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Non-canonical cholinergic anti-inflammatory pathway in IBD

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Abstract

Vagus nerve stimulation has shown promise in treating inflammatory bowel disease. A new study identifies a hepatic vagal branch pathway necessary to maintain colonic immune cell homeostasis in experimental colitis, challenging the dogma that an anti-inflammatory reflex requires an intact spleen and that $\alpha 7$ -nicotinic receptor agonists are a panacea for inflammatory conditions.

The vagus nerve is comprised of sensory and motor fibres that provide bidirectional communication between peripheral organs and the central nervous system. Vagal fibres innervate the majority of thoracic and abdominal organs and modulate physiological functions associated with these organs, such as cardiovascular baroreflex, feeding behaviour, glucose homeostasis and gastrointestinal secretion and motility¹. The ability to sense and reflexively respond to peripheral stimuli is typified by the role of the vagus nerve in the cholinergic anti-inflammatory pathway (CAIP); pro-inflammatory products and cytokines are sensed by afferent vagal fibres culminating in the release of acetylcholine (ACh) from vagal motor fibres that inhibit inflammation². In multiple disease states, such as endotoxaemia or postoperative intestinal obstruction, vagal activation of $\alpha 7$ -nicotinic ACh receptor ($\alpha 7$ -nAChR) on immune cells in the spleen reduces systemic inflammation². In mouse models of inflammatory bowel disease (IBD), vagotomy worsens colitis, whereas vagal nerve stimulation shows promise as a therapy in patients with Crohn's disease and in rodent models of colitis through poorly understood mechanisms². Now, published in *Nature*, Teratani et al.³ show the necessity of the common hepatic vagal branch in reducing susceptibility to colitis in mice via $\alpha 7$ -nAChR-independent parasympathetic-mediated regulatory T (T_{reg}) cell differentiation in the colon (FIG. 1).

Teratani et al.³ demonstrated that dextran sodium sulfate (DSS)-induced colitis recruits each neural component of the CAIP. Interestingly, selective vagotomy of the common hepatic branch (herein termed hepatic vagotomy) reduced activation of the left sensory vagal neurons and downstream circuits, leading to worsening of colitis. Using Myd88-knockout mice and antibiotic treatment, it was demonstrated that a microbiota-induced Toll-like

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Competing interests

The authors declare no competing interests.

receptor signalling mechanism is upstream of common hepatic vagal branch sensing, although the exact site of action remains unclear as these receptors are ubiquitously expressed. In the absence of the hepatic vagal branch, ACh-induced retinoic acid production is reduced in intestinal antigen-presenting cells, which resulted in a reduced number of colonic FOXP3⁺ T_{reg} cells. This result identified T_{reg} cell maturation as downstream of common hepatic branch vagal signalling. Hepatic vagotomy, unilateral left (but not right) vagotomy or subdiaphragmatic vagotomy caused similar impairment in DSS-induced colonic T cell maturation in a mouse model, suggesting a critical role for the common hepatic branch of the left vagus nerve in sensing and triggering a response to colitis.

In Teratani et al.³, hepatic vagotomy is used throughout to indicate that dysfunction of the liver–brain–gut neural arc predisposes the gut to inflammation. However, it is important to note that the common hepatic vagal branch primarily innervates the duodenum and stomach with relatively few fibres innervating the liver⁴. Certainly DSS-induced vagal sensory neuron activity outnumbered vagal sensory neurons labelled by retrograde tracer injected in the liver³. Thus, it cannot be ruled out that gastric or duodenal innervation by vagal sensory fibres of the common hepatic branch are activated following local damage to the intestinal epithelium in response to orally ingested DSS. In support of a role for liver signalling, Teratani et al.³ demonstrated that DSS increased neural fibre activation in the liver, and promoted mTOR phosphorylation in the liver, a marker of hepatic inflammation, via a microbiota-dependent mechanism (FIG. 1). Although, the hepatic portal vein transports bacteria and their products to the liver, a mechanism controlled by intestinal barrier permeability that can cause liver inflammation⁵. Whether liver inflammation causes vagal activation or maturation of colonic T cells was not tested and the provenance of the neural fibres is unknown. Thus, recruitment of a liver neural arc in response to portal vein transport of proinflammatory-rich blood from the colon is intriguing and plausible, but requires further testing, perhaps using molecular tools, such as cre-expressing retrograde viruses that enable selective targeting of vagal sensory neurons based on their organ innervation⁶.

The cholinergic anti-inflammatory pathway is classically thought to involve splenic immune cell modulation by either ACh release from postganglionic parasympathetic neurons of the coeliac plexus, or noradrenaline release from sympathetic neurons of the splanchnic nerve⁷. Teratani et al.³ elegantly exclude roles for the sympathetic system, spleen, α 7-nAChR and cervical ganglia in restoring the colonic T_{reg} cell pool following hepatic vagotomy, identifying instead a novel circuit requiring direct vagal efferent innervation of the colon. Specifically, hepatic vagotomy blunted release of parasympathetic ACh, but not sympathetic noradrenaline, within the colon, and muscarinic AChR agonist normalized colonic T_{reg} cells in vagotomized mice. Muscarinic AChR-knockout mice replicated the effects of hepatic vagotomy. Furthermore, colonic T_{reg} cell number was not restored with parabiosis, in which a hepatic vagotomy-treated animal shared circulation with a sham-operated mouse, confirming that a neural, rather than systemic mechanism, is involved in maintenance of the colonic T_{reg} pool. The extent of vagal efferent innervation of the large intestine is debated, but is thought to be sparse in the distal colon⁸. This issue is likely addressed by recruitment of enteric neurons; DSS colitis increases cFos expression in myenteric plexi, and this process is blunted after hepatic vagotomy in mice³. Furthermore, co-culture of enteric neuroblasts with primary human or mouse colonic antigen-presenting cells that express

nAChR promoted T_{reg} cell maturation³. Thus, enteric neurons could propagate ACh release and the subsequent increased abundance of peripheral T_{reg} cells along the entire length of the colon (FIG. 1).

In summary, Teratani et al.³ identify a novel peripheral vagal circuit involved in modulating colonic T cell homeostasis. This finding leads to numerous interesting questions. What other unsuspected physiological functions can be attributed to the hepatic vagal branch? Would stimulation of the hepatic vagal branch be a viable therapeutic target for IBD or other inflammatory diseases (such as obesity)? Colitis increased activity in both the left and right vagus nerve, yet only unilateral left vagotomy affected colonic T cell homeostasis in the mice. So what is the role of right vagal sensory neurons activated in response to colitis? It was recently demonstrated that polysynaptic anterograde labelling of the right and left vagal sensory neurons activated separate central circuits with the left vagus nerve extensively labelling vagal efferent neurons, and the right preferentially recruiting a dopaminergic midbrain circuit in mice⁶. Could the left vagus nerve preferentially modulate organ function and the right vagus nerve modulate neurological complications of IBD^{9,10}? Notably, Teratani et al. find that DSS-induced activity in the left vagal sensory neurons is partially retained after hepatic vagotomy³. Does this imply other vagal sensory branches are capable of sensing colitis? Endocrine mechanisms are often considered a primary mechanism of crosstalk between organs, but this new study³ highlights two alternative signalling mechanisms. Firstly, a gut to liver communication involving microbiota and their products as signals of gut damage is identified. Secondly, a vagal reflex enables communication between two organs via the central nervous system. How common are these non-canonical cross-organ signalling mechanisms? This aspect could be a fruitful new research direction for treating IBD and other gastrointestinal diseases.

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Fig. 1 |. The common hepatic branch of the vagus nerve increases abundance of colonic regulatory T cells in colitis.

In dextran sodium sulfate-induced colitis, activation of the common hepatic vagal branch by gut-derived proinflammatory products recruit vagal motor neurons to release acetylcholine in the colon. Enteric neurons propagate acetylcholine signalling throughout colon. Activation of muscarinic acetylcholine receptors on colonic antigen-presenting cells (APCs) promotes synthesis and release of retinoic acid, culminating in peripheral regulatory T (pT_{reg}) cell maturation. AP, area postrema; DMV, dorsal motor nucleus of the vagus; NG, nodose ganglion; NTS, nucleus tractus solitarius.