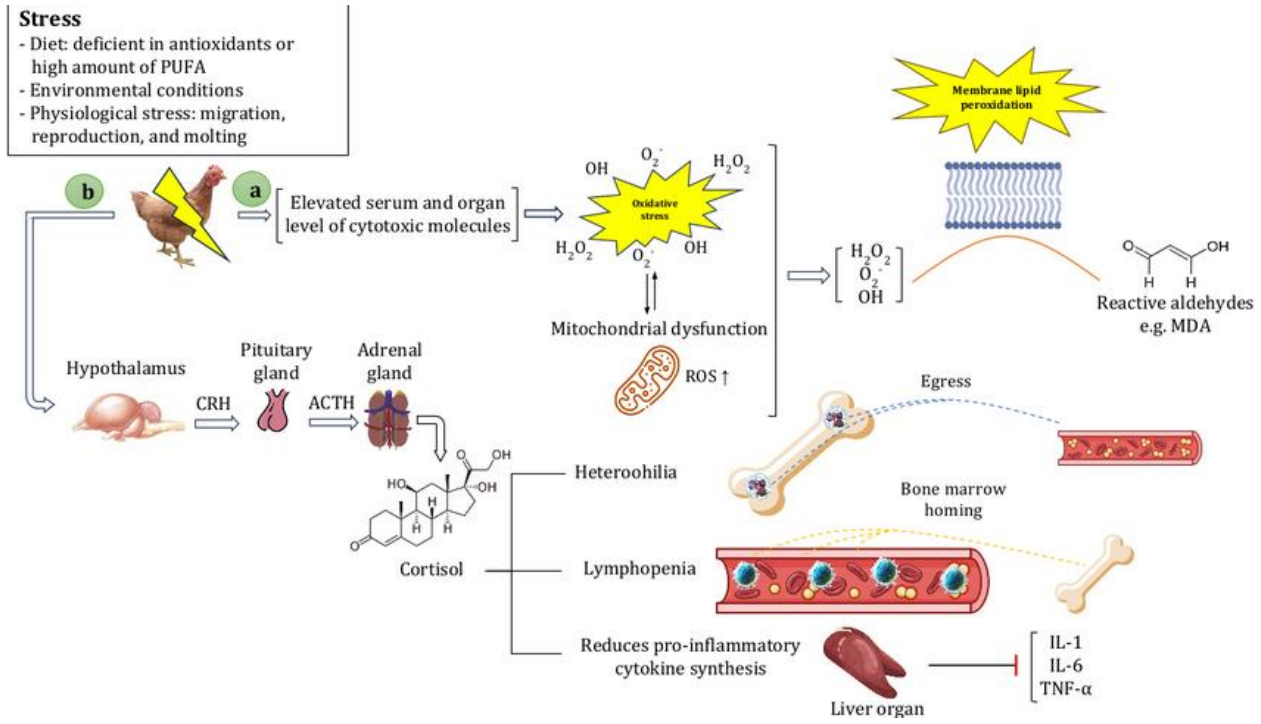

Figure 3. The effect of stressors that caused oxidative stress (OS) in avian. a) In this pathway, the level of serum ROS (cytotoxic molecules) such as OH-, O2-, and H2O2 increases, and mitochondrial dysfunction appears. Then, the required energy for cells decreases, leading to apoptosis and necrosis. One of the factors that can demonstrate OS in cells is MDA produced when cell membrane lipid peroxidation occurs followed by OS. b) The other effect of stress is its influence on the hypothalamus, subsequently releasing cortisol by the adrenal gland. Cortisol has different roles in immunity and is mainly known as down-regulating immune cells. Cortisol causes the migration of neutrophils to the bloodstream bone marrow, homing of lymphocytes. It inhibits the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, suppressing inflammation in early stages. However, resistance to the corticosteroid can appear if the stress status continues (appearance of stable chronic stress). This process leads to eventual immunosuppression and susceptibility to infectious and non-infectious bird diseases. PUFA: polyunsaturated fatty acids; MDA: Malondialdehyde; ROS: Reactive oxygen species.

2.5.2 Pro-inflammatory cytokines

Cytokines are proteins secreted by particular cells, which are crucial for activating and regulating other cells and tissues during inflammation and immune responses. Although extensively studied in various mammalian species, the understanding of cytokines in avian species still needs to be improved. Recent progress in avian genetics and immunology has allowed for the investigation of cytokines in health and disease (162, 168). One of the key cytokines is IL-1β, which has been intensively studied in mammals; IL-1β is produced by various cells in response to microbial stimulation. Its mature form, with a molecular weight of 17 kDa, is derived from a 31 kDa precursor through specific cellular proteases. IL-1β functions through two receptors (IL-1RI and IL-1RII) and an accessory protein (IL-1RAcP), activating the immune system and inducing an acute phase response. The homolog of mammalian IL-1β has been identified in chickens, sharing similarities in gene structure. Chicken IL-1β activates immune cells and is implicated in various avian infections, showing increased expression in response to inflammatory challenges (162, 168-170).

Another key pro-inflammatory cytokine is IL-6, which is a multifunctional cytokine in particularly mammals, participating in acute-phase responses, immune regulation, and hematopoiesis. A homolog of IL-6 has been identified in chickens, sharing sequence similarities with the human counterpart. Recombinant chicken IL-6 induces immune responses, including the proliferation of specific cell lines and increased serum corticosterone levels, indicative of acute phase activity. IL-6 activity is found in infectious diseases of chickens, and its response to different serovars of *Salmonella enterica* suggests a role in modulating inflammatory and immune responses (162, 171, 172). A third predominant pro-inflammatory is the TNFs group; they constitute a family of cytokines with diverse biological

effects. TNF-α, a key regulator of immune responses and inflammation, is produced by various cells. TNF-β, or lymphotoxin, is secreted by CD4+T-lymphocytes and exhibits direct cytotoxicity. While avian TNF has not been cloned, TNF-like activity is detectable in chickens following infections. Injection of chickens with TNF-like factors enhances weight loss during certain infections, and human recombinant TNF cross-reacts with chicken cells (162, 173). Paralleling their functions in mammals, the understanding of cytokines in avian species is nonetheless advancing, and their crucial roles in immune responses and inflammation are unequivocal (162).

3 Birds' adaptive immunity

3.1 An introduction to adaptive immunity in avian

Like humans, chickens have developed various defense strategies within their immune system to combat a broad spectrum of pathogens. While the fundamental principles of the immune response and habitats remain consistent among all vertebrate species, chickens possess distinct immune genes, molecules, cells, and tissues compared to mammals. This encompasses components of innate immunity, such as physical and chemical barriers that prevent the pathogen from entering and cellular and soluble elements ready to eradicate invading pathogens (174, 175).

The immune system is a complex network that employs many components to detect and eliminate various pathogens. It uses cells, molecules, and organs to identify and destroy disease-causing agents. The avian immune system comprises two functional aspects: the humoral and cell-mediated arms, which collaborate to ward off harmful microorganisms and prevent disease. However, certain avian ailments can impair either one or both of these arms, leading to temporary or permanent immunosuppression and heightening the bird's vulnerability to many diseases (176-179).

Though innate immunity is highly effective, it cannot fulfill immune responses and create immunological memory. Adaptive immunity is necessary to defend against particular invading pathogens and create memory specifically. This leads to eliminating the pathogen and provides protection in future encounters with the same pathogen (174). That is why vaccines and vaccinology have been substantially developed in avian medicine research and development. Like mammals, in chickens, the adaptive immune response begins with the processing and presentation of antigens. The host's immune system then responds by initiating either a humoral response (e.g., production of antibodies) or a cell-mediated response (activation of antiviral and antitumor mechanisms). Characteristics of both of these responses, which are produced by T-and B lymphocytes, include specificity and memory, which are crucial for effective vaccination. In chickens, the immune system comprises various immune organs, tissues, cells, and molecules (see above mentioned text and figures) to produce appropriate immune responses and immunological memory (177, 180, 181).

3.2 Immunoglobulins (Igs)

Immunoglobulins, also known as antibodies, play a crucial role in our immune system. B cells produce them with a unique three-dimensional shape that allows them to bind to foreign agents (Figure 3) selectively. This binding triggers a signal to other immune cells and molecules to eliminate the pathogen. Due to their importance in biomedical and biotechnological applications, there is a need for efficient production processes. Immunoglobulins are essential proteins that significantly affect the adaptive immune response. They are also valuable tools in biomedical research. Antibodies can be utilized to label cells or their components detect, analyze, or purify proteins, among other applications. Specific antibodies have sometimes been used to treat bacterial infections (181-183).

Antibodies most effectively remove antigens from circulation and secreta/outside the cells. When an antibody interacts with an antigen, it stimulates mechanisms that help destroy invading pathogens. These mechanisms include activating the classical complement pathway directly on the antigen, coating, clumping, or precipitating the antigen more efficiently and faster ingested mainly by phagocytes (terms opsonization, neutralization, and limiting the spread). Additionally, antibodies can help eliminate cells that may be infected or cancerous. This process is called antibody-dependent cellular cytotoxicity. In this process, the antibody links the killer cells and the target cell by binding to the antigen on the target cell using the antigen-binding portions and binding to Fc receptors on killer cells via its Fc portion. This link between the killer and the target cell, which is mediated by antibodies, results in the activation of the killer cell and the destruction of the target cell (174).

Using immunocytochemical and genetic techniques, researchers have identified three classes of avian immunoglobulins similar to mammalian IgM, IgA, and IgG. Chicken IgM is the most common B-cell antigen receptor

and the first isotype expressed during embryonic development. The structure and function of chicken IgM is comparable to its mammalian counterpart. After initial exposure to a new antigen, IgM is the predominant isotype produced during the humoral response, which is typically temporary, similar to mammals. However, in cases of chronic bacterial infection, such as Bordetella avium in turkeys, IgM can remain active even for several weeks (184-186).

IgY (almost similar to IgG) is a type of avian immunoglobulin that shares similarities with mammalian IgG and IgE. This type of immunoglobulin is the predominant form found in sera and egg yolk; IgY is produced after IgM in the primary antibody response, and the main isotype produced in the secondary antibody response. It is often referred to as IgY in the literature, as initially proposed by the first authors who described it. Salt precipitation studies indicate that the avian form of Ig has biochemical properties different from mammalian IgG, hence the name IgY. The main difference between the chicken IgY and the mammalian homolog is the longer H chain in the chicken molecule. Avian IgY consists of five domains (V, C1–C4), unlike the four found in mammalian IgG. Like mammals, based on molecular genetic evidence from chicken and duck, IgA is present in all avian species, though the phylogenetic origins of IgA are unknown. A structurally and functionally homologous form of mammalian IgA has been demonstrated in chicken secretions, especially bile. Although there were some early reports of a chicken homolog of IgD on the surface of chicken lymphocytes, it is generally accepted that there is no avian homolog for Igδ, with most chicken B cells expressing IgM (187).

The immune system of vertebrates, including birds, can produce many antibody molecules. This is likely due to the existence of multiple variables (V), diversity (D), and joining (J) elements in the genome, which make up the germline repertoire. Additionally, somatic recombination processes and point mutations further contribute to diversity. However, B-cell formation and the generation of diversity are significantly different in chickens compared to mammals. In chickens, the diversity of B-cell receptors is limited because the rearrangement of Igs genes occurs only once during early embryonic development instead of being a continuous process. As a result, the total number of possible rearrangements that generate the chicken B-cell repertoire is restricted to the number of B-cell precursors in the BF, estimated to be around 2-3×104 cells (180, 188, 189).

Avian antibodies have heavy (H) and light (L) chains encoded by two separate gene regions. In the light chain gene region, there is only one gene segment for each V and J region. Similarly, the heavy chain gene region has only one segment each for the V and J regions, but it also has about 15 D segments. Unlike mammals, where rearrangement contributes to much diversity in B-cells, the introduction of diversity in chicken B-cells is limited because there is only one gene segment each for the V and J regions. The only source of diversity comes from the D segments. In contrast, birds use pseudogenes (25 for the light chain and 100 for the heavy chain) in gene conversion, where pseudogene segments are inserted into the V region to attain antibody diversity (190).

Despite having very few immunoglobulin genes compared to mammals, chickens can produce a wide range of immune responses and diverse antibody molecules, which is a helpful process. IgY, which is similar in function to mammalian IgG, has a different structure. IgY contains two heavy (H) and two light (L) chains and has a molecular mass of 180 kDa, which is larger than that of mammalian IgG (159 kDa). IgY's H chain is heavier (68 kDa) than the H chain of mammals (50 kDa) and has four constant domains (CH1-CH4) in addition to the variable domain. In contrast, the H chain of IgG consists of four domains: the variable domain (VH) and three constant domains (CH1, CH2, and CH3). The CH1 domain is separated from CH2 by a hinge region, which provides flexibility to the Fab fragments. However, the H chain of IgY does not have a hinge region (180). Terminally differentiated B lymphocytes (plasma cells) are responsible for producing antibodies. However, in most cases, T lymphocytes (T helper cells) and antigen-presenting DCs (related to macrophages) also play a role. Antibodies can act as mediators of cell-mediated immunity, which involves the production of cytotoxic T cells or delayed hypersensitivity T cells upon exposure to a specific antigen (184, 191).

3.3 Cell-mediated Immunity

Cell-mediated immunity is a type of immune response involving destroying cells infected by foreign agents like viruses. This is achieved through direct contact between effector cells (such as activated T-cells) and target cells; T-lymphocytes, also known as T-cells, play a crucial role in cell-mediated immunity (Figure 4). They fall into two major

classes: cytotoxic T-cells that can directly destroy infected or tumor cells and helper T-cells that regulate and direct the responses of other effector cells like macrophages or B-cells by releasing chemical signal molecules. Lymphocytes also act as immune system memory cells, retaining information about the exposure to an antigen and mounting a more rapid and intense secondary immune response upon re-exposure to the same antigen. Interestingly, research on the chicken and the chick embryo provided some of the earliest clues about the central role of lymphocytes in cellular immune responses. Despite this clear evidence, it has largely been unnoticed for many years (192).

T-lymphocytes are white blood cells that play a key role in the immune system of poultry, humans, and other mammals. They are responsible for the antigen-specific component of cell-mediated immunity. T-lymphocytes express various T-cell receptors (TCRs) that can identify different antigens. Various types of T cells can be distinguished by their functional abilities and cell surface markers. Regardless of the type of TCR expressed (γδ, αβ1, or αβ2) or the antigen specificity of the TCR, all T cells express CD3 complexes with the TCR molecules. Thus, CD3 is a pan-T cell marker indicating a T cell's presence. T helper (Th) cells are a subtype of T cells critical in mammalian and avian adaptive immunity. These cells usually express CD4 molecules on their surface. Most T-cells are classical ones, which are MHC-dependent; however, no-classical T-cells (γδ T-cells), which are MHC-independent, in some mammals and birds exist (e.g., γδ T-cells in chickens are ~30% of T-cells). When Th cells recognize a specific antigen with their TCR, they secrete soluble factors like cytokines and express cell surface molecules that provide essential activation signals to innate and adaptive immunity cells. In many mammals, there are two types of Th cells. Type-1 Th (Th1) cells direct the adaptive immune response towards a cell-mediated response, while type-2 Th (Th2) cells favor a humoral response. However, once Th cells have become activated in response to intracellular antigens, the effector mechanisms initiated by Th cells leading to the destruction of the antigen or target cell appear to be very similar in poultry and mammals (174).

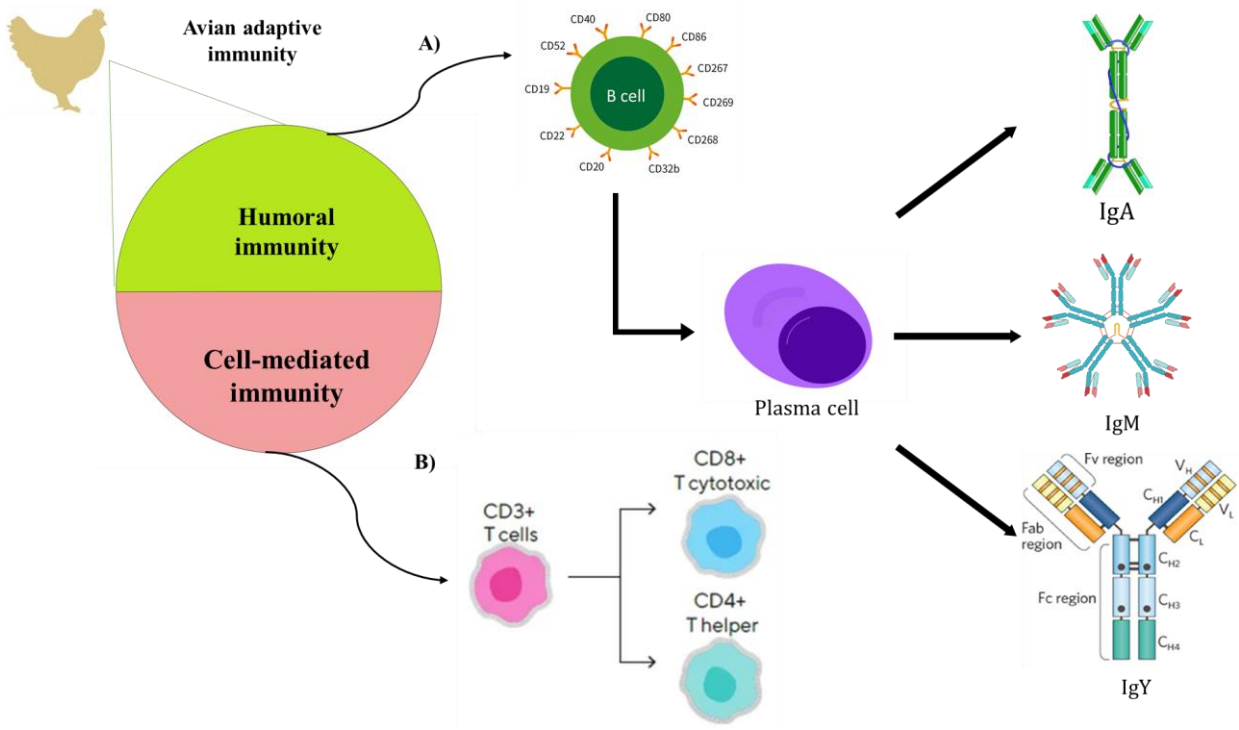

Figure 4. The avian immune system consists of two functional aspects, i.e., humoral and cellular arms, which work together to repel harmful pathogens and disease-causing microorganisms, and each of these two arms is also composed of various components. A) Humoral immunity and its components (predominantly three main classes of antibodies in birds). B) cell-mediated immunity and its components (mainly different types of T cells and cytokines).

4 Conclusion and future prospects

The immune system of avian species, particularly chickens, exhibits innate and adaptive mechanisms similar to those found in mammals, yet with distinctively unique variations. Here, we classically addressed the intricate network of avian immunity and further discussed their extensive innate and adaptive immune systems, highlighting their unique set of immune organs, cells, molecules, and genes. Adaptive immunity in birds involves both humoral and cell-mediated responses, which are crucial for combating many pathogens. However, certain avian diseases can impair these immune functions, leading to increased susceptibility to (non) infectious pathogens. We also addressed the impact of environmental and physiological stressors on avian immunity, emphasizing the role of oxidative stress in disrupting immune functions and contributing to tissue, cells, and molecular damage. Avian cytokines, such as ILs, TNFs, etc., have been identified, paralleling their mammalian counterparts in structure and functions. Immunological-based techniques need to be applied for advanced and accurate diagnostics and therapy; birds' immune organs, cells, and molecules (particularly cellular and humoral immunity) are dynamically becoming broader and more complex. Working on each of those components is urgently needed. Even many other non-well-known immune organoids in birds, like heart lymphatic organs, etc., exclusively exist, and their structural and functional roles remain to be further investigated. Many immune cells, especially APCs, B-and T cells, and their related molecules, especially Ab technologies, are increasingly being applied in the avian clinic. Viral emerging diseases, especially avian influenza, coronavirus-originated bronchitis, and Marek diseases, are dangerously rising, and those addressed to the immune system herein would hugely help improve the issues. This comprehensive overview underscores the advancements in understanding avian immunology and the potential for developing immunological-based techniques for targeted disease control strategies in poultry.

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None.

Conflict of Interest

The authors have no conflict of interest to declare.

Author Contributions

JM, designed the study, generated the research idea and schemes, organized and conducted the data collection and analysis, wrote and interpreted the text, and SS, FK, DF, HS, AK and PH, participated in the study design and manuscript reading and helped all process

Data Availability Statement

The data produced and examined during this study are not openly accessible but can be obtained from the corresponding author upon a reasonable request.

Ethical Considerations

Not applicable.

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