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Review article

T cells in the post-ischemic brain: Troopers or paramedics?

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ABSTRACT

The immune system is intricately involved in brain development and physiological neuronal function. The influence of the adaptive immune system on several brain diseases has been described in great detail. In ischemic stroke, numerous studies have particularly demonstrated a key role for T cells during the acute phase after the brain injury. Recently, a critical role for T cells has also become more evident for the chronic phase after stroke in modulating delayed neuronal (dys-) function and recovery. Here, T cells may also affect various non-immunological pathways by interacting with brain-resident immune cells and modulating mechanisms such as neurogenesis and angiogenesis. This novel concept suggests T cells as potential therapeutic targets to modulate post-stroke regeneration.

1. T cells in health

1.1. T cell subpopulations and their polarization states

T lymphocytes are part of the adaptive immune system and are divided in several subtypes depending on their functional properties, which is experimentally most widely determined by their transcriptional profile, expression of subset-specific surface markers and the cytokine secretion profile. T cells are divided in two large subpopulations—CD8+ cytotoxic T cells and CD4+ T helper (Th) cells. The former can act directly via cell-cell interaction dependent cytolytic pathways, involving the perforin-granzyme effector mechanism (Stenger et al., 1998). CD4+ Th cells have mainly indirect effector function and are able to induce proliferation of other immune cells. CD4+ Th cells are a very dynamic cell population that are able to polarize into different effector and regulatory subtypes. Terminal polarization depends on a cascade of three key signaling events that Th cells receive both from innate and adaptive immune cells: antigen-presentation, co-receptor stimulation and cytokine signaling. Interferon-gamma (IFNγ) and Interleukin (IL) -12 signal can induce the pro-inflammatory Th1 subtype (Hsieh et al., 1993; Scharton and Scott, 1993) which are characterized by secretion of the pro-inflammatory cytokine IFNγ. In contrast, polarization of Th2 cells—have a critical role in the pathophysiology of allergy—is mainly driven by IL-4 (Min et al., 2004; Shinkai et al., 2002). Over the past decade a substantial variety of other CD4+ subtypes has been described, from which pro-inflammatory Th17 cells and regulatory T cells (Treg) are the best characterized and with direct implications for neuroinflammatory diseases. Th17 cells are polarized in the presence of IL-23 and characterized by their signature cytokine IL-17 in addition to other pro-inflammatory cytokines such as IL-6 and TNF-α (Langrish et al., 2005; Weaver et al., 2006). In contrast, CD4 + CD25 + Foxp3+ Treg play a key role in self-tolerance by suppressing autoreactive T cells under physiological conditions by secretion of the anti-inflammatory molecules IL-10, CTLA-4 and TGF-β, in addition to other cell-cell contact dependent mechanisms (Sakaguchi, 2000; Sakaguchi et al., 2008; Fontenot et al., 2003). Considering the diversity of the different T cell subsets, their complexity enables them to play a role in many physiological and pathological processes including stroke.

1.2. The role of T cells in physiological brain function

In contrast to the still prevailing concept of the brain as an immune-privileged organ, several recent studies have unequivocally demonstrated constant surveillance of the brain by patrolling lymphocytes and particularly T cells. T cell migration to the healthy brain has been shown to be critical in maintaining physiological function and plasticity (Ziv et al., 2006; Kipnis et al., 2004; Lewitus et al., 2009). T cells enter the non-inflamed brain via trans-endothelial migration at post-capillary venules as well as enter the subarachnoid and perivascular space (Engelhardt and Ransohoff, 2005). However, lymphocytes are rarely found in the brain parenchyma itself and thus less is known on how they interact with brain resident cells under healthy conditions. Brain-patrolling T cells interact bi-directionally with several brain-resident

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cell populations during brain surveillance even if no overt inflammatory condition is present (Bartholomäus et al., 2009): APCs present antigens from the brain parenchyma on MHC-II molecules to T cells (Engelhardt et al., 2016). Consequently, APC-T cell-interaction can lead to the reactivation of T cells if their cognate antigen is presented by the APC (Kivisakk et al., 2009). Missing antigen recognition has been reported to terminate cerebral T cell patrolling and induce T cell egress via the CSF to cervical lymph nodes (Goldmann et al., 2006) without entering the parenchyma (Engelhardt and Ransohoff, 2005). By this mode of antigen-specific brain surveillance, the turnover of lymphocyte population presented in the brain and surrounding structures occurs almost twice a day (Engelhardt and Ransohoff, 2005). Some T cells, mainly CD4+ effector memory T cells, can reside in the choroid plexus with receptors specific for CNS antigens (Baruch et al., 2013) and provide a cell pool for immediate immune reactions. On the other side, T cells can affect microglial, astrocyte and potentially neuronal function by secreted molecules as well as cell-cell contact-dependent mechanisms; however, the cellular targets and direct consequences of T cell interactions in the healthy brain are still insufficiently understood. The choroid plexus contains large numbers of T cells also under physiological conditions and thereby provides a cell pool for immediate T cell-driven immune reactions after brain injury (Llovera et al., 2017).

T cells have been shown to promote hippocampal neurogenesis by secretion of brain-derived neurotrophic factor (BDNF) (Ziv et al., 2006; Wolf et al., 2009). In accordance with the critical role of T cell for healthy brain function, immunodeficient mice show deficits in spatial memory tasks and altered social behavior (Kipnis et al., 2004; Wolf et al., 2009; Filiano et al., 2016). However, the detailed mechanism by which T cells cause this impact is insufficiently known. Previous reports have associated cytokines—which can be derived from T cells but also other immune cell subtypes—such as IFNγ, IL-6 and IL-4 to the above-mentioned behavioral and structural effects (Filiano et al., 2016; Derecki et al., 2010; Balschun et al., 2004; Filiano et al., 2017). Further research for the analysis of T cell mechanisms in brain homeostasis are required to identify potentially novel targets of T cell-mediated pathologies in a variety of brain disorders.

2. Post-stroke neuroinflammation

2.1. Overview of dynamics of leukocyte infiltration after cerebral ischemia

Acute brain ischemia leads to sterile neuroinflammation attracting both local and systemic immune cells to the lesion site. Microglia are instantly activated by inflammatory cues released by stressed or dying neuron; in consequence, microglial cells generate a pro-inflammatory milieu by secretion of cytokines and chemoattractant molecules which then drive the recruitment of circulating lymphocytes to the damaged brain (Kuric and Ruscher, 2014; Iadecola and Anrather, 2011; Yilmaz and Granger, 2008). The dynamics of leukocyte recruitment to the brain differs substantially for different cell types of circulating leukocytes (Gelderblom et al., 2009). After stroke, invading macrophages appear within minutes to hours after ischemia at the lesion site (Gelderblom et al., 2009; Schilling et al., 2003). Thereafter, the number of invading neutrophils peaks at three days post infarct (Gelderblom et al., 2009). Their presence persists at least until day seven and declines afterwards (Gelderblom et al., 2009). In contrast, T cells migrate preferentially to the lesion borders, increase in cell number of several days after ischemia (Jander et al., 1995) and can be detected throughout at least 30 days post infarct in the brain parenchyma (Stubbe et al., 2013). More specifically, CD8+ cytotoxic T cells have been detected to invade the post-ischemic brain as the first T cell subpopulation already within hours after stroke onset (Chu et al., 2013). CD4+ and Natural Killer T cells are following approximately 24 h after ischemia (Chu et al., 2013). In contrast, Treg cells invade the brain only with a delayed kinetic several days after brain ischemia but are still present in significant cell counts more than 30 days post lesion (Stubbe et al., 2013).

2.2. The impact of T cell subsets in the acute phase

T cells play a crucial role in secondary stroke progression (Iadecola and Anrather, 2011; Gill and Veltkamp, 2016; Chamorro et al., 2012) albeit representing only a very small subpopulation of brain-invading leukocytes - about 3000 T cells compared to 65,000 neutrophils per hemisphere (Gelderblom et al., 2009). Transgenic mice deficient of lymphocytes have been consistently demonstrated to have smaller lesions after transient and permanent middle cerebral artery occlusion (MCAO) compared to immunocompetent control animals (Liesz et al., 2009; Liesz et al., 2011; Kleinschnitz et al., 2010; Yilmaz et al., 2006; Hurn et al., 2007; Subramanian et al., 2009). Further, restoring the lymphocyte population in such immunodeficient animals by adoptive cell transfer of splenocytes reversed the protective effect, resulting in infarct volumes comparable to wildtype (WT) animals (Yilmaz et al., 2006). Finally, antibody-mediated depletion of single T cell subsets, namely CD8+, CD4+ and γδ T cells, likewise attenuated secondary lesion progression (Liesz et al., 2011; Mracsko et al., 2014; Shichita et al., 2009; Gelderblom et al., 2012). Surprisingly, amelioration of stroke outcome due to T cell-targeted therapies was consistently detected as early as within the first day after experimental stroke. This is in conflict for the time-consuming process of antigen-driven stimulation and clonal expansion of T cells in the context of antigen-specific T cell activation and has therefore driven the predominant concept of T cell responses after stroke being antigen-independent at least during the acute phase after stroke (Kleinschnitz et al., 2010).

However, other studies reported marked clonal expansion of T cells in the brain and also peripheral, secondary lymphatic organs using spectratype analyses within the first week after stroke (Liesz et al., 2013a). Additionally, antigen-dependent activation of CD8+ cytotoxic T cells was associated with their increased invasion to the lesion site and secretion of neurotoxic substances such as granzymes and perforin (Mracsko et al., 2014). γδ T cells and to a lesser extent Th17 harm the peri-lesional tissue at risk by secretion of IL-17 (Shichita et al., 2009) which peaks at day three post lesion (Lin et al., 2016). Correspondingly, γδ T cell-deficient mice have reduced infarct volumes (Shichita et al., 2009). Moreover, neutralization via IL-17-specific antibodies also significantly improved stroke outcome (Gelderblom et al., 2012). Interestingly, a second peak in IL-17 expression has been described to occur in the late phase around day 28 after stroke (Lin et al., 2016). At this late time point mainly reactive astrocytes secreted the cytokine and might in this context improve neurogenesis in contrast to the rather detrimental function during the acute phase (Lin et al., 2016). This example of a potentially opposing function of a specific cytokine—pro-inflammatory functions of IL-17 in the acute phase and potentially pro-regenerative capacities in the later stages—highlights the complexity of the adaptive immune response after stroke (Fig. 1). In contrast to the above-mentioned pro-inflammatory Th subsets, Foxp3+ Treg have been identified to limit an overshooting immune response after stroke (Liesz et al., 2009). Despite still some controversies derived from single studies (Kleinschnitz et al., 2013), a large number of reports have by now verified a protective function of this cell type on parenchymal post-stroke neuroinflammation (reviewed in detail in (Liesz et al., 2015)). IL-10 has been identified as the key mediator of Treg in facilitating their neuroprotective function (Na et al., 2015; Liesz et al., 2013b). Accordingly, intraventricular IL-10 injection reversed the effect of Treg depletion (Liesz et al., 2009). IL-10 is an anti-inflammatory cytokine which acts via inhibiting IL1-ß and TNF-α. In addition to its main immunological functions, IL-10 can mediate multiple effects on several biological functions and is changing gene-expression by down-regulating over 300 genes with most of them associated to the inflammatory pathway (Liesz et al., 2014). In addition, Treg might also affect BBB integrity during acute stroke. Adoptive Treg transfer has been associated with inhibition of MMP-9 activity and as a consequence

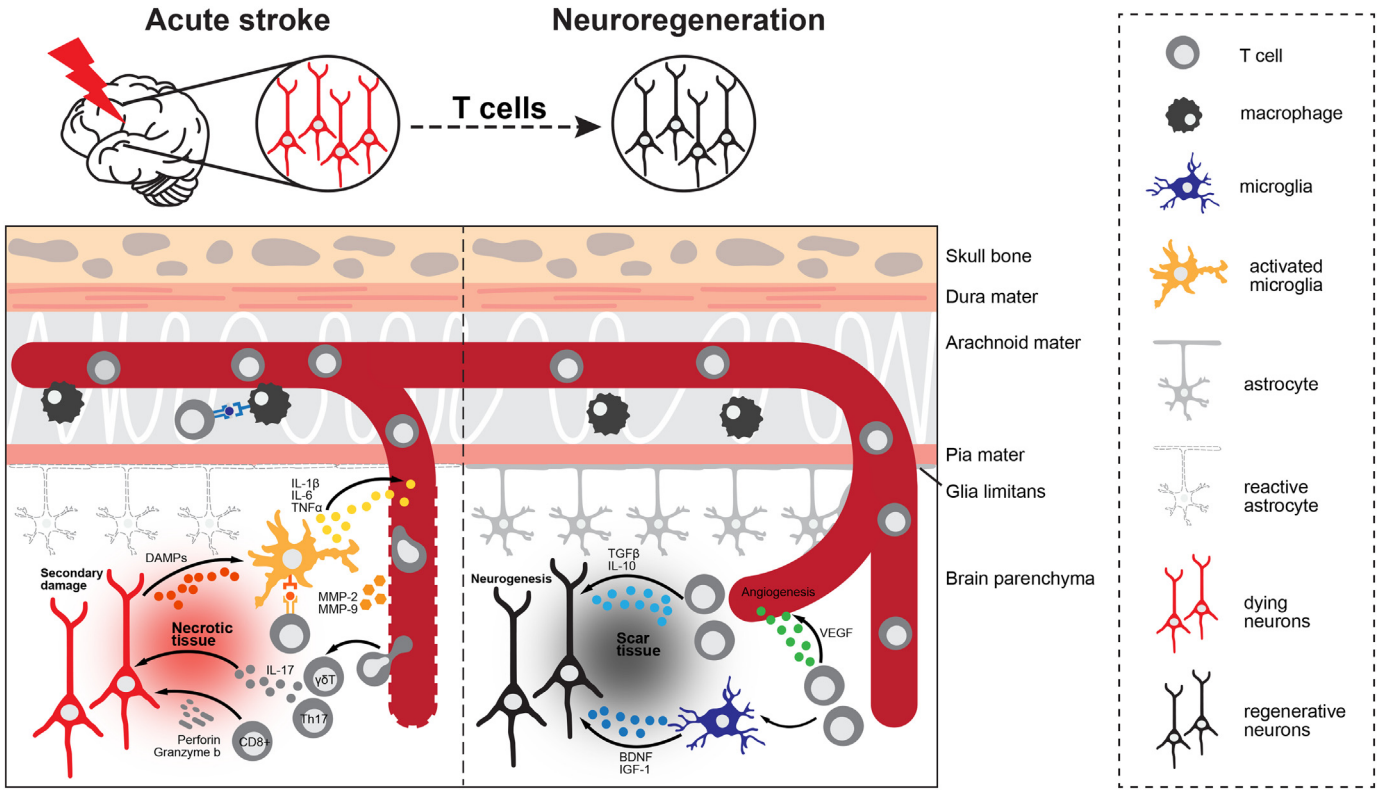

Fig. 1. Functional role of T cells in the acute phase and regeneration phase after stroke. a) In the acute phase after stroke, necrotic cells release DAMPs which activate local microglia. Activated microglia secrete cytokines and chemoattractants facilitating T cell entry to the lesion site. T cells promote exacerbation of neuroinflammation and increase secondary cell death. b) Possible roles of T cells in recovery after stroke. T cells are involved in several processes involved in tissue regeneration such as neurogenesis, angiogenesis and axonal outgrowth.

protection of the neurovascular unit integrity (Li et al., 2014). Taken together, Tregs play a central role in limiting the detrimental impact of neuroinflammation after stroke and oppose the predominantly detrimental function of pro-inflammatory T cell subpopulations during the acute phase after stroke (reviewed in greater detail in (Liesz et al., 2015; Liesz and Kleinschnitz, 2016)).

Additionally, T cells can influence the acute phase after stroke via crosstalk with microglia. Microglia—innate brain resident immune cells—can be differentially polarized to subpopulations with potentially different functions. This polarization state can be crucially influenced by T cells, whereas their polarization state can be modified via microglia in turn. Th1 cells secrete proinflammatory cytokines, such as IFN-γ, which promote microglia polarization towards a proinflammatory type and might increase secondary ischemic damage (Chabot et al., 2001). These proinflammatory microglia produce IL-12, TNF-α, etc. and stimulate Th1 polarization which is able to enhance the proinflammatory state. This putative crosstalk between T cells and microglia is discussed in detail in (Wang et al., 2016).

3. T cells in regeneration

T cells have multiple effects on other cell populations which are known to play a major role in regeneration after stroke. In the following, we will focus on the direct effects of T cells on some of the key mechanisms proposed to be involved in post-stroke regeneration.

3.1. T cells in post-stroke neurogenesis

Neurogenesis in the adult brain is limited to only few specialized localizations, namely the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus (Gage, 2000; Lois and Alvarez-Buyiia, n.d.; Kriegstein and Alvarez-Buylla, 2009). After stroke, neural precursor cells (NPC) have the ability to migrate to the lesion site (Parent et al., 2002; Arvidsson et al., 2002). Proliferation, migration and differentiation of NPC are substantially influenced by immune cells, including T cells. Vice versa, NPC might play a role in modifying the post-ischemic immune response (Einstein et al., 2003; Martino and Pluchino, 2006). Under physiological conditions, T cells have been demonstrated to affect neurogenesis and cerebral cell turnover rate (Schwartz and Shechter, 2010). After brain injury, T cells can get in direct physical contact with NPC and interact with their function (Kokaia et al., 2012). Similar to the acute phase after stroke, different T cell subsets seem to have opposing functions during recovery, in particular on NPC proliferation and differentiation. T cell deficiency, both in transgenic mice and by CD4-specific antibody-mediated cell depletion, was associated with reduced apoptosis and increased proliferation rates of NPC in a cortical lesion model (Saino et al., 2010). A specific subset of CD4+ T helper cells expressing the glucocorticoid-induced TNF receptor (GITR) has been identified to mediate this substantial impact of T cells on post-stroke neurogenesis (Takata et al., 2011). In contrast, Treg have been suggested to promote post-stroke neurogenesis. Treg depletion by CD25-specific antibodies resulted in a reduced number of NPC after experimental stroke (Saino et al., 2010). Correspondingly, increased Treg cell counts and secretion of their key cytokine IL-10 in the lateral ventricle of the ischemic brain hemisphere has been associated with increased NPC proliferation (Wang et al., 2015).

Besides direct effects on NPC proliferation, T cells might also indirectly affect NPC via their impact on glial cells such as microglia and astrocytes and thereby profoundly alter the cerebral micromilieu. Cytokines released from the different T cell subsets can activate and differentially polarize microglia depending on the secreted cytokine profile (Butovsky et al., 2005). In turn, activated microglia have been shown to have two main routes to influence neurogenesis: Studies using autoimmune encephalomyelitis models have shown that microglia are

able to secrete IGF-1, a growth hormone which reinforces NPC proliferation in general (Gudi et al., 2011). Additionally, they are in control of balancing oligodendrogenesis and neurogenesis. Activated via IL-4, microglia facilitate oligodendrogenesis albeit IFNγ shifts microglia towards a neurogenesis supporting polarization type (Butovsky et al., 2006). These concepts on the role of a potential "T cell – microglia – neuron/NPC" axis have been established in studies under physiological conditions or other brain diseases; whether the proposed mechanisms also affect regeneration after stroke is currently unknown.

3.2. T cells and axonal sprouting

Another essential process for neuronal repair is axonal sprouting. Studies in spinal cord injury demonstrated potential involvement of T cells in axonal outgrowth (Nielsen et al., 2011). In vitro experiments underscore their influence on sprouting, but again different subsets play distinct roles: CD4+ Th cells can enhance axonal growth, whereas CD8+ cytotoxic T cells might impair this process (Pool et al., 2012). So far, the impact of T cells on axonal outgrowth has not been investigated in animal stroke models. Yet, better understanding of T cell-driven mechanisms in neuronal plasticity and their impact on regeneration after stroke might open new therapeutic targets for stroke patients.

3.3. T cells and angiogenesis

Angiogenesis is a critical mechanism in the restoration of injured tissue. After stroke, endothelial cells proliferate and immature vessels begin to outgrow to regions with stimulatory signal (An et al., 2014). There is a wide variety of factors sustaining vascular growth which can be secreted by different cell types including T cells. The influence of T cells on angiogenesis has been studied in various experimental models of organ ischemia and ischemia/reperfusion injury. It was shown in a model of hind limb ischemia that the presence of CCR7+ T cells is beneficial for effective arteriogenesis (Nossent et al., 2017). In tumor and lung ischemia, pro-inflammatory Th1 cells have been proposed to inhibit vascular outgrowth while anti-inflammatory Treg were associated with increased angiogenesis (Albini et al., 2000; Zhong et al., 2016). In contrast, anti-inflammatory Treg promote angiogenesis not only by suppressing the impact of effector T cells (Zhong et al., 2016) but also by secreting chemokines, the proangiogenic vascular endothelial growth factor (VEGF) and TGF-β (Facciabene et al., 2011; D'Alessio et al., 2015). In accordance with these findings, Treg-derived TGF-β signaling is known to be essential for vascular development during embryogenesis (Larsson et al., 2001). Furthermore, T cell-derived IL-17 was shown to facilitate neovascularization of the rat cornea and promote chemotactic function in tumor vascularization by upregulation of proangiogenic factors (Numasaki et al., 2003). The named mechanisms of T cells which regulate angiogenesis in a variety of disease models have so far not been investigated in ischemic stroke. However, in light of the important function of angiogenesis in restoration of tissue function, further investigations on the specific role of T cells in these processes will be of high relevance.

4. Conclusion and outlook

The presence of T cells is critical in physiological brain function. A large body of evidence over the past decade has highlighted a key role for T cells in the pathophysiology of stroke in the acute phase. Within the first days after stroke, pro-inflammatory T cell subpopulations play a detrimental role and contribute to the exacerbation of neuronal damage. In contrast, immunosuppressive Treg cells are beneficial for stroke outcome by limiting the inflammatory collateral damage. While the role of T cells in the acute and subacute phase after stroke has been extensively investigated, the contribution of T cells to the chronic regenerative phase is so far barely understood. Nevertheless, results from basic research on T cell-brain interaction and studies in other disease models have indicated a potential role for T cells in several key pathways involved in tissue regeneration such as neurogenesis, angiogenesis and axonal plasticity. Unfortunately, experimental stroke research has so far nearly completely ignored these potential clinical implications of T cells for post-stroke recovery in the chronic phase. T cells not only open up a new field of research by extending the therapeutic window of opportunity into the chronic regenerative phase, these cells also represent ideal drugable targets by being activated and polarized in the peripheral immune compartment; hence, future studies to potentially modulate T cells in order to promote their pro-regenerative function would circumvent obstacles of drug delivery to the CNS via the blood-brain barrier or difficulties of target specificity. Therefore, further studies particularly testing the function and potential therapeutic modulation of T cells in post-stroke recovery are urgently needed for the development of novel therapeutics to improve the recovery of stroke patients.

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