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Sex differences in stroke across the lifespan: The role of T lymphocytes

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ABSTRACT

Stroke is a sexually dimorphic disease. Ischemic sensitivity changes throughout the lifespan and outcomes depend largely on variables like age, sex, hormonal status, inflammation, and other existing risk factors. Immune responses after stroke play a central role in how these factors interact. Although the post-stroke immune response has been extensively studied, the contribution of lymphocytes to stroke is still not well understood. T cells participate in both innate and adaptive immune responses at both acute and chronic stages of stroke. T cell responses also change at different ages and are modulated by hormones and sex chromosome complement. T cells have also been implicated in the development of hypertension, one of the most important risk factors for vascular disease. In this review, we highlight recent literature on the lymphocytic responses to stroke in the context of age and sex, with a focus on T cell response and the interaction with important stroke risk factors.

Contents

Abbreviations: ACE2, Angiotensin convert enzyme 2; AIS, arterial ischemic stroke; Ang-II, Angiotensin II; APCs, antigen presenting cells; AT2R, Angiotensin II receptor; BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; Breg, B regulatory cells; CNS, Central nervous system; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DAMPS, Damage associated molecular patterns; EAE, Experimental Autoimmune Encephalomyelitis; ER, Estrogen Receptor; FCG, Four core genotype; HIE, hypoxic–ischemic encephalopathy; HT, hormone therapy; HTN, Hypertension; IFNy, Interferon γ; iCOS, Inducible T-cell co-stimulator; IL, interleukin; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; MHC-II, major histocompatibility complex II; OC, oral contraception; PAMPs, Pathogen associated molecular patterns; PBMC, Peripheral blood mononuclear cells; PCOS, poly-cystic ovary syndrome; PE, pre-eclampsia; PMA/Io, phorbol 12-myristate 13-acetate/ Ionomycin stimulation; PPAR, peroxisome proliferator-activated receptors; ROS, reactive oxygen species; TCR, T cell receptor; TGF-β, transforming growth factor β; TLR, Toll-like receptor; TNF, Tumor necrosis factor; Treg, T-regulatory cells; vWF, von Willembrand factor; XCI, X-chromosome inactivation.

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1. Introduction

Stroke is the fifth leading cause of death (Murphy et al., 2015) and the most common cause of disability (Roger et al., 2011) in the United States. The economic burden of stroke was $33.0 billion in 2013 (American Heart Association Statistics Committee and Stroke Statistics Subcommittee, 2015), making the prevention and treatment of stroke a critical public health issue.

Stroke is a disease that exhibits sexual dimorphism throughout the lifespan (Mallick & O'Callaghan, 2010) (Niewada et al., 2005; Appelros et al., 2009). Accumulating data from both the laboratory and clinical studies have shown that sex differences in stroke are highly dependent on age and hormonal status (Liu and McCullough, 2012). It is widely accepted that estrogen, one of the most important female gonadal hormones, is neuroprotective and contributes to the "female resistant" stroke phenotype seen in women throughout most of the lifespan. Intriguingly, neonatal boys have a higher stroke incidence and poorer long-term outcomes than girls suffering from stroke, conversely, elderly women have both a higher incidence of stroke and more detrimental sequela than age-matched men (Hurn et al., 2005; American Heart Association Statistics Committee and Stroke Statistics Subcommittee, 2015). Little is known as to why neonatal and geriatric stroke show such striking sexual differences, as circulating hormone levels are equivalently low at both ends of the age spectrum.

The immune system plays a critical role in stroke outcomes, during both the acute stroke event and long-term post-stroke recovery. Emerging data has shown that post-stroke inflammation is shaped by both sex chromosomes and gonadal hormones (Stamova et al., 2012; Liu and McCullough, 2012; Manwani et al., 2014; McCullough et al., 2016). The contribution of these factors appears to differ based on age, and a complex interaction between hormones and genetic factors has been recently recognized (McCullough et al., 2016; Manwani et al., 2013). T lymphocytes have been shown to play a significant role in the immune response to stroke. The involvement of estrogen in sex differences in stroke has been extensively reviewed (Ritzel et al., 2013; Pernis, 2007; Koellhoffer and Mccullough, 2013). In this review, we will focus on the T-lymphocyte response to stroke as a possible contributing factor to the sexual dimorphism seen in stroke outcomes across the lifespan.

2. The importance of T cells in the immune response to stroke

Inflammatory responses to stroke are initiated by multiple mediators both inside the affected vessel and within the ischemic parenchyma (Kim et al., 2016), a process involving microglial activation and leukocyte aggregation, adhesion and migration into the injured brain. Monocytes, neutrophils and lymphocytes that are recruited into the brain collaborate with microglia to exacerbate the inflammatory responses. The principal inflammatory mechanisms of stroke are summarized in Fig. 1 (for a comprehensive review see (Benakis et al., 2016)).

One of the important components of the immune response to stroke is the activation of T lymphocytes that participate in both the innate and adaptive immunity. T lymphocytes have a crucial role in the immunopathology of ischemic stroke and have been shown to have both pro- and anti-inflammatory functions (Gagliani and Huber, 2017), contributing to brain damage as well as functional recovery after stroke (Wang et al., 2016b). In stroke, T cells are classically activated by specific pathogens or antigens presented on antigen presenting cells (APCs), acting as a major driver of the adaptive immune response. However, evidence also shows that certain classes of naïve T cells can also respond to the inflammatory milieu by secreting reactive oxygen species (ROS) and inflammatory cytokines in an antigen-independent manner, contributing to the early, innate immune response (Unutmaz et al., 1994). Traditionally, two main types of T cells have been recognized, divided by their different effector actions. Cytotoxic T cells ($CD8^+$ T Cells) can destroy infected cells by cytotoxic mechanisms, and Helper T cells ($CD4^+$ T Cells) can release cytokines to coordinate and modulate the adaptive and innate immune response. T cells of different subtypes have differential effects in inflammation and are summarized in Table 1 and the mechanisms by which T cells affect stroke are clarified in Fig. 2.

$CD8^+$ T cells not only exert a traditional cytotoxic effect in immunity but also have recently been shown to play a regulatory role via CD8 T-regulatory cells (CD8 Tregs; $CD8^+$ $CD122^+$). These cells secrete the anti-inflammatory cytokine IL-10 and have an important role in stroke immune tolerance and stroke outcome (Bodhankar et al., 2015a; Bodhankar et al. 2015b). However, the vast majority of experimental studies that have examined Tregs after stroke have only examined their function in young, male animals. B cells, which are the lymphocytes that secrete antibodies, also have important immunomodulatory effects. Specifically, B regulatory cells (B regs) participate in the suppression of immune responses by the secretion of IL-10, TGF-β and the expression of pro-apoptotic surface proteins (Berthelot et al., 2013). These cells have been shown to participate earlier than Tregs in inflammatory modulation. In a female mouse model of multiple sclerosis, estrogen treatment induced the differentiation of Bregs, promoting an anti-inflammatory response in microglia (Benedek et al., 2016). In the absence of Tregs, Bregs coordinated the immune responses in experimental autoimmune encephalomyelitis (EAE) replacing the Treg role (Subramanian et al., 2011).

Another type of lymphocyte implicated in the response to stroke is γδ T cell (Shichita et al., 2009; He et al., 2014). The γδ T cell subtype is characterized by the presence of different T cell receptor (TCR) chains than those found on classical $CD4^+$ and $CD8^+$ T lymphocytes (αβ TCR). γδ T cells can act as helper lymphocytes, and also express specific immune receptors, including Toll-like receptors (TLRs) and an invariant TCR that allows them to respond immediately after injury to pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs), giving γδ T cells innate immune-like features (Prinz et al., 2013). γδ T cells can also secrete IL-17, a pro-inflammatory cytokine that acts in concert with IL-23 to recruit monocytes and neutrophils to sites of inflammation. Neutralization of IL-17 reduced neutrophil infiltration and protected against ischemic stroke in murine models, but the sex of the animals was not specified, and all mice were young adults (Gelderblom et al., 2012). How the IL-17 signaling axis changes with age has not been well studied in experimental models, but recent evidence has shown that the IL-17 axis changes with aging in humans (Rawji et al., 2016). As the treatment with estrogen can upregulate IL-17 levels in activated splenocytes, future studies need to control for age and hormone status, especially in a disease like stroke, which primarily affects the elderly (Schmitt et al., 2013). γδ T cells can be activated by microglia through TLR-2, 4 and 9 *in vitro* (Derkow et al., 2015), and can be detected as early as 16 h in meninges after stroke (Benakis et al., 2016), where they may possibly coordinate the innate and adaptive immune responses. In humans, an imbalance of Th17 and γδ T cells, as well as an increase in their principal product IL-17, have been reported after stroke. This increase was due to a decrease in immunosuppressive Treg cells and their products, including IL-10 and TGF-β (Hu et al., 2014; Ruhnau et al., 2016).

Sex differences in the adaptive immune system have been recognized for many years. Estrogen has a significant impact on the function of immune cells, leading to dramatic immunological