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Immunological Mechanisms and Therapies in Brain Injuries and Stroke

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Immunological Mechanisms and Therapies in Brain Injuries and Stroke

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Chapter 1
Old Dogmas, Surprising Complexities, and Novel Therapeutic Targets

Ulrich Dirnagl

Abstract Immune responses to brain injury are more than a simple reaction to tissue damage. Brain and immune system are engaging in a tightly orchestrated communication, which may protect the brain, help recover lost function, or aggravate damage and impede repair. The bewildering complexity of these processes is reflected by the fact that for practically any cell type of the immune system evidence for beneficial as well as detrimental functions can be found in the literature. This introduction sets the stage for the chapters of this volume, which will summarize our current knowledge on the immunological mechanisms and therapies of brain injuries and stroke.

> *"Autopsies clearly demonstrate that the [apoplectic] brain is subject to inflammation and suppuration"*.
>
> Translated from Richelmi, [1]

Introduction

That acute brain diseases, such as "apoplexy," can be accompanied by inflammation has been realized by physicians and pathologists already a long time ago. Today, we know that immune responses to brain injury are more than a simple reaction to tissue damage, at most responsible for clearing debris. We have come to realize that brain and immune system are engaging in a tightly orchestrated communication, which may protect the brain and even help recover lost function, but may also aggravate damage and impede repair. Indeed, not only resident immune cells of the brain, such as microglia, are involved in these responses, but also practically all cell types of the innate and adaptive immune system, which may home to the lesion, or act in the periphery. The bewildering complexity of the interaction of the two

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"supersystems" [2] after brain lesion is reflected by the fact that for practically any cell type of the immune system evidence for beneficial as well as detrimental functions can be found in the literature, and the realization that despite many attempts targeting immune mechanisms has not been successful in large, randomized clinical trials of acute CNS diseases. With some general reflections, I would like to prepare the ground for the chapters of this volume, which summarize our current knowledge on the immunological mechanisms and therapies in brain injuries and stroke.

Nervous and Immune System: Precambrian Twins

Nervous and immune systems have coevolved over hundreds of millions of years. Both are engaged in the communication of the organism with the outside world. They share characteristics from a conceptual (memory, synapse, etc.) to a molecular level (e.g., identical signaling and guidance molecules). The most ancient and possibly most important task of the nervous system is to control movement and predation (or evasion from it), while the immune system protects against infection of the host by foreign organisms, parasitic, bacterial, or viral. Brain and immune system communicate intensely, sensing and controlling each other's state to maintain homeostasis. When things go wrong, however, primary diseases of the nervous system may harm the immune system, and vice versa. In fact, disorders of the immune system may lead to acute brain injury, as in atherothrombotic stroke, or acute brain injury, as in a stroke can cause brain inflammation, as well as immunodepression.

Nervous and Immune System: Friends, Foes, Then Friends Again?

For many decades, research into the pathophysiology of acute brain injury after ischemia or trauma was almost exclusively focused on the central nervous system. Involvement of the immune system was only considered insofar injury may lead to local inflammation, which involves not only brain cells, such as microglia and astrocytes, but also cells of the innate immune system which have homed to the lesion, such as granulocytes and monocytes. Early anti-inflammatory treatment in experimental models of stroke or brain trauma appears to be protective, although clinical trials were unable to confirm this effect in stroke patients. The interaction of adaptive immunity and the brain has traditionally been the domain of multiple sclerosis research, which has demonstrated that even the healthy brain is patrolled by T cells. Only recently, it was realized that cells of the adaptive immune system are players when the brain is acutely lesioned. Not only may the brain downregulate the peripheral immune system (innate and adaptive) after stroke [3], brain trauma [4], or spinal cord injury [5], cells of the adaptive immune system enter the brain where they may

aggravate or contain damage, or potentially even partake in repair. These findings, as well as the notion that inflammation is intrinsically linked to wound healing in the periphery, have promoted the concept of the Janus-facedness of inflammation after brain injury; in its most simplistic version, acute cell death in the brain within hours leads to the activation of brain parenchymal and blood-borne immune cells and consequently the generation of toxic metabolites, such as free radicals, stressing the brain on top of the initial insult. After the acute phase, however, some proinflammatory cells shift their phenotype towards anti-inflammation (e.g., M1 → M2 polarization of macrophages), and other, primary anti-inflammatory and pro-regenerative cells (e.g., regulatory T cells, Tregs) take over, helping the brain to repair damage and recover function. This dichotomous concept is highly attractive, as it suggests that ill and beneficial effects of immune responses can be separated on a temporal scale. Anti-inflammation early on and modulation of inflammation towards "wound healing" later suggest itself as straightforward and promising therapeutic approaches. Various therapeutic agents (pharmacological and cellular) are ready to be tested, the only remaining challenge appears to develop and deploy noninvasive strategies (i.e., molecular imaging, such as TSPO-PET) to stratify patients to the right type of immune therapy.

Of Concepts and Misconceptions

But is it that simple? Can the outcome of an interaction between the two supersystems of the organism be either good or bad, can they be sometimes foes, and shortly thereafter friends again? There is nothing wrong in formulating reductionist biological concepts—they help to generate testable hypotheses in the face of overwhelming complexity. However, there is a risk that flawed concepts stick and may turn into dogmas. This has happened with several concepts which are relevant to our understanding of brain–immune interactions after injury. I will therefore briefly touch upon them.

The Immune Privilege of the Brain

The unique structure and function of the brain, the risk of erratic rewiring after damage and thus restricted capacity to regenerate, as well as its tight embedding into a bony structure limiting volume expansion necessitate protection against damage from inflammation. The organ has therefore developed tolerance against the introduction of antigens—the so-called immunological privilege [6]. However, this privilege is not absolute, and it is compartmentalized. An excellent treatment of this concept and misunderstandings associated with it can be found in Galea et al. [7]. In short, only the brain parenchyma has a tightly regulated immunosuppressive environment without an adaptive efferent arm of immunity. The ventricles (including

choroid plexus and circumventricular organs), perivascular spaces, and meninges of the brain demonstrate responses of innate and adaptive immunity and antigen presentation very similar to peripheral sites. It should also be noted that the environment of the brain parenchyma rapidly loses its immunosuppressive capacity once inflammation has established itself after brain tissue damage. This is the result of blood–brain barrier breakdown, local production of chemoattractants and immunostimulants, and the appearance of dendritic or other antigen-presenting cells. Finally, although blood–brain barrier and relative immune privilege are linked, the one is not the primary consequence of the other. The immune privilege of the brain parenchyma results from a tightly regulated microenvironment and the lack of an efferent arm of adaptive immunity, rather than tight capillary endothelia.

The Blood–Brain Barrier and Leukocyte Trafficking

A "barrier" made of capillary tight junctions restricts the diffusion of molecules potentially disruptive for neurotransmission from the blood into the brain extracellular fluid and thus neuropil. However, this barrier is mostly restricted to the capillary bed, where no extravascular ("Virchow–Robin") space exists, as the basement membrane between endothelial cells and astrocytic endfeet of the glia limitans are fused—the so-called gliovascular or composite basement membrane. For an excellent treatment of the blood–brain barrier and a clarification of some prevalent misconceptions, the reader is referred to Bechmann et al. [8]. Importantly, leukocyte recruitment is a highly regulated process and does not normally involve the blood–brain barrier, as it occurs in postcapillary venules, where the cells first enter the Virchow–Robin space. Only a second step involving different molecular programs can take them into the neuropil, as they need to cross the basement membrane of the glia limitans. In other words, while solute movement in and out of the CNS is limited by properties of the endothelium, leukocyte migration is in addition hampered by extracellular matrix and membranes, which need to be actively degraded for passage [9, 10]. The lack of discrimination of the different barriers encountered by leukocytes in brain inflammation has confounded the literature. To understand the role of leukocytes in brain inflammation, we need to carefully locate and discriminate specific leukocyte subsets, such as neutrophils, monocytes, NK cells, T-cell subtypes, and B cells. A case in point is the dogma that polymorphonuclear leukocytes (PMNs) invade the brain parenchyma early after stroke, where their toxic products harm neurons. A recent study in experimental stroke and human neuropathological samples demonstrates, however, that after stroke the large majority of extravasated PMNs stay within the confines of the perivenular space and the meninges and do not gain access to the neuropil [11]. PMNs, therefore, appear to act at different sites than previously thought, which may at least partially explain the clinical failure of agents that block PMN infiltration and suggests alternative therapeutics targeting inflammation within the neurovascular unit.

Inflammation and Wound Healing

Tissue responses after brain lesions include resorption of debris, scar formation, and possibly attempted repair, and because of clear analogies have been compared to the tightly regulated process of wound healing in peripheral tissues, for example the skin. There the orchestrated response to injury includes elements of inflammation, such as leukocyte homing, in particular macrophage activity. Macrophages have been implicated in wound closure, reepithelialization, and angiogenesis. It should be noted, however, that even for wound healing in the periphery, the role of inflammation is still not clear. While some studies demonstrate disturbed wound healing by anti-inflammatory treatment or specific ablation of macrophages [12], others found normal wound healing (including angiogenesis) in the absence of inflammation [13]. It should be noted in this context that embryos demonstrate almost perfect wound healing without scarring, in the complete absence of inflammation [14]. Herz et al. [15] demonstrate that brain plasticity and repair after stroke can be fostered by anti-inflammatory therapy. Interestingly, however, Gliem et al. [16] found that bone marrow derived macrophages are critical for preventing hemorrhagic transformation of brain infarcts. Thored et al. [17] linked microglia accumulation to neurogenesis and repair after stroke. However, the same group went on to demonstrate that elimination of the microglia does not affect the neurogenic response [18]. This presents a nice illustration of the truism that correlation does not imply causation, which is unfortunately often overlooked, in particular regarding research on the relationship between brain and immune system (see below). The controversy surrounding the role of inflammation and repair or wound healing remains unresolved, and the reader is referred to the interesting debate in Crutcher et al. [19].

Correlation Versus Causation

Many experimental studies report pharmacologic manipulations, which lead to smaller infarcts via "anti-inflammatory" mechanisms. Claiming "anti-inflammatory action" quite often rests on the finding that giving the drug not only reduces damage but also many markers of inflammation, such as cytokines, influx of leukocytes, etc. Unfortunately, this conclusion is confounded by the problem that smaller infarcts (by whatever treatment) lead to a reduction of practically all mechanisms related to primary and secondary ischemic damage. For example, reducing infarct sizes by blocking the *N*-methyl-D-aspartate (NMDA) receptor (which is not found on cells of the immune system) via a reduction of tissue damage also leads to a reduction in secondary release of inflammatory cytokines or an influx of leukocytes into the affected hemisphere [20].

Resolution of Inflammation

Research on inflammation after brain lesion is highly focused on the mechanisms which induce and maintain inflammation, as well as its effects on tissue damage, protection, and repair. Surprisingly, little attention is devoted to the question how inflammation is terminated, and homeostasis is reestablished. This is achieved by an active, highly regulated process: resolution. In peripheral tissues, this process is well studied, and chemical mediators of resolution have been identified [21]. Resolution failure leads to chronic inflammation, with increased tissue injury and scarring. In the partially immune privileged CNS, resolution after injury may differ from other organs, and inflammation may in part be nonself-limiting [22]. Very little is known about resolution of inflammation after stroke and brain trauma, a field which deserves further inquiry as resolution agonists may be attractive therapeutics.

Open Issues and Future Challenges

Research of the last decades has clearly demonstrated that immunological responses to acute injury of the brain play an important role for tissue damage, protection, and repair. This research has also unraveled striking complexities in the interaction of brain and immune system: simple dichotomies, categorizing specific cells or responses as "good" or "bad" are no longer helpful [23]. We are beginning to understand the functional diversity of immune responses, which are highly context dependent. Numerous open issues remain (Table 1.1). The chapters of this volume explore these complex responses and the biological contexts in which they occur. They will also highlight a number of novel targets to inhibit secondary damage after stroke, brain trauma, or spinal cord injury. These targets include the induction or blockade of cytokines, subsets of cells of the innate and adaptive immune system, or pathways of communication between brain and immune system, such as the sympathetic and parasympathetic nervous systems.

Table 1.1 Exemplary open issues regarding immune responses to brain injuries

Can beneficial and detrimental effects of inflammation be disentangled? How can we noninvasively stratify patients to immunomodulatory therapies?
What is the role of specific types of T cells after brain injury? What is the role of antigen? If antigen presentation is needed, where does it occur? How can T cells damage neurons or regenerate neuronal function?
Does anti-inflammatory therapy affect the glial scar?
What are the sources of specific cytokines measured after brain injury in the blood?
Is immunodepression after brain injury an adaptive response? If so, does blocking it potentially exacerbate autoimmunity after brain injury?
Can adaptive immunity selectively be manipulated to protect or regenerate the brain?
How do comorbidities and aging affect immune responses after brain injury?
How do immune responses after stroke affect angio-, vasculo-, and neurogenesis?

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Chapter 2
The Critical Roles of Immune Cells in Acute Brain Injuries

Peiying Li, Yu Gan, Leilei Mao, Rehana Leak, Jun Chen, and Xiaoming Hu

Abstract Acute brain injuries elicit prompt and robust immune responses characterized by the activation of local glial cells and mobilization of peripheral leukocytes. The activation of immune cells originally aims to clear the brain of cellular debris and promote brain repair; however, the immune system can also propel and propagate neuronal cell death when overactivated. Understanding the function of each type of immune cells in the acute brain injuries and their mechanisms of action promises to unveil effective immunomodulatory therapies that beneficially regulate post-injury immune responses. In this chapter, we discuss in detail how immune cells are recruited and/or activated in the injured brain and how they contribute to the evolvement of brain damage.

Introduction

A pivotal role of immune responses in the pathogenesis of acute brain injuries has emerged in recent years. Once an injury occurs, the brain and the immune system influence each other in specific and profound ways. Bidirectional or reciprocal neuro-immune communication presumably evolved to clear the brain of infections and dead cellular debris. However, in addition to its essential role in protecting the organism from harmful microbes and the necrotic spillage of intracellular contents, the immune system can also propel and propagate neuronal cell death when overactivated. In order to elicit activation of the immune system, injured neurons and other central

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