

NEWS AND COMMENTARY

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A recent report by Carola Vinuesa and colleagues¹ describes the expression of neuronal genes in splenic B cells. This paper adds to the growing body of evidence demonstrating biological similarities between the immune and nervous systems. Morphological similarities between immune cells and neurons have long been noted. Indeed, the original description of dendritic cells (DCs) within the epidermis by Paul Langerhans² was as cells of the nervous system. Functional connections between the immune and nervous systems have also been described. Chronic physical or psychological stress has been associated with increased susceptibility to infections and decreased antibody production following vaccination.^{3,4} This is likely to be mediated by the production of endogenous corticosteroids, in turn triggered by corticotrophin release from the hypothalamus. More recent research has demonstrated specific similarities between immune and nervous systems. Firstly, immune cells can produce neurotransmitters^{5,6} and express the receptors required to respond to them.^{7–9} Macrophages, which play a central role in inflammation through the production of pro-inflammatory cytokines such as tumor necrosis factor- α , have surface receptors for a number of neurotransmitters including the nicotinic cholinergic receptor.⁷ Thus, there is a direct link between the autonomic (specifically the parasympathetic) system and inflammation; vagal stimulation, resulting in the release of acetylcholine, inhibits the production of pro-inflammatory cytokines by macrophages. This observation provides a possible explanation for the anti-inflammatory effects of acupuncture (which is thought to increase parasympathetic activity) and of nicotine. Interestingly, immune cells not only

express neurotransmitter receptors but can also produce neurotransmitters themselves, thus potentially regulating inflammation in an autocrine/paracrine manner. Macrophages and neutrophils cultured with lipopolysaccharide produce adrenaline and noradrenaline. *In vivo*, blockade of the α_2 adrenoreceptor reduced the severity of tissue damage in a model of lung inflammation injury; thus, phagocyte-derived catecholamines may enhance inflammation.⁶ The second layer of similarity between immune and neurological systems relates to the expression of genes associated with neuronal axon growth and guidance. These same molecules appear to facilitate the formation of an immunological synapse between T cells and antigen-presenting cells (APCs). During axonal growth, the leading edge of the axon is guided to its target through interactions with secreted chemotropic cues, the semaphorins. The axonal interaction with secreted semaphorins is mediated by neuropilins and plexins, which following interaction with semaphorins, induce cytoskeletal changes thus altering axon growth. DCs and T cells express neuropilin-1, T cells form clusters around neuropilin-1-expressing COS-7 cells and DC-induced T-cell proliferation can be blocked by incubation with antineuropilin-1 antibodies.¹⁰

The paper by Yu *et al.*¹ proposes that B-cell migration and the formation of physical interactions between immune cells may be controlled by molecules classically associated with neurite and dendrite growth. They compared gene expression in germinal centre (GC) B cells taken from mice immunized with either a T-dependent (TD) or T-independent (TI) antigen, with the aim of identifying specific markers of TD-GC B cells. Surprisingly, 11% of the 80 genes differentially expressed are known to be involved in the regulation of neuronal axon or dendrite growth. The group went on to confirm these findings by reverse transcriptase-PCR and

focus on the two most differentially expressed genes, BASP1 and Plexin B2, for further study. Plexin B2 is known to be highly expressed in neurons and is involved in the detection of semaphorins guiding axon migration.¹¹ BASP1 is expressed in neurons following injury and mediates neurite outgrowth and axonal repair.¹² Germinal centres are divided into dark and light zones, the dark zones containing centroblasts undergoing somatic hypermutation, and the light zone containing centrocytes, which are thought to take up antigen from follicular DCs and then present it to T cells from which they receive help. Centrocyte–T-cell interactions are short-lived and competition for T cell help may be critical for affinity maturation and subsequent survival of B cells. Yu *et al.* show that both centroblasts and particularly centrocytes isolated from human tonsils develop long neurite-like projections, and that this coincides with the expression of BASP1 and Plexin B2. This dendrite formation may facilitate centrocyte–T-cell interactions, particularly if T-cell-derived cues guide these structures. In neurons, Plexin B2 binds the semaphorin CD100, which is known to be highly expressed on activated T cells.¹³ If a Plexin B2–CD100 interaction is required for B–T-cell association in the GC, this may in part contribute to the defective TD immune responses observed in CD100^{-/-} mice. *In vitro*, BASP1 expression is absent on resting murine splenic B cells, but can be induced by B-cell activation with anti-IgM and anti-CD40. BASP1 is known to control neurite outgrowth and in the same way may control the development of the neurite-like structures observed in GC B cells. Whether the expression of these molecules play a non-redundant role in the selection of high-affinity B cells in GCs or the development of memory and plasma cells remains to be determined.

These axonal-associated genes may not only be important in guiding immune cells towards their appropriate counterparts, but

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may also control immune cell activation. CD100 is a member of the semaphorin family and is expressed constitutively on resting T cells. Its expression is significantly upregulated following stimulation and it acts as a costimulatory molecule by switching off CD72, an inhibitory receptor expressed on both B cells and splenic DCs. Thus adaptive immune responses are reduced in CD100^{-/-} mice and they are protected from inducible autoimmune disease.¹³

Yu *et al.* thus raise the intriguing possibility that antigen uptake, cell motility and process formation may be carefully regulated in a manner analogous to neuronal growth and development. It might be that many current immune phenomena might be driven in part by influencing this mechanism (for example, interleukin-4 is known to drive B-cell immune responses by downregulating B-cell inhibitory receptors¹⁴ but can also induce the formation of microvilli on B cells¹⁵). Analysis of publically available gene expression data (symatlas.gnf.org) suggests that both BASP1 and Plexin B2 are expressed in a number of other human immune cell lineages in addition to the B cell. Expression on both monocytes and DCs implies that these molecules may play a more general role in guiding interactions between APCs and T cells.

These neurological genes may also be important in immune-associated pathology, for example, by altering lymphoma cell motility and may provide new therapeutic targets in immune-mediated disease. Thus, like all good experiments, these results suggest a host of interesting further work. Dissection of the role of neuron-related genes in immunity will be greatly assisted by tissue-specific gene targeting technology, in concert with analysis of motility using modern imaging technology.

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