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Crosstalk between innate and adaptive immune responses to infectious bronchitis virus after vaccination and challenge of chickens varying in serum mannose-binding lectin concentrations

Helle R. Juul-Madsen[a,*], Liselotte R. Norup[a], Poul H. Jørgensen[b], Kurt J. Handberg[b], Eva Wattrang[c], Tina S. Dalgaard[a]

[a] *Department of Animal Science, Aarhus University, Tjele, Denmark*
[b] *DTU National Veterinary Institute, Division of Poultry, Fish and Fur Animals, Aarhus, Denmark*
[c] *Department of Virology, Immunobiology and Parasitology, National Veterinary Institute, Uppsala, Sweden*

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ABSTRACT

Mannose-binding lectin (MBL), a C-type collectin with structural similarities to C1q, is an innate pattern-recognition molecule that is sequestered to sites of inflammation and infections. MBL selectively binds distinct chemical patterns, including carbohydrates expressed on all kinds of pathogens. The present study shows that serum MBL levels influence the ability of chickens to clear the respiratory tract of virus genomes after an infectious bronchitis virus (IBV) infection. The primary IBV infection induced changes in circulating T-cell populations and in the specific antibody responses. Serum MBL levels also influenced IBV vaccine-induced changes in circulating T-cell populations. Moreover, addition of mannose to an IBV vaccine altered both vaccine-induced changes in circulating T-cell populations and IBV specific vaccine and infection-induced antibody responses in chickens with high serum MBL levels. These data demonstrate that MBL is involved in the regulation of the adaptive immune response to IBV.
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1. Introduction

The innate immune system is considered the first line of defense against infections. The innate immune system reacts promptly to invading pathogens and instructs antigen presenting cells (APCs) to activate and secrete cytokines that, among other things, regulate T- and B cells towards an appropriate adaptive effector phenotype. Activation of APCs in response to pathogenic stimuli is mediated by unique pattern-recognition receptors (PRRs) and results in the production of pro-inflammatory cytokines and co-stimulatory molecules which participate in the activation of the adaptive immune response [1–3]. Several soluble PRRs have been characterized as LPS-binding proteins, collectins, pentraxins and alternative pathway complement components in addition to cell-associated receptors like C-type lectins, scavenger receptors, Toll-like receptors (TLRs) and various intracellular receptors. Many PRRs are highly conserved and provide the cornerstones upon which the antimicrobial immune response is built. Moreover, vaccine-induced protective immunity can be regulated by PRR stimulation by pathogen-associated molecular patterns (PAMP) in order to perform the “adjuvant effect” which is central to successful vaccinations.

The serum protein mannose-binding lectin (MBL) is an important soluble PRR that belongs to the C-type collectin family. MBL binds to mannose and other sugar residues present on the cell wall of bacteria, viruses and parasites with high affinity [4]. As these sugars do not naturally occur in higher organisms, MBL represents an important mechanism for discrimination between pathogens and host. MBL exhibits a number of innate immunological properties. By binding to, e.g. microbial cell wall antigens, MBL can act as an opsonin and mediate phagocytosis directly through MBL receptors expressed on the surface of neutrophils and monocytes [5–7]. Alternatively, MBL can activate the complement system through the ‘lectin pathway’ causing pathogen lysis or phagocytosis via complement receptors on phagocytic cells. In addition, MBL is important for the removal of circulating immune complexes. Knowledge of the functional role of MBL in the immunity of both humans and animals is increasing [8–12]. Individuals with MBL deficiency are reported more susceptible to viral and bacterial infections as well as

* Corresponding author at: Department of Animals Science, Aarhus University, P.O. Box 50, 8830 Tjele, Denmark. Tel.: +45 87157837; fax: +45 87154249.
E-mail address: Helle.JuulMadsen@agrsci.dk (H.R. Juul-Madsen).

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autoimmune diseases especially during the early neonatal period or when rendered neutropenic from chemotherapy [13,14]. It has also been shown that MBL deficiency in humans has a genetic basis [15–18].

Results from our lab using chickens selected for a high or a low serum concentration of MBL have shown that a low amount of circulating MBL is associated with increased viral replication in the airway after an infectious bronchitis virus (IBV) infection [19] and reduced growth rate after an *E. coli* infection [20]. We have also shown that low MBL concentration is associated with increased numbers of *Pasteurella multocida* in the spleen in a non-selected exotic breed after an infection [21]. Finally, preliminary results with the parasite *Ascaridia galli* showed that the parasite egg burden post infection was higher in birds with low serum MBL concentration (unpublished). These results confirm that MBL, as proven in mammals, plays a major role in the outcome of various infections in chickens.

An inverse relationship between pathogen-specific antibody responses and serum MBL levels has been recorded in inbred as well as outbred chickens [19,21,22]. Recently, this was also shown in mouse models where the specific IgG response was increased in MBL-deficient mice following immunization with a Group B *streptococcus* vaccine [23] and in double MBL knockout mice injected with soluble hepatitis B surface antigen [24]. These results suggest that MBL influences the production of specific antibodies either by directing the immune response into a more cellular response (Th1 vs. Th2) by neutralizing the microorganism via the complement membrane-attack complex, and/or by inhibiting the production of pro-inflammatory cytokines via interaction with other surface receptors [13]. The latter has been shown in a human whole-blood model where a low concentration of MBL enhances the cytokine production and a high concentration suppresses the cytokine production [25].

A detailed understanding of the interaction between innate and adaptive immunity can lead to new approaches to improve vaccination efficiency, e.g. by blocking/inhibiting the MBL function. This may lead to the discovery of new adjuvants for the vaccine industry. In the future, this will be an important issue as breeding companies currently focus on selection markers that belong to the innate part of the immune system in their effort to produce more robust animals [26]. Improvement of genetically determined disease resistance is an attractive and inexpensive approach to improve the health status of our production animals. Therefore, the challenge in future vaccination strategies is to choose the optimal adjuvant design for innate robust animals. Thus, when vaccinating it may be necessary to temporarily overcome the contribution from the innate part of the immune system in order to allow the development of the adaptive immune response.

Infectious bronchitis (IB) is a highly contagious viral respiratory disease of domestic fowl occurring worldwide and causing great losses to the poultry industry due to the negative impact on the production results and the vaccination costs. The infection is extremely difficult to control because vaccination with one strain of IBV does not necessarily protect against disease caused by other strains of IBV.

The hypothesis of this study was therefore that a temporary blocking/inhibition of the MBL function by adding an MBL ligand to the vaccine would allow the adaptive immune response to produce more specific antibodies and a better development of the protective immunity. In order to address this we performed an experiment where chickens were vaccinated against IB with or without mannose added to the vaccine followed by a challenge with IBV. Immunological parameters belonging to the innate as well as the adaptive immune system were measured throughout the experimental period.

2. Materials and methods

2.1. Animals and experimental design

The experimental chickens ($n = 48$) were offspring from the AU line L10 which has been selected for low (L) vs. high (H) concentration of MBL in serum for several generations [19]. The offspring were reared together until 3 weeks of age under conventional conditions in a bio-secured IBV-free herd and then allocated to 3 different treatments groups with 8 birds from each sub-line in each group. The first group was treated with 200 μL 0.9% NaCl solution and used as a mock-vaccine control group. The second group was treated with 200 μL 0.9% NaCl solution containing one dose of live attenuated Nobilis IB Ma5 Vet (Intervet/Schering-Plough Animal Health, Ballerup, Denmark). The third group was treated with 200 μL 0.9% NaCl solution containing one dose of Nobilis IB Ma5 Vet and 100 mg/mL purified mannan from *Saccharomyces cerevisiae* (Sigma–Aldrich, Brøndby, Denmark) aiming at 100 μg mannose per gram body weight [27]. The solutions were given half nasally and half orally. At day 49 of age the birds were transferred to BSL2 facilities and randomly allocated to 6 isolators each containing 8 animals. At day 50 of age the birds were infected with 200 μL sterile allantoid solution of IBV strain Massachusetts-41 (M41; Veterinary Laboratory Agency, Weybridge, UK) containing $10^{6.5}$ ELD of IBV. The chickens were fed diets that met or exceeded NRC requirements. Feed and water were provided *ad libitum*.

2.2. Blood and swab collection

The experimental chickens were blood sampled from the jugular vein on days 0, 1, 2, 3, 4, 5, 7, 10, 14, 21 and 28 post vaccination (PV) and days 1, 2, 3, 4, 5, 7, 9, 14, 21, and 35 post infection (PI). Serum was collected from all blood sampling time points and citrate-stabilized blood for immune phenotyping was collected on days 0, 7, 14, 21, and 28 PV and days 7, 14, 21, and 35 PI. Oropharyngeal airway (OPA) swab samples were collected on days 0, 2, 3, 4, 5, and 10 PV and on days 1, 2, 3, 4, 5, 7, and 9 PI. Swab samples were kept at −20 °C until the termination of the experiment after which they were transferred to −80 °C and kept there until testing by RT-PCR.

2.3. RT-PCR of IBV

Four swab samples from each subtype, treatment and day were pooled; thus, 2 pools per group were analyzed for each time point. The tubes with the swabs were shaken vigorously for 1 h after thawing and the supernatant was collected after 10 min of centrifugation at 1000 × *g*. Purification of RNA was done according to the instructions for the RNeasy Kit from QIAGEN (Copenhagen, Denmark). The RT-PCR was carried out according to the manufacturer's instructions (TitanTM One Tube RT-PCR System, Boehringer Mannheim), which utilize avian myeloblastosis virus reverse transcriptase and a blend of *Pwo* and *Taq* DNA polymerases. Briefly, for a 50-μL reaction: 10 μL 5× reaction buffer, 2.5 μL 25 mM dithiothreitol, 0.5 μL dNTP (20 mM for each dNTP), 1 μL enzyme mixture, 100 pmol of each oligonucleotide, 5 μL of RNA and RNase-free water up to 50 μL. The stocks and mixtures were kept on ice until the transfer to the thermocycler (Abacus, Hybaid). The RT-PCR was carried out using the following program: cycle 1, 45 min at 48 °C (RT reaction); cycle 2, 95 °C for 120 s; cycle 3 to 30, 95 °C for 30 s, 60 °C for 60 s and 68 °C for 120 s; cycle 31, 68 °C for 7 min. The RT-PCR reaction was performed with the IBVN (+) and the IBVN (−) primers which identify Massachusetts/Connecticut strains:

IBVN (+): 5′-GAA-GAA-AAC-CAG-TCC-CAG-ATG-CTT-GG-3′
IBVN (−): 5′-GTT-GGA-ATA-GTG-CGC-TTG-CAA-TAC-CG-3′

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