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The Chicken Heterophil- A Short Review

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Mini Review

In the immune system of chickens along with other white blood cells namely lymphocytes, monocytes, eosinophils and basophils, heterophils are also found. Heterophils are granulocytes. The cytoplasm contains eosinophilic granules. The nucleus of mature heterophils is lobed. They are responsible for bactericidal activity. Heterophils are also classified as immature, mature and toxic heterophils. Toxic heterophils exhibit toxic changes in response to the severity of the illness [1,2]. Acquired and innate immune systems are well developed in chickens. Heterophils are the components of these two systems, protect the birds from pathogens.

Heterophils were described as early as in 1846 by Wharton-Jones [3]. Heterophils in chicken are similar to neutrophil white blood cells of humans. They are involved in defense mechanisms against pathological or inflammatory conditions. Innate and acquired immune systems play an important role in protecting the organisms against diseases. At hatch large number of heterophils is released from spleen which decline 7d post hatch. During the first few days post hatch, the innate system is not well developed. Hence the function of heterophils is also not well developed [4-7] when compared with their counter older age chickens. Hence during early days of post hatch period chicken are more vulnerable to infections. The heterophil to lymphocyte ratios are taken for assessment of stress [8]. It is also stated that this ratio is affected by plasma corticosterone levels. Even fasting and social stress increases H/L ratio in chickens. Heterophils generally outnumber lymphocytes in chicks during neonatal stage. Their numbers increase during moderate stressful conditions and consequently the heterophil/lymphocyte ratio can be used to detect the presence of physiological stress. Study by Cotter, et al. [9] suggested that estimation of single parameter such as H/L ratio cannot indicate stress. Other blood cells abnormalities also have to be taken in to account. During stressful conditions depending on physiological demand like during peak egg production phase and during molting it was observed that H/L ratio increased significantly and in addition also had effect on corticosteroid and thyroid hormones [10].

Heterophil function and cytokine gene expression studies have been used to show the resisting power of birds to salmonella infection [11,12]. In chickens, heterophils extrude granules and chromatin like structure forming extracellular traps, upon stimulation. The traps contain DNA, histone-DNA complex and elastase from heterophil cytoplasmic granules [13]. Microbial molecules stimulate degranulation. The granules are large rod shaped, medium-oval and small-core type are known [14].

Heterophils are the predominant granulocytes; they are recruited to the site of infection and are capable of killing pathogens. On exposure to pathogens, cytokines like interleukins IL-6, IL-8, IL-18 are released, which act against pathogens [15,16]. Increased production of cytokine RNA may result in population of heterophils which are primed and are efficient in responding to the pathogens [12]. Number of heterophils reaching the infection site depends on the local production of chemo attractants [17]. Early response of heterophils to pathogens is by activation and transport according to chemotactic nature.

Heterophils release granular substances, which may be proteins, peptides and other toxic substances upon encountering pathogens. The granules contain matrix-

metalloproteinases enzymes which aid in migration and in conjunction with granular substances help in killing of pathogens [18-20]. Their cytoplasmic granules contain several lysosomal and non-lysosomal enzymes including acid phosphatase, arylsulphatase, β-glucuronidase, phosphorylase, uridine diphosphate glucose-glucogen glycosyltrans-ferase, neutral and acid α-glucosidases, acid trimetaphosphatase and lysozyme [21].

Another phenomenon known as oxidative burst is also associated with granulocytes. They lack Myeloperoxidase enzyme, due to which they are not able to produce enough amount of peroxide ion which is involved in killing of pathogens. Hence in chickens heterophils depend on non oxidative antimicrobial reactions by using b defensins and cathelicidins [20,22]. Cotradictory reports with respect to presence of MPO enzyme are also available [23].

It has also been reported that phagocytozing, degranulation and oxidative burst are also linked to the genetic nature of the chicken [24,25]. Different breeds have different heterophil response to S. Enteritidis infection. In their study it was shown that, Fayoumi breed has highest level of heterophil response when compared to white leg horn and broilers. Genetic studies revealed that polymorphisms in the genes were the reason for differential activity of heterophils [26]. This is with respect to differential ability of heterophils for production of cytokines against pathogen. Based on resistance to S. *e*nteritidis, to heterophil expression, phenotypic selection of chickens has been conducted.

In neonatal chickens heterophils confer resistance to salmonella infections more than the monocyte cells [12]. Selection methods for production performance in chickens have compromised with immune functions. It was observed that heterophils of chickens infected with Staphylococcal tenosinovitis were more active when compared with the function of heterophils of healthy chickens.

When bacteria stimulate Toll like receptors on heterophils it stimulates its bactericidal functions [27]. TLR 2 and TLR 4 ligands activate heterophils for production of different cytokines and interferons, these are usually bacteria and viruses. Type 1 and P fimbriae, curli, aerobactin, lipopolysaccharide (LPS), K1 capsular antigen etc. are virulence factors associated with pathogenic E Coli [28]. Heterophils also possess Fc receptors and complement receptors. These receptors act through signalling pathways. Signalling pathways are mediated through G proteins, Ca and Protein Kinase C dependant pathways. The scavenger receptors of heterophils, stimulated by ligands caused oxidative burst and not degranulation [29]. Dectin 1 and mannose receptors are also present [30]. The Toll like receptors (TLR) on heterophils has conserved signalling system that determines the inflammatory response. TLR pathways have been reported in heterophils. TLR activation also leads to the production of cytokines through activation of MAPK and nuclear factor κB pathway [31,32].

Studies on infection of heterophils with New castle disease virus (NDV) *in vitro* showed that upon infection, they have marked reduction in phagocytozing bacteria and marked fragmentation of DNA [33]. This indicates that heterophils need not be always activated but their function can decrease depending on the severity of infection.

Heterophils contain large amount of Cathelicidin-2, localized in the large rod-shaped granules. It has both bactericidal and fungicidal activity. It is suggested that they contribute greatly to innate immunity. When broilers were challenged with Salmonella *enteritidis,* heterophils containing Cathelicidin-2 were found in the jejunum region [34]. The same peptide has been shown to act against S. a*ureus* [35]. It kills the bacteria by passing through the bacterial membrane and binding to inner components causing damage to integrity of membrane.

A study conducted on two lines of broilers revealed that heterophils from one line were more responsive than the other line. This was attributed to the differential synthesis of chemokines which in turn governs protection against bacterial infections. There was increased activity of protein Tyrosine kinase and specific MAP kinase pathway [36]. Studies on regulation of different pathways and cellular modulation in future may help us to tackle and utilise the functions of heterophils for better survival of chickens.

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