Your nose knows how to target brain inflammation

This scientific commentary refers to ‘IL-10-dependent Tr1 cells attenuate astrocyte activation and ameliorate chronic central nervous system inflammation’, by Mayo et al. (doi:10.1093/brain/aww113).

Currently approved therapies for multiple sclerosis and other chronic inflammatory diseases dampen proinflammatory immune responses, but lack selectivity. For some of these medications, the consequent immune suppression may predispose patients to serious opportunistic infections. An ideal therapy might target only those cells that are autoreactive, while maintaining the ability to discriminate and protect against foreign antigens and pathogens. Administration of anti-CD3 monoclonal antibody (referred to as anti-CD3) has been successfully used to induce immune tolerance. CD3 is the non-polymorphic multisubunit protein complex associated with the antigen-specific T cell receptors (TCR) and is expressed on all CD4+ and CD8+ T cells. Intravenous anti-CD3 has been effective in animal models of autoimmunity and has shown promise in clinical trials of type 1 diabetes mellitus (Herold et al., 2002) and psoriatic arthritis, although side effects limit its chronic parenteral use. Exposure of the mucosal immune system to antigens can lead to development of distinct regulatory T cell subsets that maintain tolerance (Fig. 1). This physiological pathway has been exploited in animal models with oral anti-CD3 (Ochi et al., 2006; Ilan et al., 2010; Wu et al., 2010), which induces transforming growth factor-beta (TGF-β)-secreting T helper type 3 regulatory cells (Th3) that suppress autoimmune responses. In contrast, nasal anti-CD3 induces anti-inflammatory interleukin-10 (IL-10)-producing type 1 regulatory T cells (Tr1) (Wu et al., 2008, 2010). Both of these mucosal routes are well tolerated. Whether therapy that induces Tr1 cells might restore tolerance in progressive multiple sclerosis is unknown. In this issue of Brain, Mayo et al. provide compelling evidence for the induction of IL-10-producing Tr1-like cells by nasal anti-CD3 antibody as a new therapeutic approach to treat progressive multiple sclerosis (Mayo et al., 2016).

The influence of nasal anti-CD3 on chronic CNS inflammation and neurodegeneration was examined by these investigators using the non-obese diabetic (NOD) model of experimental autoimmune encephalomyelitis (EAE). In this model, induced by immunization with myelin oligodendrocyte glycoprotein (MOG), the early phase of EAE is self-limiting but is followed by an irreversible chronic progressive phase, making this an attractive model for progressive forms of multiple sclerosis. Nasal anti-CD3 suppressed both clinical and histopathological disease not only when given at the start of the progressive phase, but also when the progressive phase had been established. Nasal anti-CD3 administration in the progressive phase additionally stabilized blood–brain barrier integrity and promoted axonal protection. This treatment did not affect the ability to clear pulmonary bacterial infection, demonstrating that it was not globally immunosuppressive. Oral anti-CD3, which has proven effective in acute EAE models, had no effect in progressive EAE, providing further evidence that the two different routes of mucosal anti-CD3 administration employ distinct mechanisms. Indeed, flow cytometric analysis of peripheral lymphoid organs and CNS-infiltrating CD4+ T cells revealed a profound increase in MOG-specific CD4+ T cells that expressed IL-10. When isolated ex vivo, those IL-10-producing (IL-10+) T cells suppressed T cell proliferation, Th17 polarization, and conferred tolerance when adoptively transferred in vivo. Interestingly, the T cells also expressed latency-associated peptide (LAP), a non-secreted precursor portion of TGF-β that is expressed on Th3 and Tr1 cells. However, the effects of nasal anti-CD3 were IL-10 dependent, as treatment with an IL-10 specific antibody reversed its clinical efficacy. Mayo et al. compared the transcriptional profile of nasal anti-CD3-induced IL-10+ T cells to defined T cell subsets by microarray. The collection of genes (‘transcriptome’) expressed by nasal anti-CD3-induced IL-10+ T cells was remarkably similar to the profile of Tr1 cells, but distinct from CD4+CD25+Foxp3+ regulatory T
Figure 1 Mucosal administration of anti-CD3 induces distinct types of regulatory T cells. (A) Nasal anti-CD3 promotes development of IL-10-producing type 1 regulatory T (Tr1) cells in draining cervical lymph nodes, the expansion of which is dependent on IL-10 and IL-27 produced by antigen presenting cells (APCs) (e.g. dendritic cells). Tr1 cells suppress peripheral Th17 immune responses. (B) Oral anti-CD3 induces transforming growth factor-beta (TGF-β)-producing T helper type 3 (Th3) cells in gut-associated lymphoid tissue that suppress peripheral Th1/Th17 responses and promote expansion of Foxp3+ T regulatory cells (Treg). (C) Tr1 cells induced in the periphery migrate through and enter the CNS, where they may act to suppress CNS inflammation in progressive EAE and provide neuroprotection. Tr1 cell-derived IL-10 suppresses astrocyte activation, stabilizes the blood–brain barrier, reduces CNS recruitment of peripheral monocytes, and promotes anti-inflammatory (M2) polarization of microglia and CNS infiltrating monocytes. In contrast, oral anti-CD3 may regulate acute CNS inflammation by inducing other regulatory T cell subsets (e.g. Th3 and Treg) that may also enter the CNS and suppress inflammation in a TGF-β-dependent fashion.
CD3: Cluster of differentiation 3 (CD3) is a non-polymorphic, multimeric protein complex expressed on the surface of all CD4+ and CD8+ T cells and serves as a co-receptor for the antigen-specific T cell receptor (TCR). CD3 is composed of four distinct polypeptide chains (γ, δ, ε, ζ) that assemble as three pairs of dimers (γγ, δδ, εζ).

Mucosal tolerance: Suppression of cellular and/or humoral responses to antigens that gain access to the body via the oral or nasal route.

Regulatory T cells: Regulatory T cells (Tregs) maintain tolerance by preventing unrestricted expansion of proinflammatory effector T cells. There are several major classes of Treg, including thymus-derived Foxp3+ natural (nTreg) and inducible Treg (iTreg), T helper type 3 (Th3) and T regulatory type 1 (Tr1) cells. Treg exert immune regulation through cell contact-dependent mechanisms and/or secretion of anti-inflammatory cytokines, such as TGF-beta (e.g. Th3 cells) and IL-10 (e.g. Tr1 cells).

Glossary

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A vulnerability to chronic pain and its interrelationship with resistance to analgesia

This scientific commentary refers to ‘Corticolimbic anatomical characteristics predetermine risk for chronic pain’, by Vachon-Presseau et al. (doi:10.1093/brain/aww100).

Chronic pain is a major medical health problem (IOM, 2011). The socio-economic burden is alarming, yet—to date—we have few effective treatments. A better understanding of the underlying biology leading to the development, maintenance and exacerbation of chronic pain is desperately needed to improve this bleak situation. Progress is being made, but a major unresolved question remains: ‘Why me?’ Several examples in the clinical pain literature demonstrate that only a proportion of patients with a particular disease or injury go on to develop chronic pain (see Table 1 in Denk et al., 2014). For example, diabetic neuropathy is a relatively common condition but only a minority of patients report symptoms of pain. As with many areas of chronic neurological disease, questions about vulnerability and resilience to developing chronic pain are now being asked. In this issue of Brain, Vachon-Presseau and co-workers propose answers based on an extensive longitudinal analysis of patients with subacute pain that either resolves or becomes chronic (Vachon-Presseau et al., 2016).

Epidemiological studies of patient cohorts (e.g. low back pain) and innovative studies linking presurgical assessments to pain outcomes post-surgery have identified several risk factors that predispose an individual towards chronic pain (Kehlet et al., 2006; Balague et al., 2012; Denk et al., 2014). Gender, age and genetic makeup are relevant. Additional risk factors relate to an individual’s personality and psychosocial environment alongside previous pain history, stress and depressive illness; these all conspire to negatively affect long-term pain outcome. Intriguingly, these factors lend themselves to a possible brain-based explanation for why some patients are more vulnerable (or less resilient) to developing chronic pain. Observations from preclinical and human neuroimaging studies suggest that corticolimbic networks involved with reward (e.g. subjective value of relief and analgesia), motivation and learning, as well as the brainstem’s descending pain modulatory system, might be among the culprit networks (see Denk et al., 2014 for a full review and Navratilova et al., 2016).

That is what makes the study by Vachon-Presseau and colleagues so important and interesting. They conducted a ‘tour-de-force’ set of neuroimaging experiments as part of a longitudinal observational study of patients with subacute back pain (SBP) followed over 3 years. From an initial recruitment of 159 SBP patients and 29 healthy controls, a total of 69 SBP and 20 controls completed the study at 1-year follow-up having had four imaging sessions, one at each of Weeks 0, 8, 28 and 56. At this stage, patients were dichotomized into groups with persisting pain (SBPp, n = 39) or recovery from pain (defined as >20% reduction in pain from Week 0 to Week 56; SBPr, n = 30). The 39 with SBPp then underwent a further imaging investigation at 3 years from pain onset (Week 156), and were again dichotomized into those that recovered (SBPr, n = 16) and those with persisting pain (SBPp, n = 23). The following data were obtained at each neuroimaging session: (i) T1 anatomical MRI for high resolution morphometric analysis of subcortical structures; (ii) diffusion tensor imaging for probabilistic tractography and connectivity analysis of white matter connections; and (iii) functional connectivity data to explore intrinsic brain connectivity related to simultaneously recorded spontaneous fluctuations in pain. In addition, pain characteristics, depressive mood and affect ratings were scored using standardized questionnaires. Finally, an exploratory genetic association study was carried out to assess whether any of 30 candidate single nucleotide polymorphisms (SNPs) located in 12 different genes were associated with specific brain properties identified (Fig. 1).

Earlier analyses of subsamples from this expansive dataset have been published and have shown that both functional and structural (i.e. white matter) properties of various corticolimbic regions impart risk for chronic...