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FOLLICULAR DENDRITIC CELLS IN MAMMALS – AN OVERVIEW

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ABSTRACT

Dendritic cells (DCs) are antigen-presenting cells. They recognize antigens and can present these antigens to naïve T lymphocytes. DCs play an important part in the mechanism of adaptive immunity. Namely, they control and regulate adaptive immune responses. DCs secrete cytokines involved in the removal of pathogenic agents. They represent the boundary between innate and adaptive immunity. We can see these cells in lymph nodes, spleen, mucosa and other parts of a body in mammals. Several kinds of dendritic cells differ in positions, structure and functions. One type of DCs is follicular dendritic cells (FDCs). FDCs are located in lymphoid follicles in mammals. FDCs have the main role in binding and retaining antigens by linking to complexes (mainly complement and immune). After they present these pathogenic agents to the germinal center (GC) of B lymphocytes and initiate the secondary immune response. FDCs as well as other DCs play an important part in effective humoral response towards pathogenic agents. Most studies about FDCs are in human and mice and there is a lack of studies that concentrate on bovine follicular dendritic cells (BFDCs). This review provides a brief overview of FDCs in mammals.

Keywords: follicular dendritic cells, immunity, lymphocyte, mammals, cattle

INTRODUCTION

DCs, macrophages, and B lymphocytes are important antigen-presenting cells for CD4+ T helper lymphocytes (T_h cells). Macrophages present antigens to T_h cells at sites of infection, which leads to T_h cells activation and production of molecules that further activate the macrophages. These processes are important for the eradication of microbes that are ingested by phagocytes but resist being killed. In these cases, T_h cells greatly enhance the microbicidal activities of the macrophages. B lymphocytes present antigens to T_h cells, which is a key step in the cooperation between T_h cells and B lymphocytes for producing an antibody response to protein antigens (**Abbas *et al*., 2014**).
FDCs are cells with membranous projections that are found intermingled in collections of activated B lymphocytes within follicles of lymphoid in lymph nodes, spleen and lymphoid tissues of the mucosa in mammals. They are capable of creating a connection between processes in FDCs and sensitive interaction with follicular B lymphocytes. These networks form the centers of lymphoid follicles and do not interfere with interfollicular and T lymphocytes regions. Such isolation is believed to prevent premature degradation and uptake of the opsonized and exposed FDCs antigen. FDC expresses receptors of complement – CD35, CD21 and CD32 (**Kranich and Krautler, 2016; Aguzzi *et al*., 2014).** Markers of FDCs are FDC-M1, FDC-M2 and C4 molecules in mammals (**Abbas *et al*., 2014**). FDCs don´t have MHC class II molecules of antigen, so they express several pattern-recognition receptors and take down non-opsonized antigens (**Carroll *et al*., 2018**).

Origin and function of FDCs

The origin of FDCs is still debated and remains largely unknown (**Rezk *et al*., 2013**). The life span of FDCs is several months to years. FDCs are not derived from precursors in the bone marrow. They don't have the ability to present antigens to T lymphocytes. B lymphocytes are able to recognize protein antigens on the surface of FDCs, which is critical for choosing of antigen-binding antigen expressing B lymphocytes. FDCs also contribute to the structural organization of the follicles (**Abbas *et al*., 2014**). Normally, recirculating inactive B lymphocytes traversed FDC network, while lymphocytes activated by B antigen are trapped in these networks and undergo clonal expansion, resulting in germinal centres (GCs). FDCs produce a large amount of the CXCL13 chemokine that induces migration and organization of the lymphocyte (**Aguzzi *et al*., 2014**). FDCs are captured by CR1, CR2 or FcγRIIb receptors and sustained by opsonized antigens or by complement for a long time (**Heesters *et al*., 2013**). Binding between FDC antigen and activated B lymphocyte is important for B lymphocyte survival and subsequent transformation into a memory B lymphocyte (**Kranich and Krautler, 2016**). Otherwise, the B lymphocytes receive a signal to initiate apoptosis. FDC produces a Mfge8 factor that mediates and accelerates the interaction between apoptotic bodies and phagocytes, leading to faster and more effective removal of debris from GCs. Mfge8 factor produced by FDC accelerates the removal of apoptotic bodies. This factor deficiency in mice results in a systemic lupus erythematosus-like (SLE) condition. Thus, in mice with impaired leukotriene (LT) and LT receptor production, generalized lymphatic infiltrates have been observed that may be involved in autoimmune responses. These findings indicate that FDCs may be an important factor in preventing autoimmune development (**Kitamoto *et al*., 1991**). To perform its functions, including the arrangement of follicular structures, DC is stimulated with lymphotoxin, which is produced by B lymphocytes. B lymphocytes have functioned as transporters of opsonized antigens to FDC. B lymphocytes represent immune complexes by CR1 or CR2 receptors or from macrophages, and travel to lymphoid tissues, where B lymphocytes transfer opsonized antigen of FDC. FDCs produce the chemoattractant chemokine ligand 13 (CXCL13). CXCL13 binds with CXCR5 on the surface of B lymphocyte and attracts B lymphocytes into FDC networks in mammals (**Tew *et al*., 2001**). B lymphocytes lacking the CXCR5 receptor, although entering the lymphoid tissues, are organizationally incapacitated and their movements are not systematic. CXCR5 stimulation on B lymphocytes increases leukotriene production, resulting in stimulation of FDC and subsequent increase in CXCL13 concentration. FDC and B lymphocytes adhesion occurs through intercellular and vascular cell adhesion molecules (**Heesters *et al*., 2013**). Activated B lymphocytes with affinity to the FDC anchored antigen, as well as autoreactive B lymphocytes, receive a signal from the FDC to initiate apoptosis, while FDC bound B lymphocytes over the antigen complex survive.

Receptors of FDCs

FDCs have a stromal character in using bone marrow chimaeras (**Yoshida *et al*., 1995; Humphrey *et al*., 1984**). B lymphocytes are a source of lymphotoxins (LT) and tumor necrosis factors (TNFs). TNFs bind to LTβR and TNFR1 receptors, which are on the surface of FDC, and act as the main FDCs maturation

unit in human (**Kranich and Krautler, 2016**). Signalling of LT is important after the initial generation of FDCs (**Kranich and Krautler, 2016**).
FDCs don't present antigen to T lymphocytes, nor can they express antigens associated with major histocompatibility complex (MHC) I and II class. FDCs have the receptor for the complement system and antibody components fragment crystallizable receptor (FcR) (**Tew *et al*., 2001**). Antigens and immune complexes with antibodies constitute iccosomes along FDCs surfaces and are delivered to B lymphocytes in GCs (**Ferencik *et al*., 2004**). These cells express CD23 molecule on their surface, which is the ligand for the component of CR2 of the co-receptor complex of CD19 B lymphocytes. FDCs can participate in the production of antibodies. On the other hand, the ability of these cells to hold antigenic particles long term can sometimes turn against the immune system. For instance, this can occur during HIV in human or prion infections in cattle (**Ferencik *et al*., 2004**).

FDCs in tonsils

FDCs are located in tonsils because they are part of lymph nodes (**Manesse *et al*., 1995**). In one study there is written that FDCs are involved in the pathogenesis of bovine spongiform encephalopathy (BSE) (**Rebmann and Gasse, 2008**). FDCs were found in human patients with rheumatoid arthritis (RA) and chronic inflammatory lesions (**Rebmann and Gasse, 2008**). We can characterize these pathological conditions as reaction on a previous damage of tissue (**Rebmann and Gasse, 2008**). In one study, CNA.42 and D46 (monoclonal antibodies) were used to detect BFDCs cells *in situ* (**Raymond *et al*., 1997**). CNA.42 and D46 mark the BFDCs (**Lefevre *et al*., 2007**).

FDCs cooperate with B lymphocytes

FDCs represent the main cell population in the GC. They make a contact with adjacent lymphocytes because they have long cytoplasmic extensions, which form the reticular network. Studies *in vitro* and *ex vivo* has shown that FDCs increase the proliferation, survival, and differentiation of B lymphocytes (**Matsumoto *et al*., 1996; Koni and Flavell, 1999**). FDCs catch antigen on the surface in the form of antigen-antibody complexes for a long time (**Tew and Mandel, 1979**). They have receptors for the recognition of antigen (CD16, CD21, CD23, CD32, CD35) (**Yoshida et al., 1993**). CD21 receptor can activate and proliferate FDCs. Adhesion molecules play a role in the interaction between FDCs and B lymphocytes through pathways of LFA-1/ICAM and VLA-4/VCAM-1 (**Koni and Flavell, 1999**). IL-15 is a membrane-bound form of FDC playing a key role in support of the GC of B lymphocytes proliferation (**Tew at al., 2001**).

Subtypes of FDCs in the germinal center

In the GC were identified two subtypes of FDCs by their localization, morphology and phenotype. FDCs in the light zone have higher cytoplasmic extensions and the level of membrane-bound immune complexes than in the dark zone of GC (**Yoshida *et al*., 1993**). Reticular cells in the dark zone were FDCs. This was observed by electron microscopy and phenotypic analysis (**Yoshida *et al*., 1993**). Subtypes of FDCs have common precursors. Differentiation can be caused by signals delivered in different GC compartments (**Rademakers, 1992**). Monoclonal antibodies allowed us to study the network of FDCs in normal and pathological conditions (**Lefevre *at al*., 2007**). Monoclonal antibodies stain FDC in the GC, mainly in the light zone of GC (**Lefevre *et al*., 2007**). To date, however, none have been described that stain the dark zone of FDCs specifically. DRC-1, KiM4 and 7D6 are monoclonal antibodies, which can recognize CD21 and FDC-m2. CD21 and FDC-m2 are important to determine the complement component C4 (**Lefevre *et al*., 2007**). 8D6 stimulates B lymphocytes proliferation and differentiation (**Lefevre *et al*., 2007**). One type of monoclonal antibodies recognizes FDCs in the dark zone of the GC. Using these monoclonal antibodies, the study described fibrinogen on the surface of FDCs in the dark zone GC (**Lefevre *et al*., 2007**). Fibrinogen stimulates *in vitro* the proliferation of cells of a centroblasts cell line originating from the GC.
FDCs have a typically tight and/or dense meshwork pattern (**Rezk *et al*., 2013**). In one study, FDCs were isolated and their antigen expression examined. FDCs can be isolated only in small numbers and form tight clusters with T and B lymphocytes. Therefore, they always are contaminated *in vitro* by other cells (**Rezk *et al*., 2013**). Attempts to unambiguously determine the antigenic phenotype of FDCs, either enriched or *in situ* by immunostaining, have led to contradictory and inconclusive results. False-negative phenotyping results might be caused by low levels of antigen expression. Antigen expression and cell lineage of FDCs remain unresolved, with conflicting evidence for macrophage, hematopoietic, or fibroblastic origin. One study in humans examined the antigenic profile and lineage of FDCs by defining their gene repertoires. Polymerase chain reaction (PCR) of single and highly enriched FDCs revealed a limited messenger RNA (mRNA) profile with high levels of mRNA for CD21 and absence of message characteristic for cells of hematopoietic or fibroblastic origin (**Schriever *et al*., 1991**).

BFDCs

Anti-bovine S100 protein serum was described in the lymph node and spleen (**Suzuki and Atoji, 1990**). **Suzuki and Atoji (1990)** say in their study, that S100 protein of vascular system can cohere with lymph and blood flow. S100 protein was first found in 1965 in brains of the vertebrate. In lymphoid tissues, S100 protein was limited to non-lymphoid cells, the FDCs (**Suzuki and Atoji, 1990**). Bovine S100 protein can stimulate ATPase activity. ATPase has been shown histochemically to be located in endothelial cells of the artery, capillary, and lymph vessel (**Mata and Fink, 1989; Suzuki and Atoji, 1990**). In one study, there is speculation that the S100 protein of endothelial cells plays a role in transcytosis of fatty acids from the blood **(Iwanaga *et al*., 1982**). **Rebmann (2010)** has described the immunohistochemical identification of FDCs in the lingual tonsil. **Rebmann and Gasse (2008)** had tested immunohistochemical markers (monoclonal antibodies CNA.42 and D46) for detection of FDCs in the bovine lingual tonsil. FDCs are located in secondary lymphatic organs, including tonsils. These researchers reported that this specific immunohistochemical tool can be applied for the definition and verification of a suitable anatomical landmark.
In vivo distribution of DC in bovine tissues is characterized in one study. DC markers were used as a basis for DC study in diseased tissues. MHCII, CD208, CD1b, CD205, CNA.42 and S100 were used as such markers. These proteins were expressed by FDCs (**Romero-Palomo, 2013**). CD208 is located in the T area of lymphoid organs and in lymphoid follicles. CD1b is located in thymus and interfollicular areas of lymph nodes. CD205 is only present in non-lymphoid tissues. CNA.42 and S100 were determined in primary lymphoid follicles and light zones of GCs. MHC II was determined as a sensitive marker for any DC of hematopoietic origin (**Romero-Palomo, 2013**). CD208 is glycoprotein located in the interfollicular zone of lymphoid tissues. CD1b is a transmembrane glycoprotein. CD1b is related to proteins of MHC and with beta-2-microglobulin create heterodimers (**Pierobon *et al*., 2013**). CD205 is an endocytic receptor, which is expressed by epithelial cells and subsets of DC. CNA.42 identify carbohydrates epitope located on FDCs of different species, including in cattle. S100 is intracellularly located and has many functions, examples being cellular growth, differentiation, transcription, and secretion (**Pierobon *et al*., 2013**).

CONCLUSION

DCs are important for initiating and regulating immune responses. DCs are known for their ability to take up, process and present antigen to T lymphocytes. DCs exist in all lymphoid and most non-lymphoid tissues.
Although the biology of FDCs has been studied extensively in humans and mice, many questions remain unanswered regarding these cells in cattle and other mammals. FDC lineage is not yet fully understood. FDCs belong to antigen-presenting cells. They are found in the lymphatic follicles, have numerous dendrites, have the ability to capture immunocomplexes and interact with B lymphocytes.

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REFERENCES

Abbas, K., Lichman, A., & Pillai, S. (2014). *Cellular and Molecular Immunology*, 7th Edition. Philadelphia: Saunders/Elsevier
Aguzzi, A., Kranich, J., & Krautler, N. J. (2014). Follicular dendritic cells: origin, phenotype, and function in health and disease. Trends in Immunology, 35(3), 105–113. http://dx.doi.org/10.1016/j.it.2013.11.001
Carroll, M., van der Poel, C., & Simoni, L. (2018). Follicular dendritic cell regulation of autoreactive B cells via CD21 triggering of TLR pathway. *Molecular Immunology*, 102, 138. http://dx.doi.org/10.1016/j.molimm.2018.06.039
Ferencik, M., Rovensky, J., & MATHA, V. (2004). *Ilustrovany imunologicky slovnik*, 1st Edition. Prague: Galen
Heesters, B. A., Chatterjee, P., Kim, Y.-A., Gonzalez, S. F., Kuligowski, M. P., Kirchhausen, T., & Carroll, M. C. (2013). Endocytosis and Recycling of Immune Complexes by Follicular Dendritic Cells Enhances B Cell Antigen Binding and Activation. *Immunity*, 38(6), 1164–1175. http://dx.doi.org/10.1016/j.immuni.2013.02.023
Humphrey, J. H., Grennan, D., & Sundaram, V. (1984). The origin of follicular dendritic cells in the mouse and the mechanism of trapping of immune complexes on them. *European Journal of Immunology*, 14(9), 859–864. http://dx.doi.org/10.1002/eji.1830140916
Iwanaga, T., Fujita, T., Masuda, T., & Takahashi, Y. (1982). S-100 Protein-Immunoreactive Cells in the Lymph Node and Spleen of the Rat. *Archives of Histology and Cytology*, 45(4), 393–397. http://dx.doi.org/10.1679/aohc.45.393
Kitamoto, T., Muramoto, T., Mohir, S., Doh-ura, K., & Tateishi, J. (1991). Abnormal isoform of prion protein accumulates in follicular dendritic cells in mice with Creutzfeldt-Jakob Disease. *Journal of Virology*. 65, 6292–6295.

Koni, P.A., & Flavell, R.A. (1999). Lymph node germinal centers form in the absence of follicular dendritic cells networks. *Journal of Experimental Medicine*, 189, 855–864.

Kranich, J., & Krautler, N. J. (2016). How Follicular Dendritic Cells Shape the B-Cell Antigenome. *Frontiers in Immunology*, 7. http://dx.doi.org/10.3389/fimmu.2016.00225

Lefevre, E. A., Hein, W. R., Stamataki, Z., Brackenbury, L. S., Supple, E. A., Hunt, L. G., … Charleston, B. (2007). Fibrinogen is localized on dark zone follicular dendritic cells in vivo and enhances the proliferation and survival of a centroblastic cell line in vitro. *Journal of Leukocyte Biology*, 82(3), 666–677. http://dx.doi.org/10.1189/jlb.0107050

Manesse, M., Sautet, M., Delverdier, F., Schelcher, J., Espinasse, J., & Cabanie, P. (1995). Anneau de Waldeyer des bovins: anatomie topographique et microscopique des tonsilles. *Revue de Medecine Veterinaire*, 146, 749–756.

Mata, M., & Fink, D. J. (1989). Ca++-ATPase in the central nervous system: an EM cytochemical study. *Journal of Histochemistry & Cytochemistry*, 37(7), 971–980. http://dx.doi.org/10.1177/37.7.2525142

Matsumoto, M., Lo, S. F., Carruthers, C. J. L., Min, J., Mariathasan, S., Huang, G., … Chaplin, D. D. (1996). Affinity maturation without germinal centres in lymphotoxin-α-deficient mice. *Nature*, 382(6590), 462–466. http://dx.doi.org/10.1038/382462a0

Pierobon, D., Bosco, M. C., Blengio, F., Raggi, F., Eva, A., Filippi, M., … Giovarelli, M. (2013). Chronic hypoxia reprograms human immature dendritic cells by inducing a proinflammatory phenotype and TREM-1 expression. European *Journal of Immunology*, 43(4), 949–966. http://dx.doi.org/10.1002/eji.201242709

Rademakers, L. H. P. M. (1992). Dark and light zones of germinal centres of the human tonsil: an ultrastructural study with emphasis on heterogeneity of follicular dendritic cells. *Cell & Tissue Research*, 269(2), 359–368. http://dx.doi.org/10.1007/bf00319629

Raymond, I., Al Saati, T., Tkaczuk, J., Chittal, S., & Delsol, G. (1997). CNA.42 a new monoclonal antibody directed against a fixative resistant antigen of follicular dendritic reticulum cells. *American Journal of Pathology*, 151, 1577–1585.

Rebmann, S., Kühne, M., Gasse, H., & Klein, G. (2010). Specified Risk Material and Topographical Distribution of Lymphoreticular Tissue of the Bovine Tongue. *Journal of Food Protection*, 73(5), 989–992. http://dx.doi.org/10.4315/0362-028x-73.5.989

Rebmann, S., & Gasse, H. (2008). Bovine Lingual Tonsil: Histomorphological Characteristics With Special Reference to the Follicular Dendritic Cells. *Anatomia, Histologia, Embryologia*, 37(6), 430–434. http://dx.doi.org/10.1111/j.1439-0264.2008.00874.x

Rezk, S. A., Nathwani, B. N., Zhao, X., & Weiss, L. M. (2013). Follicular dendritic cells: origin, function, and different disease-associated patterns. *Human Pathology*, 44(6), 937–950. http://dx.doi.org/10.1016/j.humpath.2012.10.005

Romero-Palomo, F., Risalde, M. A., Molina, V., Sánchez-Cordón, P. J., Pedrera, M., & Gómez-Villamandos, J. C. (2013). Immunohistochemical Detection of Dendritic Cell Markers in Cattle. *Veterinary Pathology*, 50(6), 1099–1108. http://dx.doi.org/10.1177/0300985813482951

Schriever, F., Freeman, G., & Nadler, L. (1991). Follicular dendritic cells contain a unique gene repertoire demonstrated by single-cell polymerase chain reaction. *Blood*, 77(4), 787–791. http://dx.doi.org/10.1182/blood.v77.4.787.bloodjournal774787

SuzukI, Y., & Atoji, Y. (1990). Immunohistochemical Study of S-100 Protein in the Bovine Lymph Node and Spleen. *Okajimas Folia Anatomica Japonica*, 67(4), 257–261. http://dx.doi.org/10.2535/ofaj1936.67.4_257

Tew, J.G., & Mandel, T.E. (1979). Prolonged antigen half-life in the lymphoid follicles of specifically immunized mice. *Immunology*, 37, 69–76.

Tew, J. G., Wu, J., Fakher, M., Szakal, A. K., & Qin, D. (2001). Follicular dendritic cells: beyond the necessity of T-cell help. *Trends in Immunology*, 22(7), 361–367. http://dx.doi.org/10.1016/s1471-4906(01)01942-1

Yoshida, K., Kaji, M., Takahashi, T., Van den Berg, T.K., & Dijkstra, C.D. (1995). Host origin of follicular dendritic cells induced in the spleen of SCID mice after transfer of allogeneic lymphocytes. *Immunology*, 84(1), 117–126.

Yoshida, K., Van den Berg, T.K., & Dijkstra, C.D. 1993. Two functionally different follicular dendritic cells in secondary lymphoid follicles of mouse spleen, as revealed by CR1/2 and FcR gama II-mediated immune complex trapping. *Immunology*, 80, 34–39.