Gastrointestinal post-acute COVID-19 syndrome

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The definition of gastrointestinal involvement in post-acute COVID-19 syndrome, its frequency and its pathophysiology are still not completely understood. Here, we discuss the emerging evidence supporting immunological signatures and the unique nature of the gastrointestinal tract in this syndrome.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease 2019 (COVID-19) have been associated with approximately 447 million cases and 6 million deaths worldwide. In a subset of convalescent individuals, long-term sequelae termed 'long COVID', or 'post-acute COVID-19 syndrome' (PACS) are increasingly reported, with the most common manifestations being systemic, neuropsychiatric, cardio-respiratory and gastrointestinal[1].

Owing to the robust constitutive expression of angiotensin-converting enzyme 2 on the brush border of the small intestinal mucosa, acute COVID-19 is associated with gastrointestinal symptoms such as nausea, vomiting, diarrhoea and abdominal pain[1]. In patients with PACS, gastrointestinal-related symptomatology includes loss of appetite, nausea, weight loss, abdominal pain, heartburn, dysphagia, altered bowel motility and irritable bowel syndrome[1]. The frequency of PACS gastrointestinal symptoms is still not clearly defined. In a prospective cohort of 1,783 COVID-19 survivors (with 749 responders to survey questionnaires), 220 patients (29%) self-reported gastrointestinal symptoms at 6 months that included diarrhoea (10%), constipation (11%), abdominal pain (9%), nausea and/or vomiting (7%) and heartburn (16%)[2]. In a different study of 73,435 users of the Veterans Health Administration, motility disorders (including constipation and diarrhoea), oesophageal disorders, dysphagia and abdominal pain were reported[3]. Laboratory abnormalities included an increased risk of high incident serum levels of alanine aminotransferase[3].

Emerging evidence demonstrates persistent and aberrant inflammation as well as induction of autoimmunity in a subset of patients with PACS[1] (FIG. 1). Viral persistence beyond acute COVID-19 has also been documented within multiple organs, including the gastrointestinal tract and central nervous system[1]. However, conclusive evidence linking viral persistence to PACS has not been demonstrated thus far.

A prospective, case–control study of 31 individuals with PACS found elevated serum levels of IFNβ, IFNλ1, IFNγ, CXCL9, CXCL10, IL-8 and soluble T cell immunoglobulin and mucin domain-containing protein 3 (TIM3) at 4 months post-acute COVID-19 (in both patients with PACS and those who were COVID-19 convalescent)[4]. However, in patients with PACS compared with patients who recovered from COVID-19 and did not develop PACS, circulating levels of IFNβ and IFNλ1 were persistently elevated 8 months post-infection[4]. Furthermore, expansion of peripheral blood-associated $PD1^+$ or $TIM3^+CD8^+$ memory T cells, activated ($CD86^+CD38^+$) plasmacytoid dendritic cells and $CD14^+CD16^+$ monocytes were also noted at 8 months post-infection in patients with PACS as opposed to recovered patients without PACS[4]. These data suggest a sustained inflammatory response in PACS, regardless of the severity of acute infection. Potential drivers of this aberrant immune activation include persistence of antigen, autoimmunity driven by antigenic cross-reactivity or impaired damage repair pathways[1].

PACS pathogenesis was further studied in a longitudinal cohort of 309 patients with COVID-19 evaluated from diagnosis to convalescence (2–3 months post-infection)[5]. Specific pre-existing conditions including type 2 diabetes mellitus, initial SARS-CoV-2 RNAemia, reactivation of latent viruses, in particular Epstein–Barr virus, and presence of specific autoantibodies possibly at or preceding acute COVID-19 anticipated the development of PACS[5]. Notably, specific autoantibodies such as anti-IFNα2 were linked to inhibition of interferon-dependent B cell responses (evidenced by a negative correlation between anti-SARS-CoV-2 antibodies and anti-IFNα2 antibodies). Additionally, IFNα2 inhibition was linked to the upregulation of inflammatory cytokines that characterize PACS. Furthermore, many immune cell phenotypes were enriched in patients with PACS, including cytotoxic $CD4^+$ T cells, exhausted T cells and myeloid-derived suppressor cells, which is indicative of immune dysregulation in PACS[5].

In addition to the general considerations discussed earlier, unique features of the gastrointestinal mucosal immune compartment might underlie the pathophysiology of gastrointestinal PACS. Specific mechanisms that might contribute to gastrointestinal PACS include

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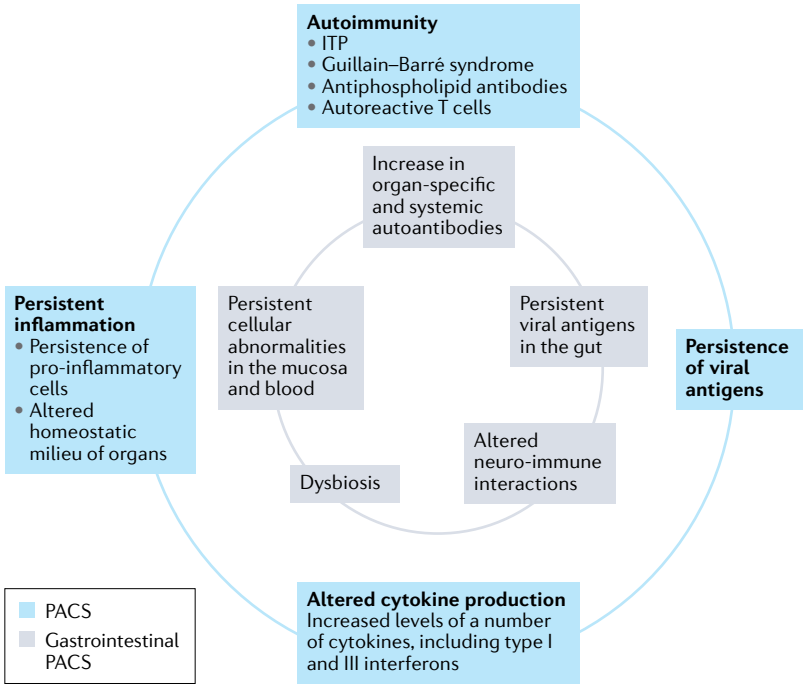

Fig. 1 | **The pathophysiology of PACS and gastrointestinal PACS.** The external blue circle represents proposed pathophysiological mechanisms in post-acute COVID-19 syndrome (PACS). The internal grey circle represents gastrointestinal-PACS-specific pathophysiological mechanisms. ITP, idiopathic thrombocytopenic purpura.

intestinal dysbiosis and maladaptive neuro-immune interactions, in addition to viral persistence and aberrant immune activation in the gastrointestinal tract[1].

To determine intestinal SARS-CoV-2 antigen persistence after resolution of clinical illness, Gaebler et al.[6] studied a cohort of 14 individuals at an average of 4 months (range 2.8–5.7 months) after initial COVID-19 diagnosis. The data demonstrated intestinal enterocyte-associated SARS-CoV-2 N protein in 5 of 14 individuals, while 3 of 14 participants produced PCR amplicons, which were sequenced and verified as SARS-CoV-2 (REF.[6]). Viral detection, which was patchy and sporadic, likely underestimated true viral persistence. Although this small cohort consisted of patients without PACS, the data provided proof of principle that SARS-CoV-2 can potentially persist in specific tissues in a manner that would be consistent with the persistence of other nonretroviral RNA viruses.

Furthermore, as evidence of the persistence of intestinal immune abnormalities, Su et al.[5] reported a substantial enrichment of the cytotoxic T cell pool in patients with gastrointestinal PACS, mainly associated with bystander activation of cytomegalovirus-specific T cells. These data suggest that gastrointestinal PACS is associated with unique T cell clonal and transcriptome dynamics.

Studies have also begun to dissect the association between the intestinal microbiome and PACS. Liu et al.[7] determined faecal microbiome composition (using shotgun metagenomic sequencing) in a prospective cohort of 106 patients with a spectrum of COVID-19 severity, followed up from admission to 6 months. Although this study might be limited considering the high representation of moderate to severe COVID-19 (73.5%) and high prevalence of PACS (73.5%), reduced microbial diversity and specific gut microbiome profiles were associated with PACS[7].

Given the high frequency of motility-related disorders associated with gastrointestinal PACS, post-infectious neuro-immune-related disorders should be considered in disease pathogenesis. Formerly known as post-infectious–functional gastrointestinal disorders, these include new-onset irritable bowel syndrome or functional dyspepsia after an episode of acute infection[8]. The pathophysiology of post-infectious-gut–brain disorders is still obscure and limited by small size studies and different time points evaluated after infection. Suggested mechanisms involve microbial dysbiosis, increased intestinal permeability and low-grade intestinal immune activation[8]. Studies in rats and mice supported the crosstalk of gut-innervating specialized sensory neurons (nociceptors) with microorganisms and intestinal epithelial cells to regulate the mucosal host defence[9]. Additionally, muscularis propria-resident macrophages, in close apposition with the cell bodies of enteric neurons, acquire tissue-protective phenotypes that prevented neuronal loss after infection[10]. Examination of neuro-immune crosstalk in gastrointestinal PACS should be illuminative.

Rigorous, high-dimensional profiling of tissues and peripheral blood, linking pathophysiological disruptions to clinical presentations and outcomes have begun to delineate the complex PACS syndromes. Emerging evidence supports aberrant immunological signatures with persistent inflammation, possibly driven by autoimmunity. Additionally, viral persistence, microbial dysbiosis and altered neuro-immune interactions in the gut might further contribute to the pathogenesis of gastrointestinal PACS. Additional delineation of the disease pathogenesis might provide much-awaited therapeutic targets in patients with gastrointestinal PACS. Furthermore, such data could enhance our understanding of other post-infection gastrointestinal disorders.

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Competing interests
H.M. and S.M. declare no competing interests.