FASCINATING DENDRITIC CELLS— SENTINEL CELLS OF THE IMMUNE SYSTEM A REVIEW

Kiššová, Z., Tkáčiková, Ľ.

Department of Microbiology and Immunology
University of Veterinary Medicine and Pharmacy in Košice
Komenského 73, 040 01 Košice
Slovakia

ludmila.tkacikova@uvlf.sk

ABSTRACT

Dendritic cells (DC) are specialized antigen presenting cells which have the unique ability to activate naive T-lymphocytes. Their role in the immune system is much more sophisticated than it seems, as they do not kill the pathogens directly, but provide a long-lasting antigen specific immune response thanks to that sufficiently bridging the innate and the adaptive immunity. In recent years, there has been a growing interest in studies of their role in immune regulation, autoimmune reactions, as well as in immune responses against pathogens and tumours. Processing and presentation capabilities of a highly specific and unique tumour antigen makes them an interesting tool for stimulating effective anti-tumour immunity. *In vitro* generations of DC represent a preferred model for more detailed studies of DC biology in other fields. The aim of this review was to discuss the main role of dendritic cells in the body as well as their current use as experimental models for further scientific studies.

Key words: anti-tumour immunity; dendritic cells; immune response; T-lymphocytes

INTRODUCTION

The immune system (IS) can be thought of as a set of interactive cellular and molecular networks where the presence of foreign invaders trigger changes in cellular activities and generates an expanding set of cellular and molecular responses. These reactions eventually result in the elimination of the invaders and increased resistance to infection in the body [66]. The IS represents all the mechanisms that allow a living organism to distinguish between “self” and “non-self” [34]. It can be activated by different molecular patterns—antigens, which the body does not recognize as its own. These antigens attach to special receptors on the immune cells triggers a whole series of processes in the body [54]. Immunity is divided into two parts based on the speed and specificity of the reactions called innate and adaptive immunity [22]. The main purpose of the innate immune response is to immediately prevent the

spread and movement of foreign pathogens in the organism. The adaptive IS provides a defense system that can recognize and destroy specific invaders and then learn from the process that if they attack a second time, they could be destroyed even more effectively [10]. Adaptive immunity in order to be triggered first needs to capture, process, and correctly present a given sample of foreign material to cells that can recognize it. The responsible cells for this antigen processing process are so-called professional APCs (antigen-presenting cells), which include dendritic cells, macrophages, and B-lymphocytes [57, 66].

Dendritic cells biology

The theory of the cell base, which links antigens presented in tissues with immune responses, was unexplained until the late 1980s [1]. Dendritic cells (DC) were discovered in 1868 by Paul Langerhans, who claimed in his work that the epidermal layer of the skin consists of a network formed by cells that are probably part of the nervous system. He described them as “tree-like” cells, so he called them dendritic cells, from the Greek word *dendreon* which means tree [43].

It took up to hundred years for Ralph Steinman and Zanvil Cohn to elucidate and publish an article in 1973 stating that dendritic cells with their specific properties belong to the group of white blood cells [62]. Subsequently, during many experimental studies of DCs, it has been clearly shown that these professional APC have unique immunostimulatory and immunomodulatory properties and are among the most important cells of the immune system [60].

Steinman proposed in his studies a classical model of how DC work and what is their function [1]. These cells are able to absorb surrounding antigens by the process of endocytosis and phagocytosis in tissues, then they migrate through lymph nodes, where they present processed antigens to naive T-lymphocytes [61].

DCs are professional antigen-presenting cells that are the only ones in the body able to activate naive T-lymphocytes and initiate a primary cellular response. After absorbing and processing foreign antigens in peripheral tissues, they migrate to secondary lymphoid organs to present these processed antigens to T-lymphocytes, providing long-lasting antigen-specific responses sufficiently bridging innate and adaptive immunity [13].

DCs have the unique ability to activate naive T cells and direct the immune response toward the production of oth-

er T cell subpopulations such as Th1, Th2, Th17, or Treg cells [4]. As a result, they allow for naive T-lymphocytes to contact with peripheral antigens that they would not otherwise encounter. Once the invader has been removed, the body continues to develop acquired immunity against a second attack by the same organism [63].

General opinions assume that dendritic cells exist in the body in two basic functional stages – as immature DCs, which induce self-tolerance, and mature DCs, which induce immunity to foreign antigens, but only mature ones are able to control clonal T cell expansion and prime immune responses [46].

DC ontogenesis and DC cells subsets

All cellular blood components are derived from haematopoietic stem cells (CD34⁺) in a process called haematopoiesis [8]. CD34⁺ stem cells found in the bone marrow can differentiate into lymphoid or myeloid progenitor cells, which have the potential to develop into both myeloid and lymphoid lineages [14, 30]. T- and B-lymphocytes, NK cells (Natural Killer cells) differentiate from a common lymphoid progenitor (CLP), while megakaryocytes, erythrocytes, granulocytes, monocytes and macrophages belong to the myeloid lineage and differentiate from common myeloid progenitor (CMP) [25, 26, 68].

Conventional lymphoid progenitors can differentiate into all types of lymphocytes under physiological conditions without visible myeloid potential; similarly, conventional myeloid progenitors can lead to all classes of myeloid cells with no or very low levels of B-cell potential [26]. DCs represent a “single” cell type that is not clearly clustered in lymphoid or myeloid lineage because, under certain conditions, they can arise from either CLP or CMP [33, 67].

Thus, DCs are derived from CD34⁺ stem cells, but represent a heterogeneous group of specialized APCs [48], where it is important to realize that key growth factors are required for their differentiation, as their differentiation process strongly depends on the cytokine microenvironment such as for example Flt3-L (fms-like tyrosine kinase 3 ligand), GM-CSF (Granulocyte-macrophage colony-stimulating factor) and M-CSF (Macrophage-colony stimulating factor) or TGF- β (Transforming growth factor-beta) [6, 21, 38].

As DCs represent heterogeneous cell type, they are classified into different subsets. With no standardized approaches for dendritic cell classification in the past, they

Fig. 1. Simplified classification of dendritic cell subsets by flowchart [6]

were roughly classified based on their origin, tissue location, phenotype, or cytokine profile [6]. Current experimental studies prove that there are several dendritic cell lineages. These include the originally identified so-called conventional cDCs, which belong to steady-state DC divided into cDC1, cDC2, and plasmacytoid DCs (pDCs), Langerhans cells (LCs), and monocyte-derived DCs (moDCs) (Fig. 1.) [2, 17, 37].

The identified DC populations differ in basic modules such as expression of various markers, transcription factor requirements, recognition of patterns from the environment, and specialized functions in initiating and modulating T-lymphocytes. As a result of this process, different DC populations acquire different phenotypes and also colonize different tissues performing different functions [2, 5, 37].

Immunological tolerance

Dendritic cells formed in the bone marrow are released into the bloodstream, where they circulate and serve as effective immunological surveillance. Immature DCs circulating in peripheral blood are characterized by low potential for T cell activation but high endocytic activity, they continuously capture proteins from the environment, digest them to short peptides, and display on their surface [61, 63].

The term mature DC is commonly used as a phenotypic characteristic to label those cells which are expressing high levels of MHC molecules and CD40, CD80, CD83, and CD86 on their surface. It is generally assumed that DCs that are mature according to phenotypic criteria are also functionally mature, so the expression of these molecules often correlates with the ability to prime T cells [46].

The study by Austyn et al. [5] showed that DCs migrating from peripheral blood to the spleen, or Langerhans

cells (LCs) migrating from skin grafts, mature during migration and lose the ability to phagocytose antigens. The phenotypic analysis of mature and immature DCs is in line with the previous statements. Freshly isolated immature LCs from the skin expressed multiple receptors for antigen uptake (such as receptors for IgG (FcγRs)), and fewer receptors for T cell activation (including MHC molecules, the integrin LFA-1 (Lymphocyte function-associated antigen 1) and the co-stimulatory molecules) than cultured mature LCs obtained from the skin. The mature one expressed on their surface a much lower number of receptors for antigens, but a higher number of receptors needed for T cell activation [28, 46, 50, 56].

DCs play an indispensable role in building self-tolerance through their ability to present their own antigens to evolving T cells in the thymus, thereby inducing negative T cell selection or differentiation of T regulatory cell (Treg) population [44]. Immune tolerance has been described in immature DCs that have low numbers of surface MHC, costimulatory and adhesive molecules, such as CD80 and CD86 [13]. In contrast, mature DCs are characterized by the presence of high expression of CD80/86 [58]. Thus, tolerogenic DCs often exhibit an immature or semi-mature phenotype, which is characterized by low expression of costimulatory and MHC molecules. The immunosuppressive mechanisms of tolerogenic DCs further show decreased secretion of IL-12 and, conversely, increased secretion of immunomodulatory cytokines such as IL-10 and TGF-β, leading to naive T-lymphocytes differentiating into Treg rather than into T-effector cells [27, 45]. These facts suggest that the induction of tolerance depends on the state of development and activation of DCs, as well as on the surrounding cytokine microenvironment and growth factors [13].

Porcine MoDC

The human and the porcine IS have many similarities with regard to DC biology [3]. The porcine model has found application in many biomedical industries such as wound healing (skin) models [51], renal anatomy models [32], or cardiac cell therapy [59], thus, there is a growing interest in porcine immunology due to the potential of the pigs as a donor in xenotransplantation [12, 23, 35, 49]. Gnotobiotic miniature pigs represent presumably the most convenient model for human immunology study tool, thanks to their cDC2 gene expression signature which is the closest to the human counterpart [3, 15, 24].

The *in vitro* generation of DC represents an advantageous model for studying DC biology. These differentiated cells have been widely used [18], mainly bone marrow-derived dendritic cells (BMDCs) cultured with cytokine cocktail containing GM-CSF and IL-4 for generating BMDCs [24].

Currently, the two most common protocols are used to generate DC from peripheral blood monocytes [39]. Porcine monocyte-derived DCs (MoDCs) can be generated by the so-called fast method (within 48 hours), but it must be taken into account that the function and phenotypic characteristics of these MoDCs are only partially developed [70]. The classical method lasts at least 7 days, when the generated MoDCs are more reliable and effective for investigating the host-pathogen interactions [29, 64]. As was mentioned before, it is well known that the biological and functional properties of immature and mature DCs are far different. From this point of view, the maturation stage of MoDCs is crucial for experimental interpretations [39]. It is important to mention that the classical method has also some limitations, frequent manipulation with harvested cells can cause undesirable DC maturation by physical and pressure stimulation and this method also requires a large amount of peripheral blood mononuclear cells [7].

In various studies, blood-derived monocytes are used for further DC studies. For instance, the Transwell co-culture system was used as an *in vitro* model for intestinal submucosal immune system (GALT) studies. This co-culture platform was established from a cell culture of porcine intestinal IPEC-J2 cells and from porcine MoDCs, which served as a model for testing the effect of enterotoxigenic *Escherichia coli* (ETEC) [31]. Intestinal epithelial cells and DCs located in the lamina propria by communicating with each other and releasing different soluble molecules,

coordinate the immune response in the presence of intestinal pathogens, so this co-culture model made it possible to assess pro-inflammatory signalling pathways induced by ETEC.

Another study used human (hMoDC) and porcine (pMoDC) MoDCs for a better understanding of Flavivirus species tropism and innate immune responses. MoDCs were selected based on their role as early target cells for several Flaviviruses. In comparison, viral infectivity and replication between hMoDC and pMoDC were minor, but some of the tested Flaviviruses were found particularly strong replication in hMoDC with Usutu virus, meanwhile, the Japanese encephalitis virus showed a stronger tropism for pMoDC [16].

Clinical implications—DC vaccines for cancer immunotherapy

Dendritic cells currently represent the most attractive platform for anti-tumour cell vaccine preparations. Their unique ability to activate naive T-lymphocytes and elicit effective specific immune responses, make them the most important candidates in this field [9]. Cancer vaccines are designed to “educate” patient’s own immune system to generate effector T cells specifically for the detection and destruction of tumour cells. The goal of a customized cancer vaccine is to focus on patient-specific tumour antigens and reduce the side effects by protecting normal tissue and maintaining the longest possible regulation of immune memory [20]. Dendritic cell vaccines represent an attractive choice for immunotherapy due to their low toxicity profile, non-invasiveness, and their potential to elicit long-term effects through immunological memory [9, 53].

The first clinical studies testing dendritic cells as vaccines in anti-tumour therapy are dated back to the late 1990s. Dendritic cells were obtained from peripheral monocytes, which were subsequently loaded with tumour antigens in various ways and used to promote immunity against tumour-specific T cells [52]. These immunostimulatory vaccines have been used for the treatment of various types of cancers such as B cell lymphoma [19], melanoma [11, 36, 40], myeloma [47], hepatocellular cancer [11] or acute myelogenous leukaemia [65]. These first experiments showed that DC vaccines were both safe and immunogenic [52].

The opportunity of preparing dendritic cells from peripheral monocytes *ex vivo* (MoDCs) has led to intensive

scientific work in order to prepare an effective antitumor vaccine from dendritic cells for various types of cancer. Although MoDCs are immunogenic they lack adjuvant capacity and immune-activating properties of natural DCs, such as cross-presentation and optimal production of IL-12 and type I interferon [48, 55]. The preparation process of anti-tumour cell vaccines uses defined tumour-associated antigens in the form of proteins, peptides, and RNA or viral vectors as a source of antigens in order to achieve their expression in the cytoplasm of DC and thus ensure efficient presentation by MHC molecules [41, 69]. DCs loaded with the desired antigens are administered to patients in a number of ways. In one approach, autologous antigen-specific T cells are expanded *ex vivo* and then re-infused into patients. Another approach is through vaccination; that is, the provision of an antigen together with an adjuvant to elicit therapeutic T cells *in vivo* [42].

CONCLUSIONS

Dendritic cells as the most effective APC in the body represent an essential part of the immune system necessary for the initiation and modulation of T cell immune responses *in vivo*. They are the only ones in the body able to directly activate antigen-specific cytotoxic CD8⁺ T cells and T cell-dependent antibody production, thus they serve as crucial component of our immune system, critical for the initiation and regulation of adaptive immune system. Their antigen presentation ability and immune-regulatory capacities hold great promise for the treatment of autoimmune diseases, cancer, and the prevention of transplant rejection.

REFERENCES

1. Amigorena, S., 2018: Dendritic cells on the way to glory. *J. Immunol.*, 200, 885—886. DOI: 10.4049/jimmunol.1701693.
2. Amon, L., Lehmann, C. H. K., Heger, L., Heidkamp, G. F., Dudziak, D., 2020: The ontogenetic path of human dendritic cells. *Mol. Immunol.*, 120, 122—129. DOI: 10.1016/j.molimm.2020.02.010.
3. Auray, G., Facci, M. R., van Kessel, J., Buchanan, R., Babuk, L. A., Gerdts, V., 2010: Differential activation and maturation of two porcine DC populations following TLR ligand stimulation. *Mol. Immunol.*, 47, 2103—2111. DOI: 10.1016/j.molimm.2010.03.016.
4. Auray, G., Keller, I., Python, S., Gerber, M., Bruggmann, R., Ruggli, N., Summerfield, A., 2016: Characterization and transcriptomic analysis of porcine blood conventional and plasmacytoid dendritic cells reveals striking species-specific differences. *J. Immunol.*, 197, 4791—4806. DOI: 10.4049/jimmunol.1600672.
5. Austyn, J. M., Kupiec-Weglinski, J. W., Morris, P. J., 1988: Migration patterns of dendritic cells in the mouse. *Adv. Exper. Med. Biol.*, 237, 583—589. DOI: 10.1007/978-1-4684-5535-9_89.
6. Balan, S., Saxena, M., Bhardwaj, N., 2019: Dendritic cell subsets and locations. *Int. Rev. Cell Mol. Biol.*, 348, 1—8. DOI: 10.1016/bs.ircmb.2019.07.004.
7. Banchereau, J., Briere, F., Caux, C., Davoust, J., Lebecque, S., Liu, Y., Palucka, K., 2000: Immunobiology of dendritic cells. *Ann. Rev. Immunol.*, 18, 767—811. DOI: 10.1146/annurev.immunol.18.1.767.
8. Birbrair, A., Frenette, P. S., 2016: Niche heterogeneity in the bone marrow. *Annals NY Acad. Sci.*, 1370, 1, 82—96. DOI: 10.1111/nyas.13016.
9. Bol, K. F., Schreiber, G., Gerritsen, W. R., De Vries, I. J. M., Figdor, C. G., 2016: Dendritic cell-based immunotherapy: State of the art and beyond. *Clin. Cancer Res.*, 22, 1897—1906. DOI: 10.1158/1078-0432.CCR-15-1399.
10. Bonilla, F. A., Oettgen, H. C., 2010: Adaptive immunity. *J. Allergy Clin. Immunol.*, 125, 33—40. DOI: 10.1016/j.jaci.2009.09.017.
11. Butterfield, L. H., Ribas, A., Disette, V. B., Amarnani, S. N., Vu, H. T., Oseguera, D., Economou, J. S., 2003: Determinant spreading associated with clinical response in dendritic cell-based immunotherapy for malignant melanoma. *Clin. Cancer Res.*, 9, 3, 998—1008.
12. Carrasco, C. P., Rigden, R. C., Schaffner, R., Gerber, H., Neuhaus, V., Inumaru, S., Summerfield, A., 2001: Porcine dendritic cells generated *in vitro*: Morphological, phenotypic and functional properties. *Immunology*, 104, 2, 175—184. DOI: 10.1046/j.1365-2567.2001.01299.x.
13. Domogalla, M. P., Rostan, P. V., Raker, V. K., Steinbrink, K., 2017: Tolerance through education: How tolerogenic dendritic cells shape immunity. *Front. Immunol.*, 8, 1—14. DOI: 10.3389/fimmu.2017.01764.
14. Doulatov, S., Notta, F., Eppert, K., Nguyen, L. T., Ohashi, P. S., Dick, J. E., 2010: Revised map of the human progenitor hierarchy shows the origin of macrophages and dendritic

- cells in early lymphoid development. *Nat. Immunol.*, 11, 7, 585—593. DOI: 10.1038/ni.1889.
15. Fairbairn, L., Kapetanovic, R., Sester, D. P., Hume, D. A., 2011: The mononuclear phagocyte system of the pig as a model for understanding human innate immunity and disease. *J. Leuk. Biol.*, 89, 6, 855—871. DOI: 10.1189/jlb.1110607.
16. García-Nicolás, O., Lewandowska, M., Ricklin, M. E., 2019: Monocyte-derived dendritic cells as model to evaluate species tropism of mosquito-borne *Flaviviruses*. *Cell. Inf. Microbiol.*, 9, 1—13. DOI: 10.3389/fcimb.2019.00005.
17. Williams, M., Ginhoux, F., Jakubzick, C., Naik, S. H., Onai, N., Schraml, B. U., Yona, S., 2014: Dendritic cells, monocytes and macrophages: A unified nomenclature based on ontogeny. *Nat. Rev. Immunol.*, 14, 8, 571—578. DOI: 10.1038/nri3712.
18. Hartmann, S. B., Mohanty, S., Skovgaard, K., Brogaard, L., Flagstad, F. B., Emnéus, J., Jungersen, G., 2016: Investigating the role of surface materials and three dimensional architecture on *in vitro* differentiation of porcine monocyte-derived dendritic cells. *PLOS ONE*, 11, 6, 1—19. DOI: 10.1371/journal.pone.0158503.
19. Hsu, F. J., Benike, C., Fagnoni, F., Liles, T. M., Czerwinski, D., 1996: Vaccination of patient with B-cell lymphoma using autologous antigen-pulsed dendritic cells. *Nat. Med.*, 2, 4, 534—539.
20. Hu, Z., Ott, P. A., Wu, C. J., 2018: Towards personalized, tumour-specific, therapeutic vaccines for cancer. *Nat. Rev. Immunol.*, 18, 3, 168—182. DOI: 10.1038/nri.2017.131.
21. Ishikawa, F., Nihiro, H., Iino, T., Yoshida, S., Saito, N., Onohara, S., Akashi, K., 2007: The developmental program of human dendritic cells is operated independently of conventional myeloid and lymphoid pathways. *Blood*, 110, 10, 3591—3600. DOI: 10.1182/blood-2007-02-071613.
22. Kellie, S., Al-Mansour, Z., 2016: Overview of the immune system. In Skwarczynski, M., Toth, I., (Eds.): *Micro and Nanotechnology in Vaccine Development*. Oxford, UK, Elsevier 63—81. DOI: 10.1016/B978-0-323-39981-4.00004-X.
23. Kenmochi, T., Mullen, Y., Miyamoto, M., Stein, E., 1994: Swine as an allotransplantation model. *Vet. Immunol. Immunopathol.*, 43, 1–3, 177—183. DOI: 10.1016/0165-2427(94)90134-1.
24. Kim, S. E., Hwang, J. H., Kim, Y. K., Lee, H. T., 2019: Heterogeneity of porcine bone marrow-derived dendritic cells induced by GM-CSF. *PLOS ONE*, 14, 11, 1—12. DOI: 10.1371/journal.pone.0223590.
25. Kondo, M., 2010: Lymphoid and myeloid lineage commitment in multipotent hematopoietic progenitors. *Immunol. Rev.*, 238, 1, 37—46. DOI: 10.1111/j.1600-065X.2010.00963.x.
26. Kondo, M., Wagers, A. J., Manz, M. G., Prohaska, S. S., Scherer, D. C., Beilhack, G. F., Weissman, I. L., 2003: Biology of hematopoietic stem cells and progenitors: Implications for clinical application. *Ann. Rev. Immunol.*, 21, 759—806. DOI: 10.1146/annurev.immunol.21.120601.141007.
27. Kryczanowsky, F., Raker, V., Graulich, E., Domogalla, M. P., Steinbrink, K., 2016: IL-10—Modulated human dendritic cells for clinical use: identification of a stable and migratory subset with improved tolerogenic activity. *J. Immunol.*, 197, 9, 3607—3617. DOI: 10.4049/jimmunol.1501769.
28. Larsen, C. P., Kitchie, S. C., Pearson, T. C., Linsley, P. S., Lowry, R. P., 1992: Functional expression of the costimulatory molecule, B7/BB1, on murine dendritic cell populations. *J. Exp. Med.*, 176, 4, 1215—1220. DOI: 10.1084/jem.176.4.1215.
29. Lecours, M. P., Segura, M., Lachance, C., Mussa, T., Surprenant, C., Montoya, M., Gottschalk, M., 2011: Characterization of porcine dendritic cell response to *Streptococcus suis*. *Vet. Res.*, 42, 1, 1—12. DOI: 10.1186/1297-9716-42-72.
30. Lee, J., Zhou, Y. J., Ma, W., Zhang, W., Aljoufi, A., Luh, T., Liu, K., 2017: Lineage specification of human dendritic cells is marked by IRF8 expression in hematopoietic stem cells and multipotent progenitors. *Nat. Immunol.*, 18, 8, 877—888. DOI: 10.1038/ni.3789.
31. Loss, H., Aschenbach, J. R., Tedin, K., Ebner, F., Lodemann, U., 2018: The inflammatory response to enterotoxigenic *E. coli* and probiotic *E. faecium* in a coculture model of porcine intestinal epithelial and dendritic cells. *Mediators of Inflammation*. Article ID: 9368295. DOI: 10.1155/2018/9368295.
32. Louie, M. K., Gamboa, A. J., Clayman, R. V., 2009: *In vivo* models for ureteral stents. *Biomater. Tissue Eng. Urol.*, 42—58. DOI: 10.1533/9781845696375.1.42.
33. Manz, M. G., Traver, D., Miyamoto, T., Weissman, I. L., Akashi, K., 2001: Dendritic cell potentials of early lymphoid and myeloid progenitors. *Blood*, 97, 11, 3333—3341. DOI: 10.1182/blood.V97.11.3333.
34. McComb, S., Thiriot, A., Krishnan, L., Stark, F., 2013: Introduction to the immune system. *Methods Mol. Biol.*, 1061, 1—20. DOI: 10.1007/978-1-62703-589-7_1.
35. Monte, A. I. LO., Damiano, G., Palumbo, V. D., Spinelli, G., Buscemi, G., 2015: Renal transplantation by automatic anastomotic device in a porcine model. *Artif. Organs*, 39, 10, 916—921. DOI: 10.1111/aor.12467.
36. Mukherji, B., Chakraborty, N. G., Yamasaki, S., Okino, T., Yamase, H., Sporn, J. R., Mauri, F., 1995: Induction of

- antigen-specific cytolytic T cells in situ in human melanoma by immunization with synthetic peptide-pulsed autologous antigen presenting cells. *Proc. Nat. Acad. Sci. USA*, 92, 17, 8078—8082. DOI: 10.1073/pnas.92.17.8078.
37. **Murphy, T. L., Grajales-Reyes, G. E., Wu, X., Tussiwand, R., Briseño, C. G., Iwata, A., Murphy, K. M., 2016:** Transcriptional control of dendritic cell development. *Ann. Rev. Immunol.*, 34, 93—119. DOI: 10.1146/annurev-immunol-032713-120204.
 38. **Naik, S. H., Proietto, A. I., Wilson, N. S., Dakic, A., Schnorrer, P., Fuchsberger, M., Wu, L., 2005:** Cutting edge: generation of splenic CD8⁺ and CD8⁻ dendritic cell equivalents in Fms-Like Tyrosine Kinase 3 Ligand bone marrow cultures. *J. Immunol.*, 174, 11, 6592—6597. DOI: 10.4049/jimmunol.174.11.6592.
 39. **Nedumpun, T., Ritprajak, P., Suradhat, S., 2016:** Generation of potent porcine monocyte-derived dendritic cells (MoDCs) by modified culture protocol. *Vet. Immunol. Immunopathol.*, 182, 63—68. DOI: 10.1016/j.vetimm.2016.10.002.
 40. **Nestle, F. O., Alijagic, S., Gilliet, M., Sun, Y., Grabbe, S., 1998:** Vaccination of melanoma patients with peptide- ora tumor lysate- pulsed dendritic cells. *Nat. Publ. Group.*, 4, 3, 328—332. DOI: 10.1038/nm0398-328.
 41. **Okada, H., Kalinski, P., Ueda, R., Hoji, A., Kohanbash, G., Donegan, T. E., Lieberman, F. S., 2011:** Induction of CD8⁺ T-cell responses against novel glioma-associated antigen peptides and clinical activity by vaccinations with α -type 1 polarized dendritic cells and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in patients. *J. Clin. Oncol.*, 29, 3, 330—336. DOI: 10.1200/JCO.2010.30.7744.
 42. **Palucka, K., Banchereau, J., 2013:** Cancer immunotherapy via dendritic cells. *Nat. Rev. Cancer*, 12, 4, 1—19. DOI: 10.1038/nrc3258.
 43. **Parquet, R. A., 2014:** Paul Langerhans. *Acta Gastroenterol. Latinoamericana*, 44, 4, 282.
 44. **Perry, J. S. A., Lio, C. W. J., Kau, A. L., Nutsch, K., Yang, Z., Gordon, J. I., Hsieh, C. S., 2014:** Distinct contributions of Aire and antigen-presenting-cell subsets to the generation of self-tolerance in the thymus. *Immunity*, 41, 3, 414—426. DOI: 10.1016/j.immuni.2014.08.007.
 45. **Raker, V. K., Domogalla, M. P., Steinbrink, K., 2015:** Tolerogenic dendritic cells for regulatory T cell induction in man. *Front. Immunol.*, 6, 1—11. DOI: 10.3389/fimmu.2015.00569.
 46. **Reis E Sousa, C., 2006:** Dendritic cells in a mature age. *Nat. Rev. Immunol.*, 6, 6, 476—483. DOI: 10.1038/nri1845.
 47. **Rosenblatt, J., Avivi, I., Vasir, B., Uhl, L., Munshi, N. C., Katz, T., Avigan, D. 2013:** Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. *Clin. Cancer Res.*, 19, 13, 3640—3648. DOI: 10.1158/1078-0432.CCR-13-0282.
 48. **Sabado, R. L., Balan, S., Bhardwaj, N., 2017:** Dendritic cell-based immunotherapy. *Cell Res.*, 27, 1, 74—95. DOI: 10.1038/cr.2016.157.
 49. **Sachs, D. H., 1994:** The pig as a potential xenograft donor. *Vet. Immunol. Immunopathol.*, 43, 1—3, 185—191. DOI: 10.1016/0165-2427(94)90135-X.
 50. **Sakuta, H., Azuma, M., Yagita, H., Okumura, K., Linsley, P. S., Ikehara, S., Steinman, R. M., 1994:** The tissue distribution of the B7-2 costimulatory molecule in mice: abundant expression on dendritic cells in situ and during maturation *in vitro*. *J. Exper. Med.*, 180, 1849—1860. DOI: 10.1084/jem.180.5.1849.
 51. **Sanon, S., Hart, D. A., Tredget, E. E., 2016:** Molecular and cellular biology of wound healing and skin regeneration. In **Albanna, H. Z. Holmes IV, J.H., (Eds.): Skin Tissue Engineering and Regenerative Medicine II.** E-Book, Elsevier. DOI: 10.1016/B978-0-12-801654-1.00002-4.
 52. **Santos, P. M., Butterfield, L. H., 2018:** Dendritic cell-based cancer vaccines. *J. Immunol.*, 2, 16, 18—19. DOI: 10.4049/jimmunol.1701024.
 53. **Sarivalasis, A., Boudousquié, C., Balint, K., Stevenson, B. J., Gannon, P. O., Iancu, E. M., Kandalaft, L. E., 2019:** A Phase I/II trial comparing autologous dendritic cell vaccine pulsed either with personalized peptides (PEP-DC) or with tumor lysate (OC-DC) in patients with advanced high-grade ovarian serous carcinoma. *J. Transl. Med.*, 17, 1, 1—10. DOI: 10.1186/s12967-019-02133-w.
 54. **Sattler, S., 2017:** The role of the immune system beyond the fight against infection. In **Sattler, S., Kennedy-Lydon T. (Eds.): The Immunology of Cardiovascular Homeostasis and Pathology** (Advances in Experimental Medicine and Biology, 1003), 1st edn., 3—14. DOI: 10.1007/978-3-319-57613-8.
 55. **Saxena, M., Balan, S., Roudko, V., Bhardwaj, N., 2018:** Towards superior dendritic-cell vaccines for cancer therapy. *Nat. Biomed. Eng.*, 2, 6, 341—346. DOI: 10.1038/s41551-018-0250-x.
 56. **Schuler, G., Steinman, R. M., 1985:** Murine epidermal langerhans cells mature into potent immunostimulatory dendritic cells *in vitro*. *J. Exper. Med.*, 161, 3, 526—546. DOI: 10.1084/jem.161.3.526.
 57. **Scully, C., Georgakopoulou, E. A., Hassona, Y., 2017:** The immune system: Basis of so much health and disease: An-

- tigens and MHC. *Dental Update*, 44, 11, 1071—1075. DOI: 10.12968/denu.2017.44.11.1071.
58. **Shortman, K., Heath, W. R., 2001:** Immunity or tolerance? That is the question for dendritic cells. *Nat. Immunol.*, 2, 11, 988—989. DOI: 10.1038/ni1101-988.
 59. **Spannbauer, A., Mester-tonczar, J., Traxler, D., Kastner, N., Zlabinger, K., Hašimbegovic, E., Gyöngyösi, M., 2020:** Large animal models of cell-free cardiac regeneration. *Bio-molecules*, 10, 10, 1—19. DOI: 10.3390/biom10101392.
 60. **Steinman, R. M., 2012:** Decisions about dendritic cells: Past, present, and future. *Ann. Rev. Immunol.*, 30, 1—22. DOI: 10.1146/annurev-immunol-100311-102839.
 61. **Steinman, R. M., 1991:** The dendritic cell system and its role in immunogenicity. *Ann. Rev. Immunol.*, 9, 271—296. DOI: 10.1146/annurev.iy.09.040191.001415.
 62. **Steinman, R. M., Cohn, Z. A., 1973:** Identification of a novel cell type in peripheral lymphoid organs of mice. *J. Exper. Med.*, 137, 1142—1162. DOI: 10.1084/jem.137.5.1142.
 63. **Steinman, R. M., Nussenzweig, M. C., 2002:** Avoiding horror autotoxicus: The importance of dendritic cells in peripheral T cell tolerance. *Proc. Nat. Acad. Sci. USA*, 99, 1, 351—358. DOI: 10.1073/pnas.231606698.
 64. **Summerfield, A., McCullough, K. C., 2009:** The porcine dendritic cell family. *Develop. Comp. Immunol.*, 33, 3, 299—309. DOI: 10.1016/j.dci.2008.05.005.
 65. **Van Tendeloo, V. F., Van De Velde, A., Van Driessche, A., Coolsa, N., Anguille, S., Ladell, K., Berneman, Z. N., 2010:** Induction of complete and molecular remissions in acute myeloid leukemia by Wilms' tumor 1 antigen-targeted dendritic cell vaccination. *Proc. Nat. Acad. Sci. USA*, 107, 31, 13824—13829. DOI: 10.1073/pnas.1008051107.
 66. **Tizard, I., 2018:** *Veterinary Immunology*. 10th edn., Elsevier, St. Louis, Missouri, 552 pp.
 67. **Traver, D., Akashi, K., Manz, M., Merad, M., Miyamoto, T., Engleman, E. G., Weissman, I. L., 2000:** Development of CD8 α -positive dendritic cells from a common myeloid progenitor. *Science*, 290, 2152—2154. DOI: 10.1126/science.290.5499.2152.
 68. **Weissman, I. L., 2000:** Translating stem and progenitor cell biology to the clinic: Barriers and opportunities. *Science*, 287, 1442—1446. DOI: 10.1126/science.287.5457.1442.
 69. **Wheeler, C. J., Black, K. L., 2011:** Vaccines for glioblastoma and high-grade glioma. *Expert Rev. Vaccines*, 10, 6, 875—886. DOI: doi.org/10.1586/erv.11.71.
 70. **Wongyanin, P., Buranapraditkul, S., Yoo, D., Thanawongnuwech, R., Roth, J. A., Suradhat, S., 2012:** Role of porcine reproductive and respiratory syndrome virus nucleocapsid protein in induction of interleukin-10 and regulatory T-lymphocytes (Treg). *J. General Virol.*, 93, 6, 1236—1246. DOI: 10.1099/vir.0.040287-0.

Received, August 25, 2021

Accepted October 4, 2021