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Mini Review

Interconnection and Communication between Bone Marrow - The Central Immune System - And the Central Nervous System

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Abstract

Bone marrow and the central nervous system are both protected by bone. The two systems are interconnected not only structurally but also functionally. In both systems specialized cells communicate through synapses. There exists a tridirectional communication within the neuroimmune network, including the hormonal system, the immune system, and the nervous system. Bone marrow is a priming site for T cell responses to blood-borne antigens including those from the central nervous system. In cases of auto (self) antigens, the responses lead to immune tolerance while in cases of neo (non-self) antigens, the responses lead to neoantigen-specific T cell activation, immune control, and finally to the generation of neoantigen-specific immunological memory. Bone marrow has an important function in the storage and maintenance of immunological memory. It is a multifunctional and very active cell-generating organ, constantly providing hematopoiesis and osteogenesis in finely-tuned homeostasis. Clinical perspectives include mesenchymal stem cell transplantation for tissue repair within the central nervous system.

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Introduction

In analogy to the Central Nervous System (CNS), Bone Marrow (BM) has recently been described as the Central Immune System (CIS) [1]. Both systems developed during vertebrate evolution, communicate through synapses and are able to learn.

The immune system has the capacity to learn and develop memory, similar to the brain. Unlike the brain with its mostly immobile network of neurons, the immune system is based on a network of mostly mobile cells. These two learning systems are interconnected. The development of immune cells is regulated by autonomic and somatosensory neurons. These nerves influence hematopoiesis as well as priming, migration, and cytokine production of immune cells. In reverse, homeostatic neural circuits that control metabolism, hypertension, and the inflammatory reflex are influenced by specific immune cell subsets [2]. Neuronal synapses transmit electrical impulses directly via gap junctions (about 3.5 nm distance) or indirectly via neurotransmitters (20 - 40 nm distance). Immunological synapses (about 13 nm distance) transmit biochemical signals. Nestin-GFP^{hi} neuron-glial antigen-2 (NG2+) elongated cells run adjacent to arteries and arterioles [3]. These adrenergic nerves are surrounded by bundles of nonmyelinating Schwann cells [3]. Recently, it was suggested that lymphoid organs are innervated in a new way [2]. It could be visualized that the cytoplasm of a subset of dendritic cells is infiltrated by adrenergic nerve fiber terminals ending at microtubular and microfilament walls [2].

The central immune system and the neuroimmune network

In 2003, bone marrow was reported for the first time to function as a priming site for T-cell responses to blood-borne antigens [4]. This was corroborated and extended ten years later by two-photon dynamic imaging of mouse brain calvaria [5]. Naïve CD8+ T cells were observed to crawl rapidly at a steady state but arrested immediately upon sensing antigenic peptides. As shown in the cartoon of [1], antigen-specific T cells decelerated, clustered together with antigen-presenting cells, upregulated CD69, and divided in situ to yield effector cells [5].

The neuroimmune network is tridirectional. It consists of immune cells and immune-derived molecules, endocrine glands and hormones, the nervous system, and neuro-derived molecules [6]. This network plays a significant role

in communication pathways. It is involved in homeostatic regulation at the level of the whole organism and at local levels [6]. Details of such neuronal–immune cell units have been studied in allergic inflammation of the nose [6]. The nervous system regulates the function of immune cells through neurotransmitters or neuropeptides. Conversely, immune cells play a key role in neuronal injury, repair, and differentiation [7].

CNS immunosurveillance

The CNS is lined by meninges - dura, arachnoid, and pia mater. Recently, a fourth meningeal layer has been described. This new Subarachnoid Lymphatic-Like Membrane (SLYM) encases blood vessels and immune cells [8]. SLYM is closely associated with the endothelial lining of the meningeal venous sinus. This permits the direct exchange of small solutes between cerebrospinal fluid and venous blood [9]. Recently, a calvarial hematopoietic niche was discovered in a distinct region of the skull. This acts as a myeloid cell reservoir to the underlying meninges [9]. The inner skull of the cortex contains vascular channels. These provide a passageway for cells and cerebrospinal fluid-derived antigens between the skull and the brain parenchyma [9].

Throughout the CNS parenchyma, a tightly controlled microglia network facilitates efficient immunosurveillance [10]. Each cell is constantly surveilling its microenvironment. During tissue surveillance, microglia screen for pathogens, remove cell debris and metabolites, groom neighboring cells, and facilitate cellular crosstalk [10]. This is an essential process for CNS homeostasis and development [11]. Also, microglia continuously monitor and sculpt synapses, thereby allowing for the remodeling of brain circuits [12]. Such glia-mediated neuroplasticity is driven by neuronal activity. It is controlled by various feedback signaling mechanisms and crucially involves extracellular matrix remodeling [12]. Molecular signatures of homeostatic microglia and disease-associated microglia have provided insights into how these cells are regulated in health and disease and how they contribute to the maintenance of the neuronal environment [13].

Astrocytes were recently demonstrated to communicate with neurons and to mediate glutamatergic gliotransmission in the CNS [14]. Nine molecularly distinct clusters of hippocampal astrocytes were identified by single-cell RNA-sequencing and patch-seq data analysis [14]. A specialized subpopulation selectively expressed a synaptic-like glutamate-release machinery and was localized to a discrete hippocampal site [14].

Neuropathologies and interventions

i. In primary CNS lymphoma, recent studies have highlighted the excellent disease control afforded by high-dose chemotherapy and stem cell transplantation [15]. Also, chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) achieved impressive increases in complete remission rates [16].

ii. For Glioblastoma Multiforme (GBM), an orphan disease, an immune landscape has been described as a double-edged sword for treatment [17]. On one hand, there are the immunosuppressive effects of tumor cells and myeloid immune cells on the tumor microenvironment, while on the other, there are the immune-stimulatory effects of lymphocyte responses against the glioma cells [17]. Clinical and translational advances in malignant glioma immunotherapy have been summarized recently [18,19]. The reviews include vaccine-based therapies, adoptive cell therapies, oncolytic virus therapy, and technical innovation [18,19]. The overall survival of IDH1 wild-type MGMT promoter-unmethylated GBM could be improved by a synergy between temozolomide chemotherapy and individualized multimodal immunotherapy [20]. The concept of randomized controlled immunotherapy clinical trials for orphan diseases like GBM has been challenged [21] and compared to the evidence obtained by real-world patient data from individualized medicine [22].

iii. Neuro-degenerative and neuro-autoimmune diseases are influenced and affected by the immune system. The immune system is involved in neurodegenerative diseases such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and amyotrophic lateral sclerosis (ALS) [23]. CD4+ T cells, CD8+ T cells, and regulatory T cells (Tregs) play an important role in cerebral infarction and autoimmune diseases of the CNS, such as Multiple Sclerosis (MS), N-Methyl-D-Aspartate (NMDA) receptor encephalitis, and narcolepsy (23). An important auto (self)-antigen of the CNS is Myelin Oligodendrocyte Glycoprotein (MOG) [24].

iv. Ischemic stroke involves complex interactions between neuronal, glial, and immune cell subsets across multiple immunological compartments. These include the blood-brain barrier, the meningeal lymphatic vessels, the choroid plexus, and the skull bone marrow [25].

v. From Alzheimer's models, it was reported that neuronal expression of a single-chain antibody selective for Aß oligomers protects synapses and rescues memory [26].

vi. New diagnostic tools. Immuno-positron emission tomography (immunoPET) is a non-invasive in vivo imaging method based on tracking and quantifying radiolabeled monoclonal antibodies [27]. ImmunoPET could be a new approach to developing more specific PET probes directed to different brain targets [27].

vii. Extracellular vesicles. Neural-derived and immune-

derived extracellular vesicles from blood appear to be good specific biomarkers in Multiple Sclerosis (MS) for reflecting the disease state [28].

viii. New interventional tools. To increase the brain bioavailability of certain drugs polymer- and lipid-based micro- and nanoparticles are being developed. For bypassing the blood-brain barrier, the intranasal route of drug administration offers numerous advantages. It provides a direct entrance to the brain through the olfactory and trigeminal neurons [29].

ix. Bone Marrow-derived Mesenchymal Stem Cells (BM MSCs) have a dampening effect on neurological diseases. One example is Intracerebral Hemorrhage (ICH). This is a common acute nervous system disease that causes severe disability and high mortality. Alleviation of brain injury after ICH was demonstrated following BM MSC transplantation in mice. This was affected by the Hippo signaling pathway [30]. It was also reported that polarized anti-inflammatory MSCs increase hippocampal neurogenesis and improve cognitive function in aged mice [31]. Another example is Alzheimer`s Disease (AD). In an AD mouse model, the transplantation of nasal olfactory mucosa MSCs resulted in benefits [32]. A dampening effect of BM MSCs has been ascribed to microRNA. An exosomal microRNA (miR-146a) secreted from BM-MSCs was reported to be taken up into astrocytes [33]. Intracerebral-ventricular injected BM-MSCs were shown to improve cognitive impairment by increasing the expression of miR-146a in the hippocampus [34]. This can be explained by an effect on astrocytes - key cells for the formation of synapses. Restoration of astrocyte function may lead to synaptogenesis and improvement of cognitive function [35]. In conclusion, MSC-based therapy is an important means of ameliorating neurological impairment [31-35].

Conclusion and perspectives

The evolution of vertebrates went along with the co-evolution of the bones, the BM, and the CNS. BM is a central, multifunctional, and protective immune organ and should receive more attention in the future. Among all antigen-responsive immune organs (BM, spleen, lymph nodes), BM is the largest. It is also the most prominent source of de novo cellular generation within the body. Newly described functions of this central immune organ include i) capacity of antigen presentation by specialized Antigen-Presenting Cells (APCs), ii) T cell-APC interaction capacity, iii) memory cell storage capacity, iv) capacity of maintaining self-tolerance and immune homeostasis, v) capacity of tissue repair by mesenchymal stem cells, vi) ability to sense signals via adrenergic nerve fibers from the autonomous peripheral nervous system and vii) capacity of immunosurveillance of the CNS.

Because the BM is of great importance for general health, new drug approvals should minimize detrimental drug effects on the BM. Among the available immunotherapeutic drugs, the most important are immune checkpoint inhibitors, anti-cancer vaccines, oncolytic viruses, and adoptive T-cell therapies. All of these have to be assessed with regard to their side effects on the BM.

Examples are given for neuropathologies and immunological interventions. This area of research is considered in the future of great medical relevance.

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