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Circulating Dendritic Cells with their Dual Function are the Link Connecting Lymphatic Tissue and Brain

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Author's contribution

The only author performed the whole research work. Author AVK wrote the first draft of the paper. Author AVK read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: The objective of the paper is to reveal the sources in which the data about the main characteristics of the DCs have been shown and prove the theses of the "Theory of Duality of Protective Systems" (TDPS) formulated earlier.
Study Design: To compare the own DCs data with later DCs data of other authors.
Place and Duration of Study: Department of Human Anatomy of Novosibirsk State Medical University and Scientific Research Institute of Clinical and Experimental Lymphology, Novosibirsk, between December 1986 and November 1998.
Methodology: DCs were obtained from central lymph of thoracic duct (cistern chyle), intestinal and liver lymph, bone morrow, thymus, spleen, mesenteric lymph, adrenal, palatine tonsils and CNS/brain of general anesthetized rabbits and rats. The cistern chyle, liver and mesenteric lymphatic vessels were punctured with original glass micropipettes. Scrapes specimens from the organs (as smears) were studied by light and electronic microscopes. Percentage of DCs was calculated.
Results: The DCs migrate from different organs of lymphatic/immune systems, periphery blood, skin, mucous membranes and brain to lymphatic drainage, then into blood via thoracic duct. The data induced the author to formulate the TDPS. The theses of TDPS are: 1. Lymphatic and immune systems guard an organism against any antigen and at the same time defend antigen structures of the organism, the brain. 2. These

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functions and the relation of the systems with brain are realized by DCs. DCs of lymph nodes, thymus, spleen, adrenal, red marrow, palatine tonsils, skin and brain are the same as DCs of peripheral and central lymph. The DCs migrate from different organs of the systems, periphery blood, skin, mucous membranes and brain to lymphatic drainage, then to blood. Thus, they circulate. 3. The DCs of central lymph are a special system, which plays an important role in regulation of homeostasis.
Conclusion: The TDPS formulated in 1998 is proved by modern research.

Keywords: Thoracic duct; circulating DCs; dual function; brain; theory.

1. INTRODUCTION

DCs serve as an immunological window to the foreign word. While the latter are found among non-lymphoid cells, professionals antigen-presenting cells, such as dendritic cells, form an integral part of the immune system. DCs are most potent initiators of the immune response and, in particular, are responsible for the induction of primary antigen-specific immune reactions [1]. In 1986 B. Barfoot with his colleagues made reference to some scientific sources: It should be born in mind that although most of the lymph DCs appear to be retained by the first node they come to, their arrest is not quanta. Small but significant numbers do escape into intermediate lymph [2]. Numerous data proving that DCs migrate from the brain into lymphoid tissue and back and ensure the relations between the brain and lymphatic tissue/immune system have been accumulated within the last 10 years. A lot of data received by different scientists prove that DCs migrate from the brain into lymphoid tissue and insure the link between the brain and lymphoid tissue. The DCs circulate. This statement was put forward in the “Theory of Duality of Protective Systems” in 1998. The theses of the theory are as follows: 1. Lymphatic and immune systems guard an organism against any antigen and at the same time defend antigen structures of the organism, the CNS/brain. 2. These functions and relation of immune system with the brain is realized by circulating DCs. Some types of DCs of lymph nodes, thymus, spleen, adrenal, red marrow, palatine tonsils, skin, mucous membrane, peripheral lymph and brain are the same as DCs of central lymph. The DCs migrate from different organs of lymphatic and immune systems, periphery blood, skin, mucous membranes and brain to lymphatic drainage, then to blood. 3. The DCs of central lymph are a special system, which plays an important role in regulation of homeostasis [3]. The dual function of protective systems realized by the DCs was postulated in the TDPS and had to be proved.

2. MATERIALS AND METHODS

DCs were obtained from central lymph of thoracic duct (cistern chyle), intestinal and liver lymph, bone morrow, thymus, spleen, mesenteric lymph, adrenal, palatine tonsils and brain of generally anesthetized rabbits, rats and mice. The cistern chyle, liver and mesenteric lymphatic vessels were punctured with original glass micropipettes: the Russian’s patent No. 1495076. Scrapes specimens from the organs were transferred as smears to microscopic slides and stained by Giemsa. The smears were studied by light and electronic microscopes. Percentage of DCs was calculated. Morphology of the central lymph DCs of the thoracic duct were compared to morphology of the above cited DCs of different organs: a shape and a size of the cells’ body, the number of the extensions (protrusions/branches) of cytoplasm.

3. RESULTS AND DISCUSSION

One of the main tasks of the lymphatic system is transport of antigens from tissues to lymphoid organs in a soluble form or by immune cells and inducing immune reaction to infiltrating foreign antigens but tolerance to one's own antigens. Tissue DCs are the elements preventing immune reactivity against one's own antigens [4]. The dual role of CNS DCs was confirmed in 2007 by Deshpande P., et al. [5]. DCs were found in central lymph by original procedure for sampling lymph from animals' cistern chyle (thoracic duct) by glass micropipettes (Fig. 1 - 21) [6,7].

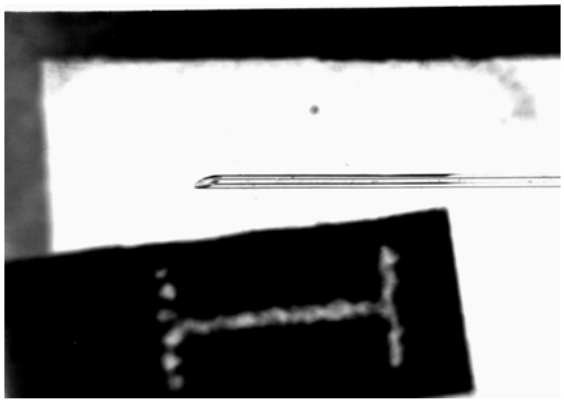


Fig. 1. The glass micropipette between number "one" and a dot of a typing machine

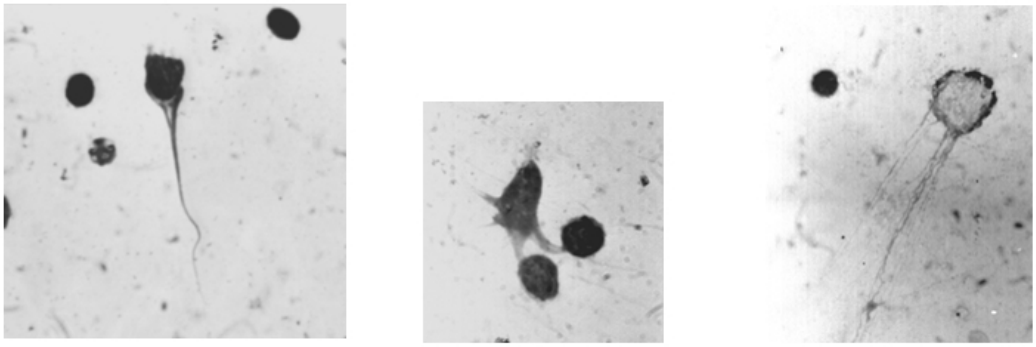


Fig. 2. DCs of central lymph (thoracic duct), a - type 1 (with one branch of cytoplasm), b - type 2 (with two contacting branches),and c - type 3 (with many branches). Giemsa, X 600.

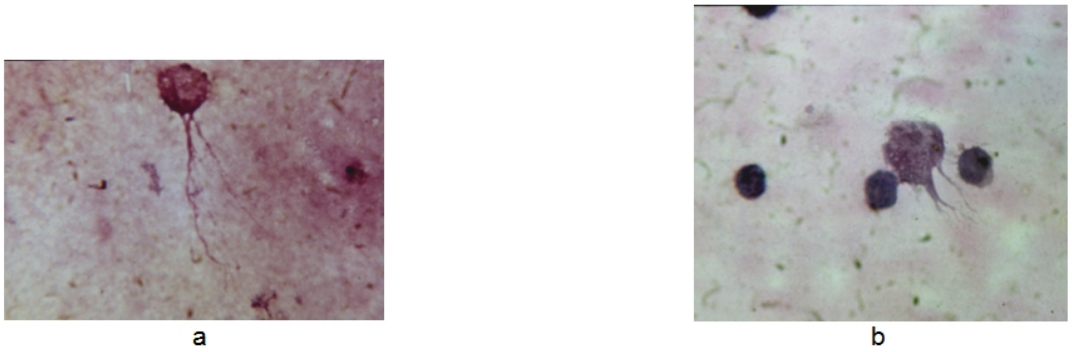
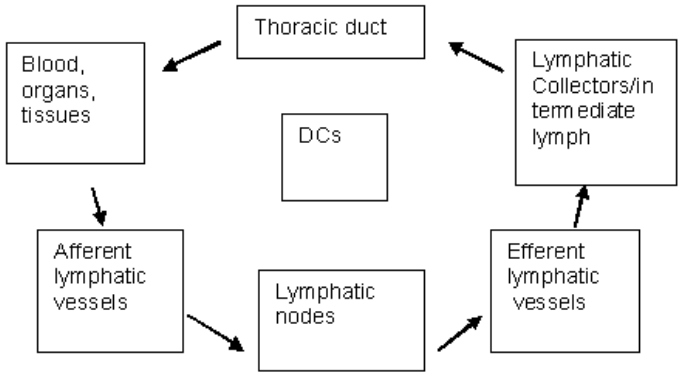


Fig. 3. DCs of central lymph (thoracic duct), a – DC not contacting with any lymphocytes, b - DC contacting with lymphocytes. Giemsa, X 600.

A conclusion was made that DCs migrate from different lymphatic and non-lymphatic organs, periphery blood, skin into lymphatic drainage (lymphatic capillaries, afferent lymphatic vessels, lymph nodes, efferent lymphatic vessels, thoracic duct), then to blood [3,8,9,10,11]. The cistern of the thoracic duct, hepatic lymphatic vessels and intestinal duct of rabbits and rats were punctured by glass micropipettes, which allowed DCs to be detected in central lymph of thoracic duct, hepatic lymph and intermediate lymph. Taking the received data into account it was concluded that lymph DCs circulate [8]. The circulation scheme is below.

The DCs circulation scheme



DCs of central lymph of animals have been indentified according to the form of the cells body, characteristics of formation and branches of its processes. Three types of DCs circulating in central lymph were revealed. Some of them get into contact with lymphocytes. In 1996 DCs were obtained from central lymph, intestinal and liver lymph, bone morrow, thymus, spleen, mesenteric lymph, adrenal, palatine tonsils and brain (mice, rats and rabbits). It was found that the DCs are the same, and, possibly, derived from microglia [8]. DCs are a large class (huge family) of cells [1].

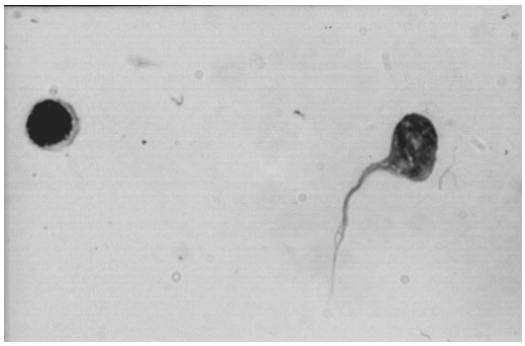


Fig. 4. DC of central lymph (thoracic duct) with one branch. Giemsa, X 600.

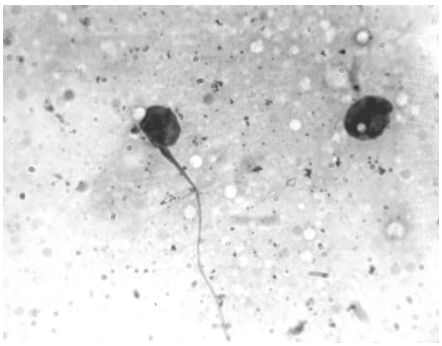


Fig. 5. DC of brain with one branch. Ciemsa, X 600.

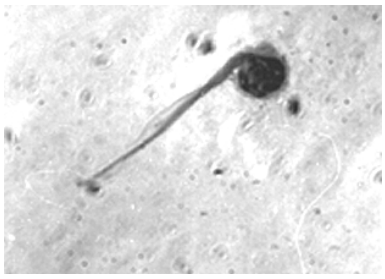


Fig. 6. DC of Intestinal lymph. Giemsa, X 600.

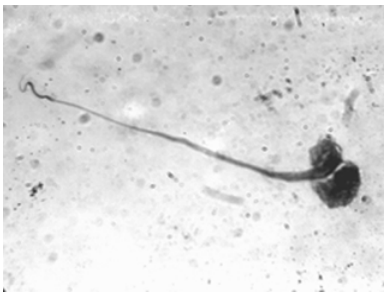


Fig. 7. DC of brain. Ciemsa, X 600.

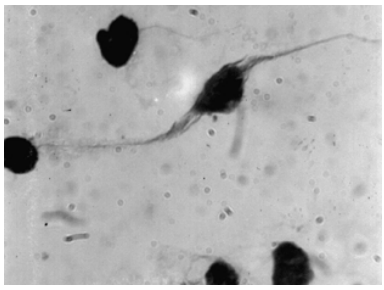


Fig. 8. DC of central lymph (thoracic duct) with the body of irregular form and two branches at opposite poles. Giemsa, X 600.

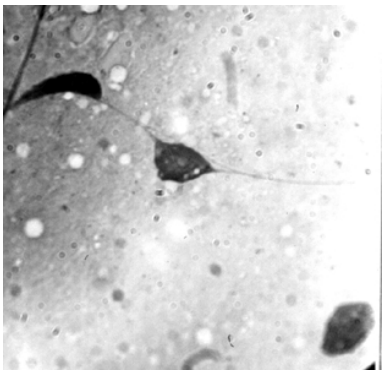


Fig. 9. DC of brain with the body of irregular form and two branches at opposite poles. Ciemsa, X 600.

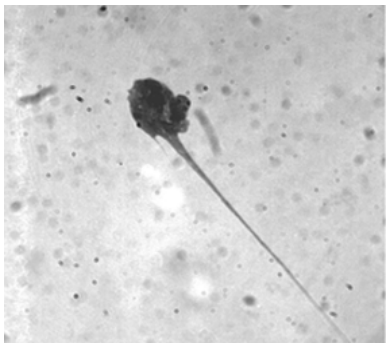


Fig. 10. DC of central lymph (thoracic duct) with a drop-like body and one compact branch. Giemsa, X 600.

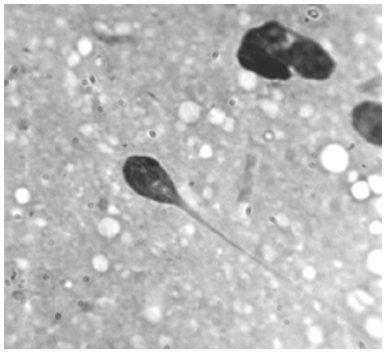


Fig. 11. DC of brain with a drop-like body and one compact branch. Ciemsa, X 600.

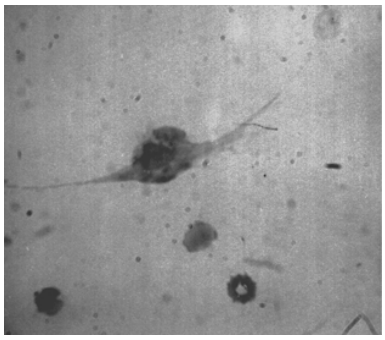


Fig. 12. DC of central lymph (thoracic duct). Giemsa, X 600.

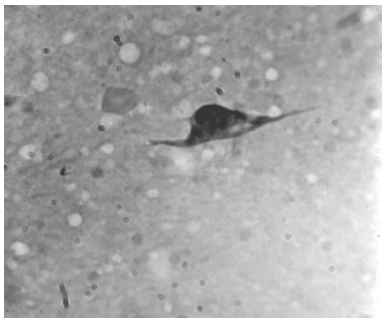


Fig. 13. DC of brain. Ciemsa, X 600.

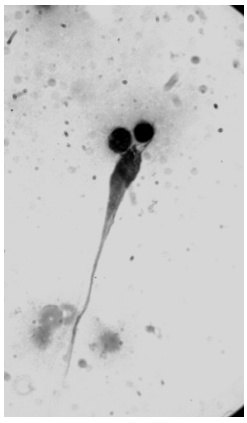


Fig. 14. DC of central lymph (thoracic duct). Giemsa, X 600.

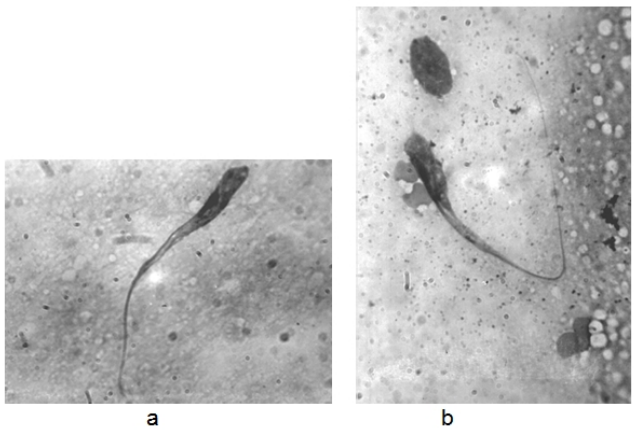


Fig. 15 (a,b). Two DCs of brain. Ciemsa, X 600.

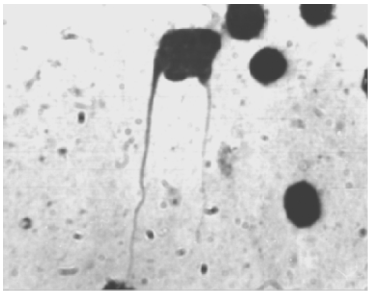


Fig. 16. DC of central lymph (thoracic duct). Giemsa, X 600.

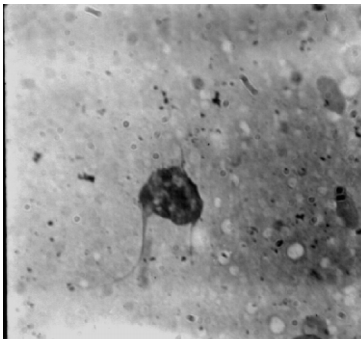


Fig. 17. DC of brain. Ciemsa, X 600.

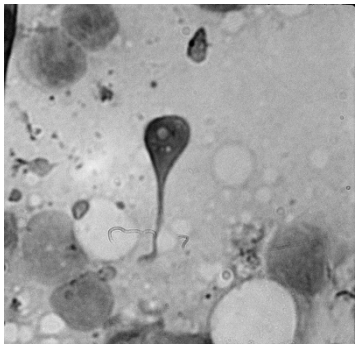


Fig. 18. DC of a liver lymph node. with a drop-like body and one compact branch. Ciemsa, X 600.

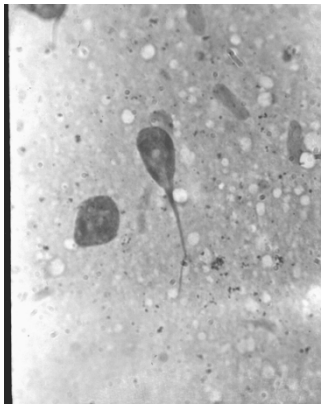


Fig. 19. DC of brain with a drop-like body and one compact branch. Ciemsa, X 600.

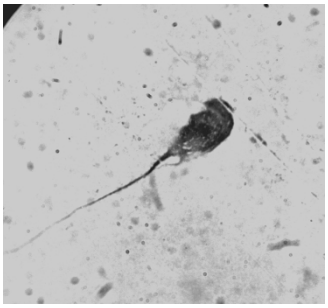


Fig. 20. DC of central lymph (thoracic duct). Giemsa, X 600.

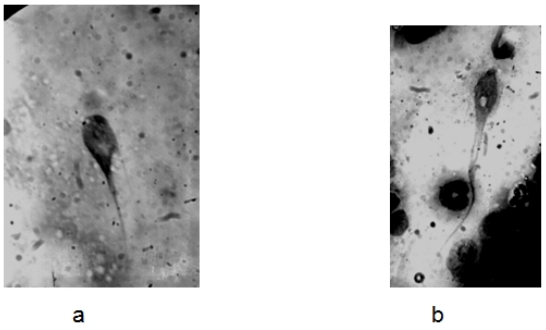


Fig. 21. DCs of (a) brain and (b) bone marrow. Ciemsa, X 600.

Thus, DCs were found on both sides of blood-brain barrier (BBB). These data suggested that some types of the DCs are migrating cells with immune activity, a critical link between the lymphatic/immune and nervous systems and the DCs of central lymph may express biogenic amines capability [10,11]. The theses of the theory were proved by different investigators later. It was found that histamine acts directly upon immature DCs and the DCs express two active histamine receptors [12], induce the generation of CD la-CD 14+ cells of DCs [13], stimulate histamine receptors in mast cells, macrophages, DCs, as well as T lymphocytes [14]. Some of chemokines may contribute to immature DC recruitment to the inflamed CNS [15], enhance DCs survival and promote tumor antigen-specific T cell priming: relation to central nervous system antitumor immunity [16] and induce apoptosis in DCs, thus, it is a potential target for immune suppression in encephalomyelitis [17]. In normal brain CD205 (+) DCs were present in the meninges and choroid plexus. Post infection, CD205(+) DCs were also detected in the cervical cortex, subcortical white matter, thalamus and medulla oblongata [18]. Peripherally derived CD11b(+) myeloid dendritic cells (mDCs), plasmacytoid DCs, CD8alpha(+) DCs and macrophages accumulate in the central nervous system during relapsing experimental autoimmune encephalomyelitis (EAE). During acute relapsing EAE induced by a proteolipid protein peptide of amino acids 178-191, transgenic T cells (139TCR cells) specific for the relapse epitope consisting of proteolipid protein peptide amino acids 139-151 clustered with mDCs in the central nervous system, were activated and differentiated into T helper cells producing interleukin 17 (T(H)-17 cells). CNS mDCs presented endogenously acquired peptide, driving the proliferation of and production of interleukin 17 by naive 139TCR cells in vitro and in vivo. The mDCs uniquely biased T(H)-17 and not T(H)1 differentiation, correlating with their enhanced expression of transforming growth factor-beta1 and interleukins 6 and 23. Plasmacytoid DCs and CD8alpha(+) DCs were superior to macrophages but were much less efficient than mDCs in presenting endogenous peptide to induce T(H)-17 cells [19]. DCs appear within the brain as a consequence of inflammatory [20]. DCs and microglia maintain tissue homeostasis and provide a first line of defense against invading pathogens [21,22]. DCs are protagonists of the complex immune network involved in multiple sclerosis lesion formation [23], may by critically involved in the pathogenesis of multiple sclerosis [24]. The DCs are recruited and are maturing in MS lesions [25]. In the suprafollicular dome of mouse Peyer's patches DCs are connected via their cytoplasmic extensions with M cells. Similar connections between DCs, T cells, nerve fibres, follicular DCs and B-cells are seen in the interfollicular region and inside germinal center [26]. It was shown that immunological synapse occurring at the DC-T cell interface can fine-tune the balance between tolerance and immunity [27]. Treatment with IFN-beta decreased the number of circulating myeloid DCs in multiple sclerosis patients [28]. Effective intervention might be in the form of systemic injection of DCs specific to CNS antigens [29]. DCs migrate from brain to cervical lymph nodes [30,31]. The migration of antigen presenting cells (DCs) from nervous tissue to peripheral lymphoid tissues is similarly to that in other organs [30]. The lack of draining lymphatic vessels in the central nervous system (CNS) contributes to the so-called "CNS-immune privilege". However, despite such a unique anatomic feature, DCs are able to migrate from CNS to cervical lymph nodes through a yet unknown pathway [31]. In 2007 Zozulya A.L., et al., reported that DCs transmigrate through brain microvessel endothelium [32]. Numerous data proving that DCs migrate from the brain into lymphoid tissue [30,31] and back [18,32]. The migrating intestinal lymph DCs (ilDCs) were collected from the thoracic duct in 2010 [33]. Transmigration of circulating dendritic cells (DCs) into the central nervous system (CNS) across the blood-brain barrier (BBB) has not thus far been investigated. An increase in immune cell infiltration across the BBB, uncontrolled activation and antigen presentation are influenced by chemokines. CNS recruitment of DCs correlates with disease severity in experimental autoimmune encephalomyelitis via CCL2 chemotaxis and paracellular transmigration across the BBB,

which is facilitated by ERK activation. Overall, these comprehensive studies provide a state-of-the-art view of DCs within the CNS, elucidate their path across the BBB, and highlight potential mechanisms involved in CCL2-mediated DC trafficking [34]. The development of both Langerhans cells (LCs) and microglia is highly dependent on Csf-1 receptor signaling but independent of Csf-1. Here we show that in both mice and humans, interleukin-34 (IL-34), an alternative ligand for Csf-1 receptor, is produced by keratinocytes in the epidermis and by neurons in the brain. Mice lacking IL-34 displayed a marked reduction of LCs and a decrease of microglia, whereas monocytes, dermal, and lymphoid tissue macrophages and DCs were unaffected. We identified IL-34 as a nonredundant cytokine for the development of LCs during embryogenesis as well as for their homeostasis in the adult skin. Whereas inflammation-induced repopulation of LCs appears to be dependent on Csf-1, once inflammation is resolved, LC survival is again IL-34-dependent. In contrast, microglia and their yolk sac precursors develop independently of IL-34 but rely on it for their maintenance in the adult brain [35]. Exogenous γ-aminobutyric acid (GABA) receptors or supernatant from infected DCs restored the migration of infected DC in vitro. In a mouse model of toxoplasmosis, adoptive transfer of infected DCs pre-treated with GABAergic inhibitors reduced parasite dissemination and parasite loads in target organs, e.g. the central nervous system. Altogether, it was found that GABAergic signaling modulates the migratory properties of DCs and that T. gondii likely makes use of this pathway for dissemination. The findings unveil that GABA, the principal inhibitory neurotransmitter in the brain, has activation functions in the immune system that may be hijacked by intracellular pathogens [36]. Autoimmune diseases are the result of an imbalanced immune regulatory network. Tolerogenic dendritic cells (tolDCs) are key players of this network by inducing and maintaining both central and peripheral tolerance. Therefore, ex vivo generated tolDCs are considered as therapeutic vaccines to re-establish (antigen-specific) tolerance in autoimmune disorders. TolDCs represent a heterogeneous group of dendritic cells that reside in different tissues and maintain tolerance by inducing anergy or apoptosis of autoreactive T cells, phenotypic skewing and induction of different types of regulatory T cells (Tregs). Both experimental animal models of autoimmune diseases and in vitro experiments with ex vivo generated human tolDCs have demonstrated their potency in re-establishing antigen-specific tolerance. The identified key mechanisms are induction of antigen-specific T cell anergy and/or promoting Tregs [37]. It was shown that new insights on the immune response within the CNS. In particular, new light has been shed on the trafficking of the immune cells inside and outside the CNS. Dendritic cells have been described in the context of structures in direct contact with the cerebrospinal fluid (CSF) and their migration, upon antigen encounter, outside the CNS into deep cervical lymph nodes (DCLNs) has been further clarified. T-cells, B-cells, and antibody-secreting cells (ASCs) have been found in the CSF and CNS parenchymal lesions of inflammatory disorders and their phenotype depicted. Moreover, in chronically inflamed CNS, ectopic lymphoid structures have been observed and a germinal center reaction similar to the one found in peripheral lymph nodes has been described. These structures may play a role in the maintenance and expansion of the local autoimmune response. Although the complex interactions between immune and neural cells still remain far to be elucidated, the data discussed here suggest that the physiopathology of the adaptive immune response inside the CNS mimics, although in a mitigated fashion, what occurs in other organs and tissues [38]. Immune cells are modulated by neurotransmitters and hormones. Apart Langerhans cells, studies about dendritic cells and these peptides are very rare. But their effects on monocytes or macrophages are known. Substance P, VIP, CGRP, prolactin, ACTH are among the most important. These effects are supported by an anatomical reality: connexions between nerve and immune cells. Immune cells are capable to product neuromediators and hormones. Neuroimmunology is probably the next great subject of research about dendritic cells [39]. The clinical syndrome associated with

secondary syphilis (SS) reflects the propensity of Treponema pallidum (Tp) to escape immune recognition while simultaneously inducing inflammation. SS subjects had substantial decreases in circulating DCs and in IFNγ-producing and cytotoxic NK-cells, along with an emergent CD56-/CD16+ NK-cell subset in blood. Skin lesions, which had visible Tp by IHC and substantial amounts of Tp-DNA, had large numbers of macrophages (CD68+), a relative increase in CD8+ T-cells over CD4+ T-cells and were enriched for CD56+ NK-cells. Skin lesions contained transcripts for cytokines (IFN-γ, TNF-α), chemokines (CCL2, CXCL10), macrophages and DCs activation markers (CD40, CD86), Fc-mediated phagocytosis receptors (FcγRI, FcγR3), IFN-β and effector molecules associated with CD8 and NK-cell cytotoxic responses. While human syphilitic sera (HSS) promoted uptake of Tp in conjunction with monocyte activation, most spirochetes were not internalized [40]. The findings demonstrate that vorinostat inhibited human CD14 (+) monocyte-derived DCs differentiation, maturation, endocytosis, and further inhibited mDCs' stimulation of allogeneic T-cell proliferation. In addition, vorinostat inhibited DCs-directed Th1- (Type 1T helper) and Th17-polarizing cytokine production. Furthermore, vorinostat ameliorated Th1- and Th17-mediated EAE by reducing CNS inflammation and demyelination. What's more, Th1 and Th17 cell functions were suppressed in vorinostat-treated EAE mice. Finally, vorinostat suppressed expression of costimulatory molecules of DCs in EAE mice. These suggest therapeutic effects of vorinostat on EAE which may by suppress DCs and DCs-mediated Th1 and Th17 cell functions. Our findings warrant further investigation in the potential of vorinostat for the treatment of human multiple sclerosis [41]. Blood-derived myeloid antigen-presenting cells (APCs) along with activated microglia are thought to be pivotal in the initiation of the central nervous system (CNS)-targeted immune response in MS and EAE. However, the exact molecules that direct the migration of myeloid cells from the periphery across the blood-brain barrier (BBB) remain largely unknown. Ninjurin-1 neutralization specifically abrogated the adhesion and migration of human monocytes across BBB-ECs, without affecting lymphocyte recruitment. Finally, Ninjurin-1 blockade reduced clinical disease activity and histopathological indices of EAE and decreased infiltration of macrophages, dendritic cells, and APCs into the CNS. The study uncovers an important cell-specific role for Ninjurin-1 in the transmigration of inflammatory APCs across the BBB and further emphasizes the importance of myeloid cell recruitment during the development of neuroinflammatory lesions [42]. Migration of dendritic cells into the brain in a mouse model of prion disease is revealed [18]. The DCs injected i.t. survived in the tumor and migrated into cervical lymph node. In vitro migration assays revealed the ability of DCs to migrate toward the tumor, suggesting that i.t. injected DCs migrate through the glioma. Taken together, this combination of gene therapy and cellular immunotherapy may be an effective future strategy for treating human gliomas [43]. An aliquot of blood from each subject was first employed to count the number of white blood cells (WBCs) within each mm^3 of blood, and the absolute number per mm^3 of myeloid DCs (mDCs), plasmacytoid DCs (pDCs) and total DCs were next calculated as described. Unlike the percentage of mDCs in total PBMCs, a significant increase for the absolute number of mDCs was noted in the smoking subjects as compared with that of control subjects (34.44 ± 12.29 vs. 28.06 ± 8.57, $p = 0.016$). Of importantly note, an approximately 50% increase for the absolute pDC number was found in the smoking subject as compared with that of control subjects (29.73 ± 10.94 vs. 17.93 ± 6.68, $p < 0.00001$). Similarly, the absolute number for total DCs in the smoking group was significant higher than the control group (64.17 ± 18.11 vs. 45.99 ± 15.52, $p < 0.0001$) [44]. The number of central lymph DCs in thoracic duct of intact rabbits are 2,0% $\pm$ 0.9, $p<0.05$ [45].The DCs of central lymph of thoracic duct had branching processes. In fact, this type is mainly detected in atherosclerosis and its correction (Fig. 2). The prevalence of the above phenotypes of the DCs is attributed to the response of the immune system to atherosclerosis and its correction [6]. Later the data were confirmed [46,47].

4. CONCLUSION

The above given latest data about the important functions of DCs: their circulation, duality and ability to connect lymphatic tissue and brain prove the theses of the "Theory of Duality of Protective Systems" formulated in 1998. The research of DCs is being continued now. The "Theory of Duality of Protective Systems" must be right in regard to the nervous system in general and might be right in regard to other tissues and organs separated from lymphatic tissue/system by blood-brain barrier or any other biological barriers.

CONSENT

There were no patients.

ETHICAL APPROVAL

The author declares that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

The author has declared that no competing interests exist.

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