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Flaviviruses Hit a Moving Target

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Abstract

The enteric nervous system (ENS) is central to intestinal motility and a candidate target for the heterogeneous spectrum of dysmotility diseases. White et al. reveal that relapsing intestinal dysmotility occurs when partial ENS depletion by enteric neurotropic viruses is followed by functional impairment due to intermittent nonspecific intestinal inflammation.

The intestine is an orchestrated kinetic system segmentally propelling lumenal contents to enable nutrient absorption and preservation of a healthy microbiome ecology (Sonnenburg and Bäckhed, 2016). Intestinal propulsion is coordinated by the enteric nervous system (ENS), a neuronal and glial network spanning the intestine that integrates local physiologic and pathologic sensory cues to direct adjacent circular and longitudinal smooth muscle activity, and the local control of intestinal blood flow, epithelial growth, and repair (Furness, 2012). Intestinal dysmotility is common and underlies a spectrum of often debilitating diseases that are usually acquired and clinical heterogeneous. Even the most common category, irritable bowel syndrome, is a complex of phenotypes and potential contributory mechanisms, confounding efforts to resolve mechanisms of onset, and strategies for treatment (Klem et al., 2017). Due to its central role in intestinal motility, ENS dysfunction or cellular loss is a likely target in dysmotility diseases. In this issue of *Cell*, White et al. (2018) find that relapsing dysmotility, the typical clinical phenotype, actually involves both. Neurotropic flaviviruses broadly have the capacity to infect the ENS, inducing $CD8^+$ T cell-mediated neuronal depletion and acute dysmotility. And after active infection and adaptive immunity subside, the depleted ENS state is uniquely susceptible to relapse of dysmotility induced by nonspecific local inflammation. These observations provide a new biologic framework to integrate previously paradoxical factors in dysmotility pathogenesis and raise new concerns and opportunities for the health burdens of neurotropic viruses and nonspecific intestinal inflammation (Figure 1).

The intriguing starting point of this study is that immune-mediated depletion of the ENS following viral infection may be a prevalent property of neurotropic viruses. White et al. focus on neurotropic flaviviruses, which recently gained global attention due to dramatic multi-national epidemics of acute and developmental diseases of the central nervous system due to West Nile and Zika viruses. Prior evidence indicated that these and other neurotropic

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DECLARATION OF INTERESTS

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flaviruses also infect the intestine, but their direct relationship to primary ENS injury has been unclear. This new mouse-based study formally demonstrates that the ENS is a consistent target of infection by divergent species of neurotropic flaviviruses. Infection causes an acute period of selective enteric neuronal infection and cell death without evidence of infection or injury to glial, macrophage, and epithelial populations. Although the myenteric plexus experiences only minimal increases in innate or adaptive immune cell types, a striking invasion of virus-specific $CD8^+$ T cells is detected. Neuronal cell death and associated dysmotility are equivalent with attenuated virus and shown to depend on virus-specific $CD8^+$ T cells by several experimental and genetic criteria. Moreover, ENS dysfunction is not observed with systemic, non-neurotropic viral infection and its attendant T cell response. Thus, acute ENS damage is largely the result of direct neuronal targeting by antiviral T cells.

Like most viral infections, the acute phase proceeds to viral clearance and local immune quiescence, permitting restoration of ENS function and normal intestinal motility. However, the investigators further probed the resilience of the post-infection ENS to systemic nonspecific immune stimulation (subcutaneous inoculation of an unrelated live-attenuated vaccine, or intraperitoneal administration of poly(I:C)). Indeed, post-infection mice, but not control mice, suffer renewed dysmotility in a process unassociated with local intestinal augmentation of innate or adaptive immune cell types. This finding is evocative of clinical studies reporting the exacerbation of clinical dysmotility syndromes by inflammatory states (Mayer et al., 2015). Taken together, these findings reveal an integrated relationship between viral infection, T cell injury, and nonspecific inflammation in recapitulating the common clinical phenotype of episodic disease in dysmotility syndromes.

So what now do we need to better understand ENS and dysmotility pathogenesis? First, these findings suggest that ENS depletion (neuronal but also potentially glial) is a necessary initial step in acquired dysmotility. While the present study focused on flaviviruses, there are many taxa of neurotropic viruses (e.g., herpesviruses, enteroviruses, astroviruses) that in aggregate may represent a common risk for viral targeting and damage to the ENS. In parallel, acute dysmotility is a frequent symptom of many categories of illness, produced by divergent, indirect mechanisms (Furness, 2012). Thus, acute neurotropic ENS infection may not be clinically distinguishable from other common acute illnesses and may be a more common event than currently appreciated. Determining the prevalence of ENS depletion is conceivable and could be assessed by population-level samples already accrued in many centers (from colonoscopy screening or colonic resection).

Second, by what mechanism does systemic inflammation induce dysmotility in the previously targeted ENS? White et al. do not find that such inflammatory stimuli augment gross accumulation of innate or adaptive immune cell infiltration in the myenteric plexus. However, remote immune stimuli produce systemic cytokines and other bioactive metabolites that can induce local immune cell activation and endothelial microvascular changes that promote local trafficking of innate and adaptive immune effector cell types (Bamias et al., 2012). In the present study, the effectiveness of poly(I:C) offers the clue that type 1 interferons may be candidate mediators for such action. Neuronal and glial cells also express receptors for and are responsive to many classes of cytokines and

immunologic metabolites that can impair neurologic functionality (Chavan and Tracey, 2017). In the context of prior ENS cellular depletion, such impairment may reach a threshold of ENS dysfunction not detectable in the non-depleted ENS. Moreover, the molecular stress response is a common, down-stream pathway among various immune and cellular metabolic challenges (Todd et al., 2008). Thus, local intestinal metabolic events induced by luminal food or microbial products may analogously induce dysmotility in those at risk. Work yet to come may determine which mediators, and what target immune or non-immune cell subsets, are indeed required for reactivation of ENS dysfunction.

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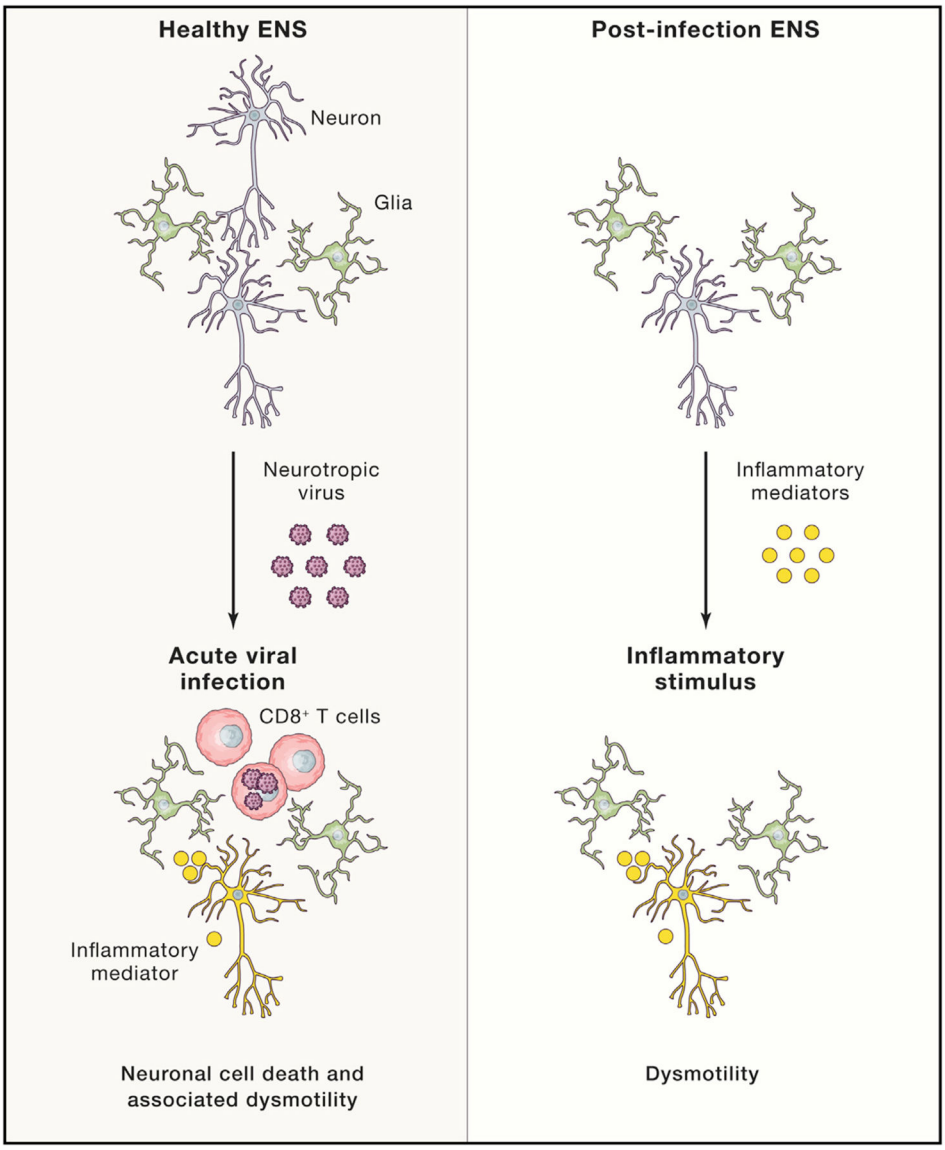

Figure 1. Infection and Intestinal Motility

Intestinal dysmotility can happen as an acute viral infection or post infection in the presence of inflammatory mediators.