Developmental and Comparative Immunology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Developmental and Comparative Immunology

journal homepage: www.elsevier.com/locate/dci

Regulation of macrophage and dendritic cell function by pathogens and through immunomodulation in the avian mucosa

Eveline D. de Geus [a,*], Lonneke Vervelde [b]

[a] Department of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, Utrecht University, Yalelaan 1, 3584 CL Utrecht, The Netherlands
[b] The Roslin Institute and Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush, Midlothian EH25 9PS, UK

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Macrophages
Dendritic cells
Mucosal
Infection
Immunomodulation

ABSTRACT

Macrophages (MPh) and dendritic cells (DC) are members of the mononuclear phagocyte system. In chickens, markers to distinguish MPh from DC are lacking, but whether MPh and DC can be distinguished in humans and mice is under debate, despite the availability of numerous markers. Mucosal MPh and DC are strategically located to ingest foreign antigens, suggesting they can rapidly respond to invading pathogens.

This review addresses our current understanding of DC and MPh function, the receptors expressed by MPh and DC involved in pathogen recognition, and the responses of DC and MPh against respiratory and intestinal pathogens in the chicken. Furthermore, potential opportunities are described to modulate MPh and DC responses to enhance disease resistance, highlighting modulation through nutraceuticals and vaccination.

1. Functional differences between macrophages and dendritic cells

Macrophages (MPh) and dendritic cells (DC) are members of the mononuclear phagocyte system. The main function of DC is related to the initiation of the adaptive immune response and maintenance of tolerance, while MPh are well equipped to destroy invading pathogens. In chicken it is not known which cell type is responsible for priming of naive T cells and whether a functional distinction between MPh and DC in priming capacity exists. Despite the availability of numerous markers, it is difficult to distinguish DC and MPh on the basis of marker expression in mice and humans (Geissmann et al., 2010). In mice and human studies CD11c is commonly used as a marker for DC. However, CD11c is expressed by many MPh as well, especially on populations associated with epithelia and on inflammatory MPh (reviewed by Hume, 2008).

MPh and DC can be distinguished on basis of function. Mouse DC have developed means to control their endocytic functions to efficiently present antigen (Ag). DC have low levels of lysosomal proteases (Delamarre et al., 2005) and actively alkalinizate their phagosomal compartments (Savina et al., 2006). This decreased phagosomal acidification in DC reduces Ag proteolysis to a level that allows processing but does not fully destroy antigenic peptides, contributing to the high Ag-presenting capacity of DC (Mantegazza et al., 2008; Ramachandra et al., 2009). MPh have much higher levels of proteolysis than DC, which limits their efficiency as Ag-presenting cells (APC; Delamarre et al., 2005). We recently identified cells in the chicken lung that decreased the pH of their endosomal compartment following uptake of an LPS or avian influenza virus (AIV)-coated polystyrene bead and cells that did not decrease the pH of their endosomal compartment. The cells with a decreased pH were characterized as CD11+, KUL01+, CD40+ phagocytes, whereas the cells that did not decrease the pH of their endosomal compartment were MHC II+ and CD80+ phagocytes. These findings suggest that also in chicken MPh are distinct from DC (de Geus et al., 2012a). However, it remains to be studied whether chicken DC and MPh actually exert different immunological functions.

Abbreviations: Ag, antigen; APC, antigen-presenting cells; AIV, avian influenza virus; BM, bone marrow; BALT, bronchus-associated lymphoid tissue; CG, chicken galectin; cLL, chicken lung lectin; CLR, C-type lectin receptors; DC, dendritic cells; DC-SIGN, DC-specific intercellular adhesion molecule-3-grabbing non-integrin; dLN, (Draining) lymph nodes; GALT, gut-associated lymphoid tissue; HA, haemagglutinin; HPAI, highly-pathogenic avian influenza; IBV, infectious bronchitis virus; IBDV, infectious bursal diease virus; IAV, influenza A virus; LGP2, laboratory of genetics and physiology 2; LPS, lipopolysaccharide; LPAI, low pathogenic influenza; MPh, macrophages; MGL, macrophage galactose binding lectin; MMR, macrophage mannose receptor; MDA5, melanoma differentiation-associated protein 5; NALT, nasal associated lymphoid tissue; NA, neuraminidase; NDV, newcastle disease virus; PRR, pattern recognition receptors; RT, respiratory tract; RIG-I, retinoic acid-inducible gene I; TLR, toll-like receptors.

* Corresponding author. Tel.: +31 302531872; fax: +31 302533555.
E-mail address: e.d.degeus@uu.nl (E.D. de Geus).

0145-305X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.dci.2013.03.008

2. Pathogen recognition by macrophages and dendritic cells

Cells of the innate immune system recognize pathogens based on the specific recognition of pathogen-associated molecular patterns by pattern recognition receptors (PRR), including toll-like receptors (TLR), CD14, C-type lectin receptors (CLR) and RIG-I-like receptors (RLR). The TLR expression profile of chicken mononuclear phagocytes was reviewed recently by Wu and Kaiser (2011) and will not be discussed here. Below we will highlight important PRR involved in recognition of avian pathogens.

2.1. CD14

CD14 is a membrane protein that binds lipopolysaccharides (LPS), peptidoglycans and lipoteichoic acid. Beside the membrane bound form, it can also be found as a soluble serum protein (reviewed by Ulevitch and Tobias, 1995). It was the first identified PRR that directly binds to LPS (Wright et al., 1990), chaperoning LPS to TLR4 (da Silva Correia et al., 2001; Gioannini et al., 2004). CD14 regulates the internalization of TLR4 after binding to LPS (Zanoni et al., 2011). Recently it was shown that in mice CD14 can also act together with TLR2 in recognition and control of *Listeria monocytogenes* (Janot et al., 2008).

Chicken CD14 shares many structural features with mammalian CD14. However, unlike mammalian CD14 which is a glycosylphosphatidylinositol (GPI)-anchored protein, chicken CD14 is a transmembrane protein (Dil and Qureshi, 2002; Wu et al., 2009). In chicken LPS-induced NO production by peritoneal MPh depends on CD14 and TLR4. Furthermore, protein expression of CD14 is up regulated by LPS exposure (Dil and Qureshi, 2002). CD14 mRNA is highly expressed in blood monocytes and MPh and in KUL01+ splenocytes, and at lower levels in other cell types (Wu et al., 2009).

2.2. Carbohydrate-binding proteins – lectins

Glycan structures expressed on the surface of pathogens can be recognized by lectins, i.e. carbohydrate-binding proteins that are either soluble or membrane-bound. Various classes of lectins exist and include galectins, the Ca^{2+}-dependent CLR and siglecs (reviewed by van Kooyk and Rabinovich, 2008) and collectins (reviewed by Ng et al., 2012). CLR are considered attractive targets for specific targeting of vaccins to DC (reviewed by Unger and van Kooyk, 2011) because these membrane-bound lectins can function as endocytic PRR (reviewed by Osorio and Reis e Sousa, 2011). Well-known CLR on myeloid cells include the macrophage mannose receptor (MMR), DEC205, DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and macrophage galactose binding lectin (MGL).

Two siglecs are identified in avian species: siglec-4, which is expressed on oligodendrocytes and Schwann cells (Dulac et al., 1992) and a siglec-15 gene is present in the chicken genome. Expression patterns of siglec-15 on chicken cells are not known, but in human tissues, Siglec-15 is expressed in MPh and DC present in spleen and LN (Angata et al., 2007). Five chicken galectins (CG) have been described: CG-1A, CG-1B, CG-3 and CG-8 (Beyer et al., 1980; Kaltner et al., 2008, 2009, 2011; Lopez-Lucendo et al., 2009). Limited information is available on membrane-bound CLR in the chicken. DEC205, an endocytic receptor belonging to the CLR family is expressed by chicken bone marrow-derived (BM)-DC (Wu et al., 2010) and a DC-SIGN/CD209 homolog has been identified in the chicken based on sequence homology (Lin et al., 2009). In the chicken 5 collectins have been described, MBL (Laursen et al., 1998), SP-A and chicken collectins 1, 2, and 3 which resemble the mammalian proteins CL-L1, collectin 11, and CL-P1, respectively (Hogenkamp et al., 2006). In addition, chicken lung lectin (cLL) was identified as a C-type lectin but not as a collectin due to its lack of a collagenous domain (Hogenkamp et al., 2008). CLL is a Ca^{2+}-dependent mannose-specific lectin and together with SP-A it is predominantly expressed in the respiratory tract (RT; Hogenkamp et al., 2006, 2008). Other chicken PRR have been described but these receptors were not expressed on MPh or DC.

2.3. Cytosolic nucleic acid sensors

Microbial nucleic acids are important pathogen-associated molecular patterns and can be discriminated from self-nucleic acids based on sequence, structure, molecular modifications and location (Barbalat et al., 2011; Pichlmair and Reis e Sousa, 2007). Nucleic acid sensing PRR are either located in endosomes (Chicken TLR3, TLR7 and TLR21) or in the cytosol.

The RIG-I-like receptors retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5) and laboratory of genetics and physiology 2 (LGP2) act as cytosolic RNA sensors. In mammals, these are broadly expressed by immune and non-immune cells (reviewed by Desmet and Ishii, 2012). RIG-I and MDA5 recognize a variety of viruses and are important inducers of innate responses to these viruses by driving type-I IFN production (reviewed by Loo and Gale, 2011). Furthermore RIG-I-like receptors have been shown to play a role in the IFN response to bacteria (Li et al., 2011; Monroe et al., 2009). RIG-I is expressed in the duck, but is absent in chicken (Barber et al., 2010). MDA5 has been identified and is functional in both chicken and duck, but the absence of RIG-I in the chicken may contribute to increased susceptibility of chickens to AIV-infection as compared to ducks (Karpala et al., 2011).

Nod-like receptors are another family of cytosolic receptors, of which NOD1 and NOD2 play a role in pathogen recognition (Moreira and Zamboni, 2012). NOD1 is widely expressed in mammalian cells, NOD2 expression was mainly found in MPh, DC and intestinal and lung epithelial cells (Moreira and Zamboni, 2012). They sense bacterial cell wall components, such as peptidoglycans and muramyl dipeptide and NOD2 was also shown to be involved in viral ssRNA recognition (Desmet and Ishii, 2012; Moreira and Zamboni, 2012; Sabbah et al., 2009). The Nod-like receptors have not been studied extensively in chickens. Recently it was reported that NLRC5, which is evolutionary related to NOD1 and NOD2 (Proell et al., 2008), was induced after exposure of HD11 cells to *Salmonella* endotoxin (Ciraci et al., 2010).

3. Mucosal immune responses – respiratory immune responses

Major immunological differences between mammalian and avian lung are the lack of draining lymph nodes (dLN), lack of alveoli and alveolar MPh in avian lung. The chicken RT contains fewer free-residing MPh ("avian respiratory phagocytes") than mammals and MPh are absent from the surface of the air capillaries (Maina, 2002). However, in avian species a large network of MPh and DC is present in the mucosa of the larger airways, in linings of parabronchi (Maina, 2002) and in the connective tissue (Klika et al., 1996; Fig. 1). Phagocytic cells are strategically localized at the start of the gas-exchange area to clear the air of inhaled particles, before it reaches the thin and vulnerable air capillaries (Reese et al., 2006). Most diffusely distributed leukocytes in interstitial lung tissue belong to the monocyte/MPh and DC type, because of their expression of MHC-II, 68.1 and 74.2 (Jeurissen et al., 1989a,b). Directly surrounding the muscle fibers that form the parabronchi, the lumen is bordered by 74.3+ cells, which are thought to act as mammalian alveolar MPh (Jeurissen et al., 1994; Kocsis et al., 2012). Due to the lack of free-residing MPh poultry are expected to depend

Please cite this article in press as: de Geus, E.D., Vervelde, L. Regulation of macrophage and dendritic cell function by pathogens and through immunomodulation in the avian mucosa. Dev. Comp. Immunol. (2013), http://dx.doi.org/10.1016/j.dci.2013.03.008