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Short communication

Protective autoimmunity and protein localization

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ABSTRACT

The influence of the immune system was originally thought to be harmful regarding injuries and infarctions of the brain. Recently, there has been increasing evidence for the protective, positive effects of cells of the immune system on brain tissue. From an evolutionary biology standpoint, this hypothesis is more compelling than viewing the immune system only as a harmful influence. Herein we emphasize how physiological activation of immune cells following tissue damage and/or by infarcts of brain tissue can lead to an activation of T-lymphocytes. These activated T-lymphocytes are then regarded to perform several protective effects.

1. Introduction

For a long time, the influence of the immune system on the healing process of damage to the central nervous system (CNS) was regarded to be harmful. Lately, according to Schwartz et al., this problem is more differentiated (Moalem et al., 1999; Yoles et al., 2001). Thus, it is now generally accepted that the influence of the immune system on CNS traumatic damage and ischemia of the CNS is quite beneficial and neuroprotective (Moalem et al., 1999; Yoles et al., 2001). In these instances, activation of the immune system is caused by self-tissues. Thus, we are speaking of protective autoimmunity, even if it is so far unclear how and why it results in the activation of mainly T-lymphocytes of the immune system. Nevertheless, the group led by Professor Schwartz impressively showed that this activation of T-cells is beneficial and neuroprotective, resulting in less damage (Moalem et al., 1999). In the following sections, we emphasize that these results fit very well with the results of further studies by the author, where we demonstrate that activation of T-lymphocytes results from self intracellular proteins being released and coming into contact with self T-lymphocytes. To that extent, the work of Professor Schwartz's group and the work quoted here complement each other and can obtain a good picture of the processes, resulting in damage to the CNS by trauma or ischemia.

2. Theory

Protective autoimmunity is a concept in which cells of the immune system contribute to maintenance of the completeness of tissue function or facilitate tissue repair following injury. As such, the concept of protective autoimmunity was first described by Professor Michal Schwartz of the Weizmann Institute of Science in Israel. Schwartz et al. documented a beneficial role of autoimmune T-lymphocytes in the repair and follow-up of injury to the central nervous system (CNS). Experimental set-ups of different CNS pathologies made the most investigations to this phenomenon of protective autoimmunity. Within the immune system two cell types exist, T- and B-lymphocytes, which can react with specific antigens and acquire immunological memory. The activity of the immune system is important in the defense against pathogens. Cells of the immune system, which react to self-antigens, are called autoimmune cells. The activity of autoimmune cells is often designated in the context of autoimmune diseases as a pathological condition, caused by an overwhelming activity of autoimmune T-cells. Furthermore, it is possible to bring a substantial quantity of T-lymphocytes and/or antibodies from one ill animal to a healthy animal and to transfer certain diseases. Similarly, autoimmune diseases can be acquired by the transmission of autoimmune T-cells or antibodies.

In a 1999 study of Schwartz and colleagues, it could be shown that the same autoimmune T-cells that provoke experimental autoimmune encephalomyelitis (EAE) are also linked to and are able to protect injured CNS tissue versus a secondary degeneration, often following trauma (Moalem et al., 1999). A further experiment showed that after partial injury of the optic nerve in rats, if activated T-cells were injected (activated against MBP), functional, intact new nerve cells were formed. Rats, which were injected with activated T-cells, were better protected against injury than those injected with T-cells activated for other specific antigens. These discoveries indicated that at least under certain circumstances, autoimmune activity could have favorable effects. Autoreactive T-cells can be favorable by protecting injured neurons against the spreading of traumatic and ischemic damage. Additional work by the Schwartz group has shown that protective autoimmunity is a naturally occurring physiological

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phenomenon—taking place in the CNS following injury (Yoles et al., 2001). Mice lacking T-cells (called SCID mice), able to recognize CNS antigens, exhibit reduced levels of neural survival after CNS injury in relation to normal wild type mice. On the other hand, MBP T-cell receptor over expressing mice, which were genetically constructed, showed an increased rate of neural survival after CNS injury. These experiments were also carried out with animal models of back injury (Hauben et al., 2000, 2001), brain injury (Kipnis et al., 2003); glaucoma (Bakalash et al., 2003), stroke and ischemia (Frenkel et al., 2003; Ziv et al., 2007), neuronal degeneration (Angelov et al., 2003), Alzheimer's disease (Frenkel et al., 2005; Butovsky et al., 2006) and Parkinson (Laurie et al., 2007). The importance of immune cells and in particular T-cells, recognizing CNS antigens in acute and chronic neurodegenerative conditions, is still not totally understood. T-cells, recognizing CNS antigens, were also shown to be important for maintaining the complete function of the adult CNS under normal non-pathological conditions. Immune insufficient mice and mice lacking T-cells, which recognize brain antigens, also had more impairments in spatial learning and in memory and had reduced levels of cell renewal in the hippocampus and in other brain structures (Kipnis et al., 2004; Ziv et al., 2006a,b). This immune response, taking place after a CNS injury, involves a cascade of molecular and cellular events, which finally results in a function that protects the CNS of the organism. Immediately after CNS injury, there is a local immune response (Hanisch and Kettenmann, 2007). Microglial cells mainly provide this response. Phagocytes and CD4+ T helper cells, specifically activated by autoantigens, are also shown to arrive at the site of injury and to interact with affected microglial cells. The characteristics of the antigen cells determine the profile of the following T-cell response. The interaction between T-cells and the microglia results in the production of inflammatory cytokines and chemokines.

Immune cells, arriving at the damaged area, prevent the spread of the damage by absorbing excessive levels of toxic transmitters such as glutamate and by producing growth factors such as insulin like growth factor-1. In this way, they prevent neural death (Butovsky et al., 2005) and stimulate axonal growth (Rapalino et al., 1998). Additionally, those chemokines, which are produced at the area of injury, attract endogenous stem cells and progenitor cells that can help repair the CNS by employing a source of new neurons and glial cells and by limiting the local immune response through a negative feedback mechanism. This is the mechanism known up to now by which protective autoimmunity maintains the completeness of function of the brain. One further model suggests that CNS-specific autoimmune T-cells constantly circulate through the cerebrospinal liquid (CSF) to dendritic cells, which are located at the choride plexus and the meninges (Schwartz and Ziv, 2008). One of the most important autoimmune regulating mechanisms is the suppression of T-cells through regulatory T-cells (T reg cells), which limit autoimmune activity (Shevach, 2000). Experiments in animal models of CNS injury show that depletion of regulating T-cells led to an increased neuroprotective autoimmune response (Kipnis et al., 2002). However, such an increase of autoreactive T-cells can develop susceptibility for autoimmune diseases at the same time (McHugh and Shevach, 2002). Stem cells and progenitor cells were also confirmed to serve to modulate immune activity (Pluchino et al., 2005; Ziv et al., 2006a,b).

Thereby the hypothesis of protective autoimmunity contrasts the thesis, “Horror autotoxicus,” by Paul Ehrlich. The neuroprotective effect of autoreactive T-cells has been experimentally confirmed by different groups:

- Carson et al. demonstrated that microglial cells regulate the activity and reaction of T-lymphocytes and monocytes and thus steer neuroprotective effects (Carson et al., 2006). Their work was based on the assumption of a neuroprotective effect of cerebral T-cells, which they confirmed experimentally.
- Chen et al. found that certain CD8+ T-cell subtypes modulate and suppress experimental autoimmune encephalitis (EAE) in an animal model (Chen et al., 2009).
- In a rat model of optic nerve crush, Johnson et al. found that CD4 and CD25 double-positive T-cells turned out to be suppressed after nervous lesion set to the optic nerves, while CD4-positive and CD25-negative T-cells turned out to be activated in this model. Due to this differentiated pattern of activation, a neuroprotective effect can be achieved (Johnson et al., 2007).
- Hofstetter et al. showed that after induction of autoimmunity by myelin oligodendrocyte protein (MOG) and subsequent aseptic cerebral injury (ACI) in a mouse model, a neuroprotective reaction developed. The authors noted that only additional immunization against bacterial antigens, such as pertussis toxin (PTX), led to nerve-damaging reactions of the immune system (Hofstetter et al., 2003).
- Garg et al. performed in vitro experiments to clarify the mechanism of T-cell-mediated neuroprotection. In addition to T-cells, astrocytes appear to play an important role. These cells, cocultured with T-cells, led to a decrease in glutamate levels and an increase in neuroprotective thioles (Garg et al., 2008).

Furthermore it is notable that in recent times, cerebral T-cells have been highlighted in the context of brain function and cognition (Kipnis et al., 2008). This remarkable connection is supported by the clinical observation that dysfunction of the immune system (in particular, of T-lymphocytes) frequently accompanies impairments of the brain. Thus, (1) the aged brain leads to both immune weakness and dementia, and (2) HIV primarily a disease of CD4 T-lymphocytes of the immune system also can affect brain function (so-called HIV encephalopathy). Similarly, a connection between T-cells and brain function can be recognized with the so-called “chemo-brain” (3): during intensive immunosuppressive chemotherapy, frequently cognitive impairment develops in the patient concerned. Furthermore in animal experiments, bone marrow as well as T-lymphocyte transfers from unaffected wild-type mice into impaired (irradiated) mice induced positive effects with regard to cognitive brain function (Kipnis et al., 2008).

However, none of these concepts or experiments until now has been able to explain why autoreactive T-cells exist and why they expand in cases of neuronal damage, yet these phenomena could be well explained by a theory of the author. According to this theory, intracellular proteins should be immunogenic via the major histocompatibility complex II (MHC II) and should subsequently lead to CD4 T-cell activation (Arneth, 2004; Arneth, 2008; Arneth, 2009). In cases of neuronal damage (traumatic damage as well as ischemic damage), cells should die via necrotic processes. As such, many intracellular proteins should be released, leading to an activation of immune cells as described (Arneth, 2004, 2008, 2009). Overall, this theory and its findings fit very well with the neuroimmunologic findings described above.

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