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WORLD'S POULTRY SCIENCE ASSOCIATION INVITED LECTURE

Avian Macrophage and Immune Response: An Overview[1]

M. A. Qureshi[2]

Department of Poultry Science and Interdisciplinary Graduate Program of Immunology, North Carolina State University, Raleigh, North Carolina 27695-7608

ABSTRACT Macrophages belong to the mononuclear phagocytic system lineage. This cell type is unique in that it is a crucial player in both the innate and adaptive immune responses. The material described in this overview is a brief description of what I presented as a World's Poultry Science Association-sponsored lecture at the annual meetings of the Poultry Science Association in 2002. Therefore, I have not attempted to present an up-to-date review of literature on this topic. Rather, I have summarized some salient research accomplishments made by our research group over the years in the area of avian macrophage biology and function.

(*Key words*: macrophage, macrophage functions, avians)

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MACROPHAGE DEVELOPMENT

Macrophages originate from bone marrow stem cells. About 6 d are required for a monoblast to develop into a pro-monocyte and then into a monocyte under the influence of colony stimulating factor(s). Monocytes enter the blood stream where they constitute a major phagocytic cellular component in the chicken's blood. The second developmental stage of blood monocytes is the macrophages, and they are present in a variety of the body's tissues. It takes about 3 d for blood monocytes, after their arrival into the bloodstream, to seed various tissues and organs. Macrophages are, therefore, tissue forms of blood monocytes. Tissue macrophages can be found in the lungs where they are called alveolar macrophages. Only about 30% of the alveolar macrophages that are present in the lungs have their direct derivation from blood monocytes; the other 70% of alveolar macrophages develop by cell division inside the lungs. On the other hand, almost 100% of Kupffer cells, the macrophages found in the liver, are derived directly from blood monocytes. Macrophages are also present in bones where they are called osteoblasts. They are present in the brain as microglia cells and in the connective tissues where they are called histiocytes. Some of our studies involving chicken bone marrow stem cell differentiation have shown that such cells are fully capable of differentiating into several types of cells lineages including macrophages (Figure 1A, B, and C), even at day of hatch or prior to hatching. When we compared broilers with White Leghorn layers for the ability of embryonic hemopoietic progenitors to differentiate into macrophage lineage cells, we found that starting with the same numbers of bone marrow stem cells, broilers produced significantly lower numbers of macrophage-type colonies than White Leghorn chickens. This difference may be one indication of why broiler type chickens are perceived as being a little more susceptible perinatally than are White Leghorn type chickens (Nicolas-Bolnet et al., 1995).

MACROPHAGE ACTIVATION AND SOURCE

In addition to developmental maturation, cells of the mononuclear phagocytic system (MPS) lineage such as monocytes and macrophages also undergo functional maturation. In the murine system, resident macrophages isolated from the peritoneal cavity can be primed and activated in response to biological signals such as γ- interferon and lipopolysaccharide (LPS). In chickens, however, there are no (or just a few) resident macrophages present in the abdominal cavity. Therefore, as a result of an active inflammatory response at a tissue site such as the abdominal cavity, monocytes can be recruited into the tissues (Qureshi et al., 1986; Qureshi and Dietert, 1995). Macrophages can then be purified from the inflammatory abdominal exudate cells (AEC) by adherence to glass (coverslips) or plastic (Petri dish) surfaces. It has been shown that Sephadex-elicited macrophages are very phagocytic

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[2]To whom correspondence should be addressed: M_Qureshi@ncsu.edu.

Abbreviation Key: AEC = abdominal exudate cells; CD14 = LPS-binding molecule; iNOS = inducible isoform nitric oxide synthase; LPS = lipopolysaccharide; MPS = mononuclear phagocytic system; NO = nitric oxide; NOS = nitric oxide synthase; TLR = toll-like receptor.

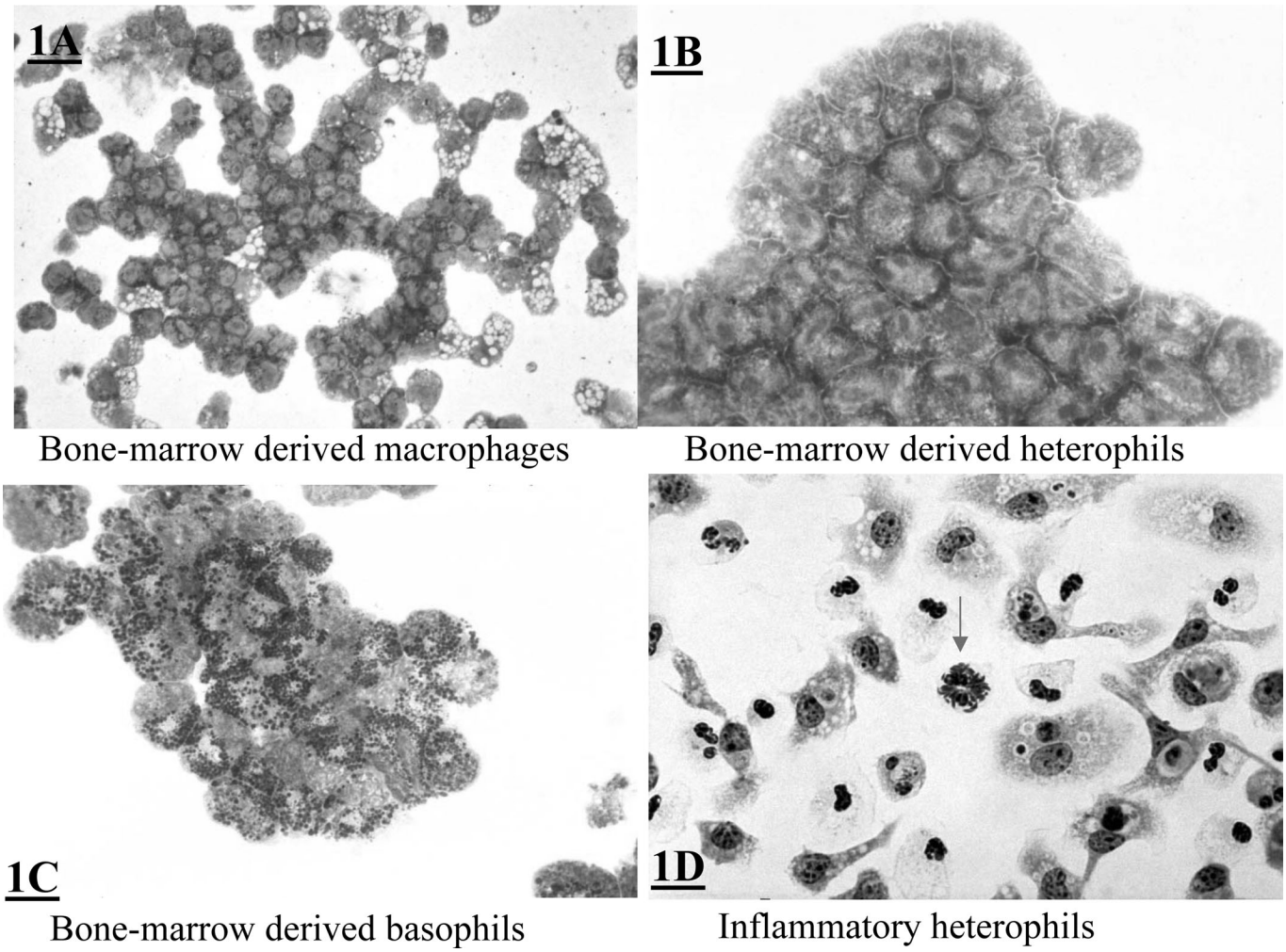

FIGURE 1. A: Macrophages, B: heterophils, and C: basophils derived from bone-marrow progenitors from 1-d-old Cornell White Leghorn chicken. D: Heterophils in a mixed inflammatory cell population in abdominal exudate isolated from 2-wk-old broilers after 30 h of abdominal Sepahadex-elicitation. Arrow indicates heterophils with granules, while several bilobed degranulated heterophils and macrophages are also visible.

for particulate antigens such sheep red blood cells or bacteria (Qureshi et al., 1986). However, Sephadex-elicited macrophages are not capable of performing certain specialized effector functions such as tumor cell killing. Our studies have shown that one can drive Sephadex-elicited macrophages towards tumoricidal pathways by providing biological signals such as bacterial LPS and lymphokines (Qureshi and Miller, 1991a). Therefore, as with the murine macrophages, chicken macrophages could also be defined as undergoing at least three different stages of functional maturation, i.e., responsive, primed, and activated macrophages. There are studies in the literature describing the antigenic uptake/trapping function of spleen- and liver-sourced macrophages during embryonic development. Working with Sephadex-elicited macrophages, we have shown that turkey poults are fully capable of responding to an inflammatory challenge received at day of hatch with the recruitment of blood monocytes into the challenged tissue. Sephadex-elicited abdominal exudate macrophages collected at 3, 5, or 7 d of age are quite efficient in phagocytizing antibody-coated or uncoated antigen targets (Qureshi et al., 2000). Macrophages obtained after Sephadex elicitation show very typical macrophage morphology. They are quite spread out with several visible vacuoles in the cytoplasm. Depending on the time after a single Sephadex injection at which the AEC are harvested, one can also see quite a few heterophils being recruited into the abdominal cavity along with the other AEC (Figure 1D). In our experience, AEC collected between 30 to 40 h after a single injection of a 3% Sephadex suspension given as 1 cc/100 g BW, yields greater than 90% macrophages in the AEC (Figure 2A). In addition to the development of a method for the isolation of macrophages from live chickens, our laboratory has established a transformed macrophage chicken cell line (MQ-NCSU), which serves as a unique tool to examine various aspects of chicken macrophage biology and function in many laboratories throughout the world (Qureshi et al., 1990).

MACROPHAGE FUNCTIONS

Some of the classical macrophage functions include chemotaxis, phagocytosis, the killing of bacteria and tu-

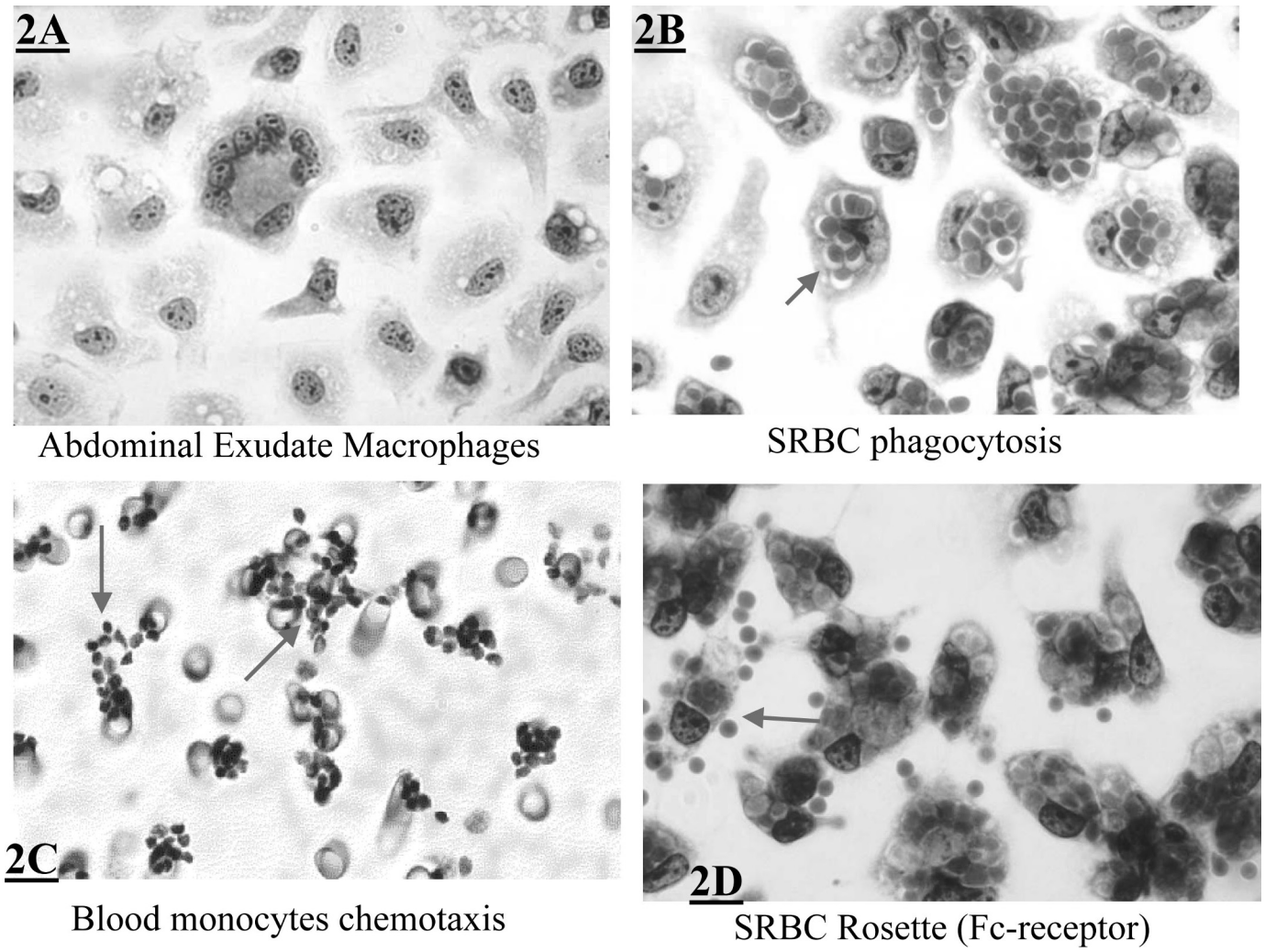

FIGURE 2. An example of A: Sephadex-elicited glass-adherent chicken abdominal macrophages, B: phagocytosis of antibody-coated sheep red blood cell, and C: chemotaxis of peripheral blood monocytes against f-met-leu-phe. Monocytes migrating through the pores are shown by the arrows; D: antibody-coated SRBC bound to Fc-receptors on macrophage membrane in the form of a rosette.

mor cells, and cytokine production. In addition, nutrition, genetics, and numerous environmental factors have been demonstrated to modulate some macrophage functions.

Chemotaxis is a function of both monocytes and macrophages, which involves migration toward an inflammatory gradient. Chemotactic signals can be derived from bacterial products, by certain synthetic peptides such as f-met-leu-phe, by certain products of the immune reaction such as complement, or by certain factors released by the damaged cells and extracellular matrix. For example, neutrophils, upon dying, release elastase or collagenase, which are chemotactic in nature. Furthermore, collagen, elastin, and fibrinogen are also chemotactic in nature. The chemotactic potential can easily be demonstrated by using chicken blood monocytes and incubating them in the presence of a synthetic bacterial signal peptide such as f-met-leu-phe, or with the supernatants from bacterial cultures. Using a chemotactic assay (Figure 2C), we have demonstrated that chicken blood monocytes are very active in responding to chemotactic signals, and that there are differences in the chemotactic potential of blood monocytes depending upon their genetic origin (Qureshi et al., 1988).

Phagocytosis is perhaps the most evolutionary conserved function of the macrophage. Macrophages perform phagocytic functions via several different mechanisms. Most of the phagocytic functions for particulate antigens are mediated via specific receptors present on the surfaces of macrophage cells. These receptors are capable of binding specific targets for phagocytosis. For example, certain pattern recognition molecules present as receptors on the macrophage surface enhance the binding of bacteria with mannose and fructose by their correct spacing. Macrophages also have specific receptors for mannose, and because of this, certain bacterial or viral agents having mannose expressed on their outer surfaces will preferentially bind to the macrophage via those mannose receptors. Macrophages also have scavenger receptors. Scavenger receptors are utilized to internalize pathogens as well as old and dying red blood cells. There are other specialized receptors such as the Fc-receptor that are present on the surface of the macrophage that specifically

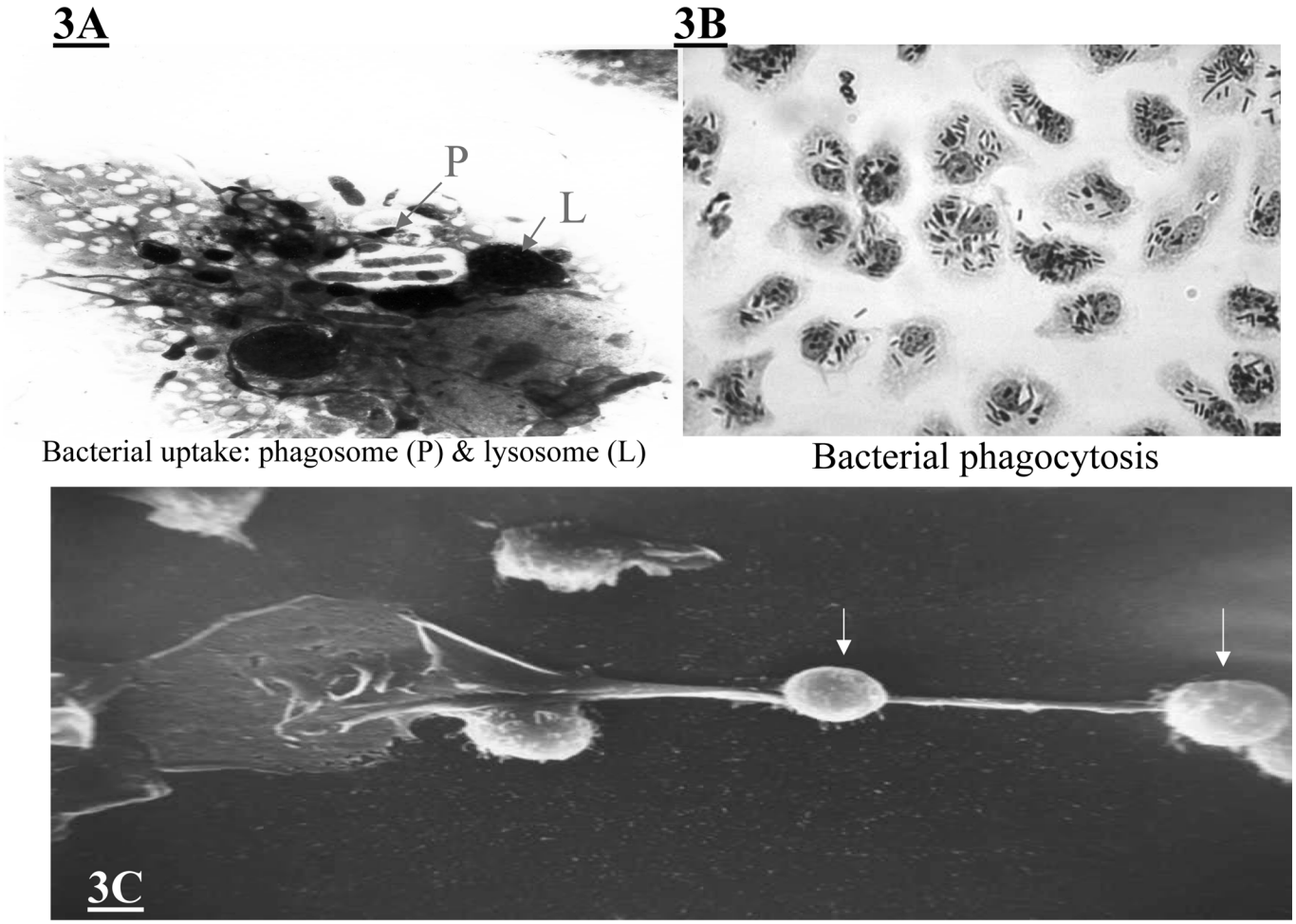

FIGURE 3. An example of bacterial uptake by macrophage: A: an electron micrograph of whole macrophage with engulf bacteria in a phagosome (arrow). Several acid-phosphatase-filled lysomes are visible surrounding the phagosome; B: uptake of *Salmonella typhimurium* by macrophage. Several bacteria are visible in individual macrophage cytoplasm; C: tumoricidal potential of macrophages. A macrophage is shown with several tumor cells bound to its cytoplasmic membrane.

target antigens that are coated with their antibody (Figure 2D). Also, an antigenic target that is coated with complement can be preferentially bound to the surface of the macrophage via the complement receptor. Additionally, there are receptors present on the surface of the macrophage that may not necessarily be directly involved in phagocytosis but which can mediate an activation signal for the LPS-binding receptors. The percentage of macrophages that are phagocytic is dependent upon the type of target being phagocytized. For example, in a typical phagocytosis assay, utilizing nonantibody coated SRBC, one would see approximately 20 to 40% of the adherent macrophage population capable of internalizing two to three sheep red blood cells per phagocytic macrophage. On the contrary, the percentage of phagocytic macrophages increases significantly to 70 to 95%, if the SRBC are coated with a specific antibody (Figure 2B). Furthermore, by utilizing opsonized SRBC, the presence of Fc-receptors can be demonstrated on the surface of chicken macrophages where antibody-coated SRBC are bound to the external surface of the macrophage in a typical rosette formation.

Bacterial killing or antigen degradation is a logical next step following the process of phagocytosis. For bactericidal function, macrophages can very efficiently bind bacteria to their outer surfaces and bring them into their cytoplasm in the form of a phagosome (Figure 3A). Usually one macrophage is capable of internalizing several bacteria (Figure 3B), and some of our studies have shown that nearly 90% of internalized bacteria are killed by Sephadex-elicited macrophages in the first 15 min of internalization (Qureshi et al., 1986). After the bacteria are brought into a phagosome, the fusion of the phagosome with a lysosome must occur so that the enzyme(s) present in the lysosome can degrade the internalized bacteria (Qureshi and Dietert, 1995). After degradation, macrophages are fully capable of presenting bacterial peptides or antigenic determinants to immune cells such as the B- and T-lymphocytes in the context of either class I or class

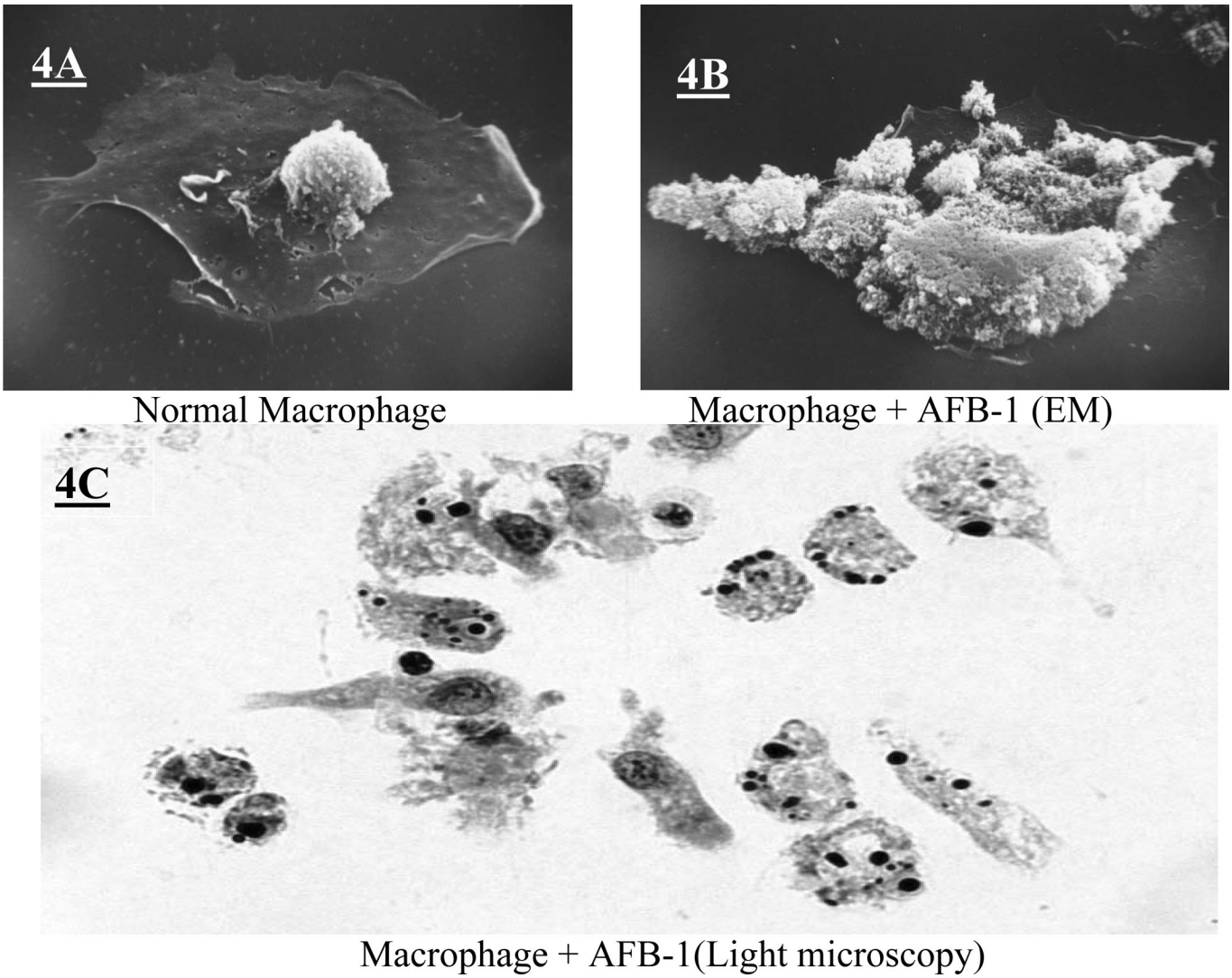

FIGURE 4. An example of genotoxic damage to macrophage by mycotoxins. A: Electron micrograph of a sham-exposed macrophage and B: aflatoxin-B1-treated macrophage in vitro. Nuclear disintegration is evident in B. C: light micrograph showing nuclear disintegration in macrophages after aflatoxin-B1 exposure.

II major histocompatibility complex (MHC, *B*-complex) molecules.

Tumoricidal ability of macrophages is a specialized function requiring macrophage activation. Upon coculture, macrophages bind tumor cell targets very efficiently, as tumor targets are much bigger than bacteria (Figure 3B). Macrophages cannot phagocytize tumor cells. However, once tumors are bound to the surface of a macrophage, the macrophage can secrete substances such as tumor necrosis factor (Qureshi and Miller, 1991a) or several biologically active metabolites such as nitric oxide (NO) which can mediate either bacterial or tumor cell killing. A detailed account of NO production by chicken macrophages is presented in a later section.

In addition to macrophages being phagocytic as well as bacteriostatic, bactericidal, tumoristatic, or tumoricidal cells, chicken macrophages are fully capable of producing several types of cytokines. For example, chicken macrophages following activation with a biological signal, or after phagocytosis of an antigen, secrete Interleukin-1. We have shown that chicken macrophages from different sources differ in their ability to produce Interlukin-1 when stimulated with either *E. coli* LPS or Streptococcus antigens. For example, abdominal exudate macrophages produced lower levels of Interlukin-1 than those from two transformed chicken macrophage cell lines, the HD11 and MQ-NCSU (Qureshi et al., 1994).

NUTRITIONAL INFLUENCES ON MACROPHAGE FUNCTIONS

Chicken macrophage functions have been shown to be very responsive to several dietary immune modulators. Some of these macrophage function modulators include β1-3, 1-6, glucan, β- hydroxy β-methylbutyrate, vitamins A, D, E, and B-complex, vanadium, arginine, spirulina, zinc-methionine, electrolytes, etc. Our studies have shown that avian macrophage functions are improved by the dietary use of all of these compounds (see review Qureshi et al., 2000). Using β 1-3, 1-6 glucan as an example,

our studies have shown that macrophage phagocytic function is significantly enhanced if chickens are fed a diet containing 20 or 40 mg/kg of β 1-3, 1-6 glucan as compared with chickens fed a basal diet. In vitro exposure of macrophages to β1-3, 1-6 glucan induces proliferation greater than seen in sham-exposed macrophages. Furthermore, macrophages exposed in vitro to β 1-3,1-6 glucan also secrete higher levels of nitrite in their culture supernate, which is an indication of macrophage activation by β1-3, 1-6 glucan (Guo et al., 2003). We have also shown that vitamin E exposure can help up-regulate macrophage phagocytic function. For example, in ovo vitamin E administration improved the phagocytic potential and nitrite production by macrophages isolated at 4 wk of age (Gore and Qureshi, 1997).

ARGININE AND NITRIC OXIDE SYNTHASE

Another important nutrient, which has received considerable attention in the field of immunology, especially when as it relates to macrophage activation and function, is arginine. Arginine is utilized as a substrate by the enzyme nitric oxide synthase (NOS) which catalyzes the biosynthesis of free radical nitric oxide (NO) as a by-product of an oxidative reaction using the guanidino nitrogen group of L-arginine to make L-citruline. Nitric oxide is a highly reactive, low molecular weight, short-lived cytotoxic entity and is converted to nitrite and nitrate that are more stable products. We have shown that chicken macrophages express a 4.5-kb NOS in its inducible isoform (iNOS) when macrophages are exposed to bacterial LPS. Furthermore, iNOS is fully functional in utilizing arginine as quantitated by the presence of nitrite in macrophage culture supernatants as well as when iNOS activity was quantitated in macrophage cell-lysates (Hussain and Qureshi, 1997, 1998).

NITRIC OXIDE SYNTHASE AND CHICKEN GENOTYPES

Our studies have shown that the expression of iNOS in macrophages is variable among chickens of several genotypes. These differences in gene expression are not due to a differential post-transcriptional regulatory mechanism(s), but rather due to enhanced transcriptional activity in iNOS hyper-responder genotypes (Hussain and Qureshi, 1998). Based on LPS-induced iNOS expression, lines of chicken have been identified as either hyper- or hypo-responders for iNOS (Hussain and Qureshi, 1997, 1998). It was clear that these differences are genetically intrinsic and are not specific to the commonly used *E. coli* LPS, since iNOS hyper-and hypo-responsiveness of these strains was maintained regardless of the source of bacterial LPS used (Dil and Qureshi, 2002a). Because LPS represents a pathogen-associated molecular pattern (PAMP) for which there are unique recognition factors called Toll-like receptors (TLR), we hypothesized that the differential expression of iNOS in macrophages from various chicken genotypes may be due to the differential expression of the LPS-binding molecule CD14 or their signaling molecules, the TLRs. This hypothesis was proven from the findings that macrophages from iNOS hyper-responder genotypes express significantly higher inducible CD14 as well as TLR4 as compared with the hypo-responder genotypes (Dil and Qureshi, 2002a). The fact that the CD14 and TLR4 are critical in LPS-induced iNOS expression by macrophages was proven in a subsequent study in which CD14 and TLR4 were blocked with appropriate antibodies which resulted in a significant reduction in iNOS expression and activity (Dil and Qureshi, 2002b). The involvement of nuclear factor (B (NF(B) was also shown to be relevant in hyper-iNOS expression because the hyper-responder genotypes contained greater levels of DNA-bound NFκB than the low-responder genotypes (Dil and Qureshi, 2002b). Interestingly, interleukin-1 β did not contribute to genetic-based differences in iNOS expression and activity in chicken macrophages (Dil and Qureshi, 2003).

MACROPHAGE FUNCTIONS AND GENETIC FACTORS

Several macrophage functions are modulated by the genetic makeup of the chickens, especially with regard to the genetic alleles present in the major histocompatibility complex (called *B*-complex in chickens). For example, our studies have shown that macrophages from chicken lines congenic for their *B*-complex alleles vary in their chemotactic (Qureshi et al., 1988), phagocytic, and bactericidal response (Qureshi et al., 1986). Furthermore, macrophage activation for specialized effector functions, such as tumor necrosis factor production, is also influenced by genotype (Qureshi and Taylor, 1993). Differences also exist among various commercial broiler lines in macrophage effector function, such as phagocytosis and bacterial and tumor cell killing (Qureshi and Miller, 1991b), suggesting an opportunity to exploit macrophage-based immunocompetence in commercial breeding and selection programs.

MACROPHAGE FUNCTIONS AND ENVIRONMENTAL/ TOXICOLOGICAL FACTORS

Chicken macrophages are susceptible to both environmental and toxicological insult. For example, macrophage viability and functions are adversely affected by mycotoxins such as aflatoxins (Figure 4) (Neldon-Ortiz and Qureshi, 1991), Fumonisin-B1 (Qureshi and Hagler, Jr., 1992), trichothecenes (Kidd et al., 1995), T-2 toxin (Kidd et al., 1997), and others. Embryonic exposure of chicks to aflatoxin-B1 either through in ovo injection (Neldon-Ortiz and Qureshi, 1992) or maternal transfer of toxin metabolites to progeny chicks (Qureshi et al., 1998) down regulates macrophage phagocytic function post-hatch. Examples of environmental stressors affecting macrophage functions include heat stress (Miller and Qureshi, 1992a,b,c) and exposure to microbes. While existing microbes change to escape the immune system, new mi-

crobes evolve continuously. Recent isolation of new variants of *E. coli* from turkeys (Edens et al., 1997a,b) is a good example of microbial antigenic modulation. Macrophages do recognize such antigenic change by differential phagocytosis of variant strains of *E. coli* (Miller et al., 1990). The same is true for viruses, examples of which include new variants of astrovirus (Yu et al., 2000) and reovirus ARV-CU98 (Heggen-Peay et al., 2002a) isolated from cases of poult enteritis and mortality syndrome in turkeys. While macrophages may not allow infection or virus replication, the ARV-CU98 reovirus has been shown to induce functional alterations in the macrophage, such as the up-regulation of interleukin-1 mRNA, even without any signs of viral replication (Heggen-Peay et al., 2002b). In fact, in situations where multifactorial infections overwhelm the immune system, such as in poult enteritis and mortality syndrome, macrophage-mediated cytokine-induced immune dysfunction may be a cause of some of the observed clinical pathophysiological signs in the affected poults (Heggen et al., 2000).

CONCLUDING REMARKS

Macrophages are crucial cell types in innate immunity and they are potent microbicidal and tumoricidal cells. Macrophages are pivotal in acquired immunity as antigen presenting cells. Macrophages can greatly influence the local and systemic immune response through the production of cytokines. Enhanced functional capacity of the animal's macrophages has the potential of being achieved by using classical breeding techniques such as MHC-based selection, dietary manipulations (via selected compounds with known immunomodulatory potential, adequate feeding), and new vaccine strategies (e.g., the use of novel adjuvants) geared towards maximizing the antigen-presentation capacity of macrophages.

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