18 Regional neural activation defines a gateway for autoreactive T cells to cross the blood-brain barrier.

Arima Y, Harada M, Kamimura D, Park JH, Kawano F, Yull FE, Kawamoto T, Iwakura Y, Betz UA, Márquez G, Blackwell TS, Ohira Y, Hirano T, Murakami M

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Luc Teyton, The Scripps Research Institute, CA, USA. F1000 Immunology

22 Feb 2012 | New Finding

10 EXCEPTIONAL

This remarkable paper describes how T cells access the central nervous system through the stimulation of a local arc reflex that triggers the local release of CCL20 by the blood vessels surrounding the fifth lumbar spinal cord.

The reflex that controls CCL20 secretion, and subsequent IL6 amplification loops, is a sensory circuit of the lower leg that can be turned on or off by soleus stimulation.

The findings are made in a mouse model of multiple sclerosis, the experimental autoimmune encephalomyelitis, but open a new gate for corresponding human studies. If a similar circuitry exists in man, this paper will be cited as a turning point.

Competing interests
None declared

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E Charles Snow, University of Kentucky Medical Center, KY, USA. F1000 Immunology

24 Feb 2012 | New Finding

8 MUST READ

Dogma maintains that the blood/brain barrier serves to limit the accessibility of immune cells into the central nervous system (CNS) so as to prevent unwanted or destructive immune-mediated responses which could cause either bystander damage or autoreactive lymphocyte-mediated CNS disease. This paper provides compelling data indicating that gateways for leukocyte entry into the CNS exist in the spinal cord and are regularly open, allowing the routine trafficking of leukocytes through the CNS.

The authors provide evidence for the existence of neuronal reflex arches initiated by sensory neurons emanating from voluntary skeletal muscles which alter the ability of endothelial cells of the spinal cord dorsal vessels to effectively transport immune cells across the blood/brain barrier. These reflex arches elicit production by the endothelial cells of at least 10 distinct chemokines, indicating the potential for multiple different leukocyte subsets being able to enter the CNS through these gateways. It will be necessary to extend these data by examining the adhesion molecules operative at such sites. These data also suggest that effector lymphocytes and myeloid cells routinely exit the vasculature at these sites for entrance into the CNS proper and that this may represent a CNS-protective mechanism not fully appreciated. Of course, and as the authors show, such gateways will also enable the free passage of autoreactive lymphocytes into the CNS. This is important because it negates the necessity of identifying how CNS-directed autoimmune diseases, such as multiple sclerosis, break down the blood/brain barrier.

Competing interests
None declared

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Tsutomu Takeuchi and **Hideto Kameda**, Keio University, Japan. F1000 Rheumatology & Clinical Immunology

27 Feb 2012

6 RECOMMENDED

The molecular mechanisms of the accumulation and infiltration of pathogenic T lymphocytes into the central nervous system (CNS) were demonstrated here. The gate is regulated by the local expression of chemokines through gravity, blood flow and neural activation, all of which forming a 'neuro-immune' circuit.

The induction of autoimmune diseases chiefly mediated by autoreactive T cells requires both the development of

autoreactive T cells and their accumulation in the specific organs/tissues. The latter is likely to be elicited by site-specific expression of chemokines. For example, the CCL20 production by inflamed synovial cells has been demonstrated to be critically involved in an arthritis model {1}. However, the initial event or baseline activity leading to the site-specific chemokine expression has not been identified so far. By studying the mouse model of multiple sclerosis known as experimental allergic encephalomyelitis, Arima et al. implicated the importance of constitutive site-specific expression of chemokines maintained by ordinary activity of muscles and neurons, which may be upregulated upon the injury to a specific site.

Moreover, the gate for leukocytes entering the CNS was identified as the fifth lumbar spinal cord, which could be sensoring the surroundings and tuning the response (chemokine expression) levels, resembling the baroreceptors. Thus, future investigations should further identify the specific gates for other organs, which, in turn, may elucidate the pathogenesis of autoimmune diseases affecting organs other than the CNS, or systemic autoimmune diseases such as systemic lupus erythematosus.

References

1. Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model.
Hirota K, Yoshitomi H, Hashimoto M, Maeda S, Teradaira S, Sugimoto N, Yamaguchi T, Nomura T, Ito H, Nakamura T, Sakaguchi N, Sakaguchi S
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Competing interests
None declared

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Barry Rouse, University of Tennessee, TN, USA. F1000 Microbiology

8
MUST READ

28 Feb 2012 | New Finding

For T cells to mediate inflammatory lesions in the central nervous system (CNS), as occurs in multiple sclerosis (MS), they need to cross the quite formidable blood-brain barrier. However, as with the Maginot line in the Second World War, it seems that the barrier has soft spots where (cell) passage is facilitated. Working with the experimental autoimmune encephalomyelitis (EAE) mouse model of MS, Arima and colleagues demonstrate that one soft spot, or 'gate' as they refer to it, is the sympathetic ganglion associated with the 5th lumbar vertebra.

Apparently, this ganglion is under constant stimulation in quadripeds such as the mouse because of gravitational effects that stimulate the soleus muscle. The consequence is activation of the interleukin (IL)-6 amplifier in the ganglion that serves the muscle site. This leads, in turn, to increased levels of chemokines that attract the pathogenic CD4 T cells to where they can cross blood vessels into the spinal cord. Curiously, they showed that preventing soleus muscle stimulation or blocking sympathetic nerve stimulation with norepinephrine antagonists closed the gate and the animals were more resistant to EAE. One wonders if similar gates exist in bipedals such as ourselves and what we might do to keep such gates closed, perhaps thus curtailing the onset of MS.

Competing interests
None declared

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Rachel R Caspi and **Jennifer Kielczewski**, National Institute of Health, MD, USA. F1000 Immunology

6
RECOMMENDED

05 Apr 2012 | New Finding

The paper authored by Arima and colleagues reports a fascinating new finding regarding factors that affect the onset of multiple sclerosis (MS). Using a mouse model of MS, experimental autoimmune encephalomyelitis (EAE), the authors show that autoreactive T cells enter the central nervous system (CNS) through the fifth lumbar (L5) spinal cord region that enervates the legs, and that their homing to that particular spot is regulated via a reflex neural circuit originating from leg muscle contractions.

By manipulating the level of activity of the legs in their mice, the authors demonstrated that sympathetic nerve stimulation connected to activity of the soleus muscle leads to expression of the chemokine CCL20 (a ligand for Th17 cells, known to be causally involved in EAE pathology) in the L5 spinal cord. This was dependent on activation of the transcription factors, NFkappaB and STAT3, in the local vascular endothelial cells that are part of the blood-brain barrier. These neuroimmune interactions induced regional alterations in blood vessels and venules, permitting the pathogenic CD4+ T cells to enter the CNS. This novel paper thus shows that physical stimulation leading to neural activation can trigger an inflammatory cascade that results in autoimmune disease in a model of MS.

The authors suggest that L5 spinal cord region may be a therapeutic target for treating MS patients. Their results would predict that, all else being equal, physically active persons might be more susceptible to onset of MS, a hypothesis which could be examined through retrospective clinical studies in humans.

Competing interests
None declared

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Lieping Chen, Yale University School of Medicine, CT, USA. F1000 Immunology

8
MUST READ

10 May 2012 | New Finding, Interesting Hypothesis, Novel Drug Target

This paper presents a surprise finding that an entry point for CD4+ T cells in the blood-brain barrier is located in the fifth lumbar spinal cord with a pre-existing enriched chemokine environment in mice. In addition, this study also established a possible association between the movement of the soleus muscle in the leg and the triggering of inflammatory cytokines.

Competing interests
None declared

Cite this evaluation

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