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Editorial

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Chronic Abdominal Pain in IBD Research Initiative: Unraveling Biological Mechanisms and Patient Heterogeneity to Personalize Treatment and Improve Clinical Outcomes

Introduction

Abdominal pain in patients with inflammatory bowel diseases (IBDs) is very common and up to 80% of patients experience some type of acute pain as a result of inflammation and/or obstruction, which resolves once the underlying inflammatory or obstructive condition has been effectively treated. However, at least 30%–50% of patients with IBD experience chronic abdominal pain, which is defined as pain that occurs consistently for 3 months or intermittently for 6 months, and which can persist even in the relative absence of inflammation or in patients in endoscopic remission.[1,2]

Abdominal pain usually starts with the stimulation of sensory receptors in visceral sensory neurons (nociceptors), which transmit nociceptive (pain) information via the dorsal horn of the spinal cord to the central nervous system (CNS), which is then integrated in the brain, resulting in an unpleasant sensory and emotional experience[3] (Fig. 1). Nociceptors selectively respond to peripheral noxious or potentially tissue-damaging stimuli. Visceral sensation, and visceral pain in particular, is a critically important physiological mechanism required to protect the organism. An important property of nociceptors is that they can be sensitized, which means that their excitability is increased. Sensitization, which typically develops as a consequence of tissue insult and inflammation, is defined as a reduction in the threshold and an increase in the magnitude of a response to noxious stimulation.[4,5] It has been suggested that peripheral sensitization due to activation of pronociceptive pathways and/or suppression of antinociceptive pathways[2,5] drives the decreased pain thresholds seen in IBD patients in endoscopic remission.[6,7] However, not only peripheral sensitization but also central sensitization is believed to play a role in chronic abdominal pain in IBD.[2,5,8] Central sensitization results from changes in the properties of neurons in the CNS, and therefore the pain is no longer coupled, as acute nociception is, to the presence, intensity or duration of the noxious peripheral stimuli.[9] The involvement of both central and peripheral sensitization leading to visceral hypersensitivity supports the concept that chronic abdominal pain is a disorder of the bidirectional communication of the gut–brain axis.[5]

Moreover, consistent with this concept, it has been proposed that pain is a complex sensory and emotional experience that varies among patients depending on the psychological state of the person, a concept that is known as the biopsychosocial theory of pain.[10,11]

The consequences of chronic abdominal pain in IBD can lead to impaired quality of life characterized by psychological morbidity, stress, interrupted daily life activities, and in some cases incapacitation. Given the complex interaction between multiple factors leading to abdominal pain and its debilitating outcomes, effective management is critical. Unfortunately, current treatments provide limited relief, and/or have deleterious side effects.[1,2,12] Therefore, the development of new treatment modalities to effectively manage chronic abdominal pain in IBD is a pressing priority. Given this pressing need from patients and healthcare providers, the Crohn's & Colitis Foundation (Foundation) convened a virtual workshop in November 2020 to identify the current knowledge gaps and strategies to move the field forward regarding both the understanding of the biology of chronic abdominal pain in IBD and its clinical management. These concepts inform the Foundation's newly launched initiative focused on chronic abdominal pain in IBD, which aims to improve the mechanistic and clinical understanding of chronic abdominal pain as experienced by patients, with the ultimate goal to support the identification of novel and more effective therapies. To ensure the workshop discussions were comprehensive and influenced by diverse perspectives, multidisciplinary experts were invited including neurobiologists, neurogastroenterologists, psychiatrists, neuroimaging experts, geneticists, nurses, digital health and integrative technology researchers, pain specialists, anesthesiologists, and IBD clinical experts and IBD patients. The cross-fertilization of ideas between basic, translational, and clinical researchers helped identify key challenges and opportunities to advance the field, which are summarized below.

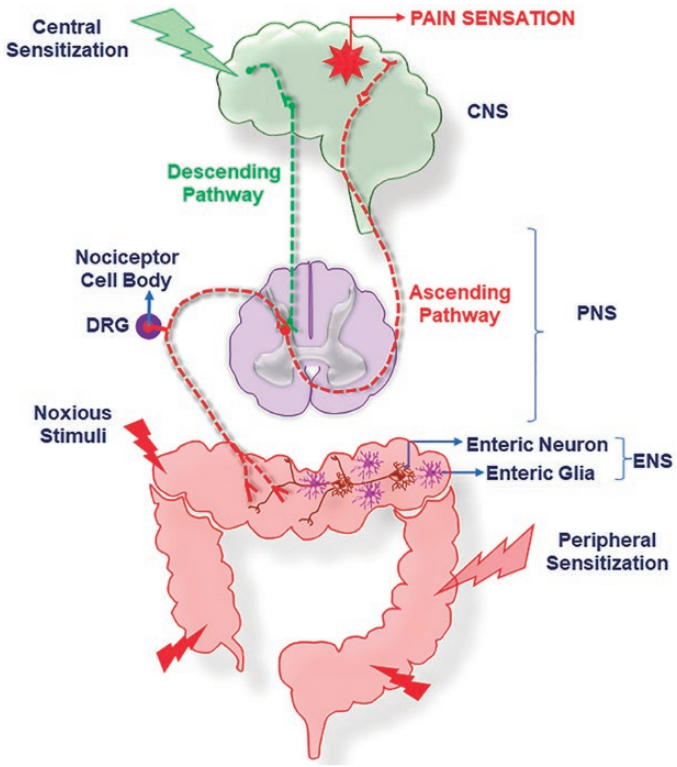

Figure 1. Nociceptive pathways in visceral pain. Nociceptors are afferent sensory neurons of the peripheral nervous system (PNS) that respond to noxious stimuli. Cell bodies of nociceptors are in the dorsal root ganglia (DRG) and transmit, through their axons, nociceptive (pain) information via the dorsal horn of the spinal cord to the CNS, resulting in pain sensation. The increased sensitivity of afferent neurons refers to peripheral sensitization. Central sensitization is the increased excitability of neurons in the CNS, in which pain is no longer coupled to the peripheral stimuli. In addition to the CNS and PNS the ENS also plays a role in nociceptive pathways in IBD.

Challenges and Opportunities

While several advances have been made in the understanding of the biological mechanisms underlying acute pain in IBD, the biology underlying the transition to chronic pain remains largely uncharted, which is reflected in inadequate therapeutics, characterized by insufficient and limited relief and significant side effects.[1] Thus, several knowledge gaps remain in terms of: (1) categorization of the phenotypic and endotypic heterogeneity of patients with chronic pain, (2) development of translational experimental models, (3) determination of the role of the interaction between epithelial and inflammatory cells with the peripheral, enteric, and CNS and the intestinal microbiota, and (4) identification of novel therapeutic targets and their exact mechanisms of action.

Categorization of the Phenotypic and Endotypic Heterogeneity of Patients With Chronic Abdominal Pain

One of the most challenging aspects of chronic pain in IBD is the fact that in about 30%–50% of patients who have achieved clinical and endoscopic remission, pain remains for prolonged periods of time. This suggests that even in the absence of inflammation or apparent tissue damage or overt pathophysiological cause, there is misfiring of the normal nociceptive pathway triggered by a peripheral stimulus derived from the IBD-related alteration of the gut homeostasis and leading to the aberrant neural activation that causes persistent pain.[1,2] Conversely, many patients experience significant inflammation in the absence of reported pain, a phenomenon referred to as "silent IBD," suggesting that chronic suppression of pain pathways can also occur; this can also contribute to poor outcomes as these patients may not seek medical attention despite inflammation which can irreversibly damage the bowel.[13] Many IBD patients also present with extraintestinal pain[8] and/or comorbidities, such as inflammatory bowel syndrome (IBS), that could contribute to pain phenotypes, complicating the clinical picture.[14,15]

None of the current analgesic options are particularly effective to treat chronic pain in IBD and all are associated with significant risks and adverse effects.[1,11] As a result of this, it is evident that new more effective and safe treatments are required. An important step toward advancement of new pharmacological and nonpharmacological treatment options is a better understanding of the biological mechanisms underlying chronic pain in IBD. To achieve this goal the implementation of a reverse translation research approach, in which observations in the clinic and from the analysis of biological samples and data derived from patients with chronic pain, is needed.[16] With this reverse translation approach, the identification of alterations at the molecular, biochemical, and cellular level in these patients will then provide a starting point to investigate in the laboratory how these changes relate to misfiring of the normal nociceptive pathway leading to peripheral and/or central sensitization. An effective reverse translation approach depends on a clinically meaningful categorization of the various phenotypes of patients with chronic pain. For instance, responders and nonresponders to different types of treatments; differential frequency, duration, and inten-

sity of pain; the presence or absence of concomitant symptoms, such as vomiting, fatigue, excessive sweating, or with psychological comorbidities such as anxiety and depression; or concomitant with secondary hyperalgesia, among others.[17,18]

In parallel with the effort to categorize clinical phenotypes, it is critical to determine the biological heterogeneity underlying these phenotypes, in order to identify subtypes of chronic pain, based on distinct biological pathways driving them, also known as endotypes[19] (Fig. 2). Three main advantages of endotyping the heterogeneity of patients with chronic pain are: (1) endotyping is a reverse translation approach in which the elucidation of the genetic, molecular, cellular, and brain function heterogeneity of patients, is based on the analysis of patient derived biosamples, and/or brain imaging or other physiological assessments, which in turn provides an invaluable source of patient-based data to generate hypotheses about the pathophysiological mechanisms underlying the heterogeneity of chronic pain in patient subpopulations. These hypotheses can then be tested experimentally in the laboratory leading to an improved and more precise understanding of the biology driving the different manifestations of chronic pain as experienced by patients. (2) Biological signatures identified as drivers of the pathophysiology of chronic pain can also be implemented as biomarkers to stratify patients in clinical practice and to tailor their treatment to the precise biological drivers of chronic pain in these patients. (3) These endotypic biomarkers can also be used by drug developers and clinical investigators to better stratify patients in clinical trials to select patients most likely to respond to novel interventions targeting specific pathways (Fig. 3). This is important because despite the identification of novel drug targets for pain and the enormous efforts by pharmaceutical companies to develop new analgesics, failure of clinical trials has been significant.[20] This does not necessarily mean that the drug targets are not the right ones but may relate to the fact that the patients in which that target is altered, and thus most likely to respond, were not specifically selected.

While endotyping of IBD patients in general and those with chronic pain in particular is in its infancy, the extensive development of *multi-omics* technological platforms represents a great opportunity to identify the diverse biological pathways underlying the phenotypic heterogeneity of chronic pain in IBD.[21] *Multi-omics* technological platforms in this setting include genomics, transcriptomics, microbiomics, metabolomics, and brainomics (Fig. 2).

Genomics

Not all patients with IBD develop chronic pain and in many cases the extent of disease activity does not correlate with the severity of chronic pain. These observations together with the evidence that pain sensitivity runs in families suggest that the heritability of genetic factors contributes to differential pain sensitivity.[22–24] The analysis of genetic variants has been successfully used to identify endotypes and common genetic pathways underlying chronic pain in other disease states.[25–27] Therefore, genomics studies to identify chronic pain endotypes, based of genetic polymorphisms underlying altered biological nociceptive pathways, may also lead to the identification of discrete phenotypic subpopulations of IBD patients and their biological drivers.

Transcriptomics

While research related to the use of transcriptomics to identify pathways underlying pain phenotypes is scarce, implementation of single-cell RNA sequencing (scRNAseq) has led to the identification of unanticipated diversity of colonic sensory neurons[28] and the enteric nervous system (ENS), which is linked to transcriptional pathways driving neuro-epithelial, neuro-stomal, and neuro-immune interactions.[29]

In addition to mRNA-based transcriptomics, profiling of microRNA (miRNA) expression has been useful for the identification of etiological factors, biomarkers, and therapeutics targets of visceral pain.[30] Thus, it is important to expand these transcriptomics analyses to identify subpopulations of IBD patients with chronic pain, who can be stratified according to transcriptional endotypes for understanding of the underlying biology and development of personalized therapies.

Microbiomics

A correlation between visceral hypersensitivity and microbial dysbiosis exists in IBS patients[31–33] and in experimental models.[34–36] While clinical and preclinical studies of the role of microbiota in visceral hypersensitivity in IBD remains scarce

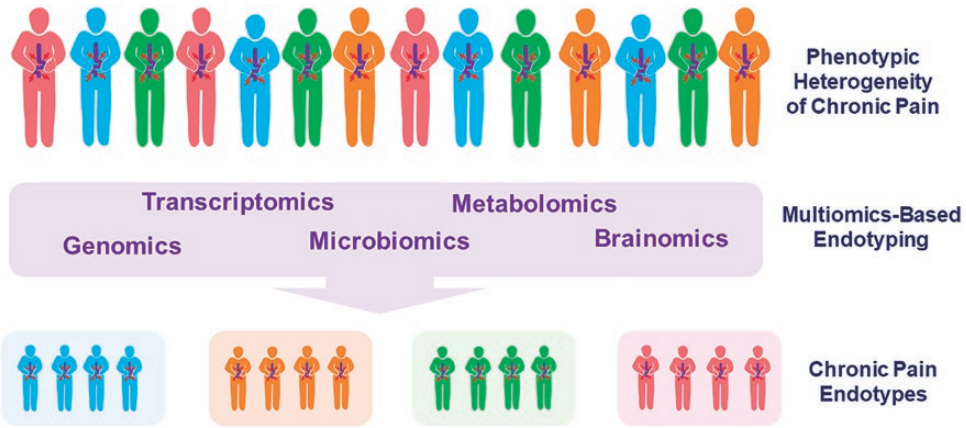

Figure 2. Multi-omics-based endotyping to address patient heterogeneity. Categorization and assessment of phenotypic variability in patients with chronic pain remains a challenge which is reflected in poor treatment outcomes. Multi-omics-based endotyping provides a research strategy to identify stratification biomarkers, novel therapeutic targets and a systems-level understanding of the specific biology driving variability across pain phenotypes. Stratification of patient heterogeneity in subpopulations based on biological pathways driving phenotypic variability or endotypes, offers the opportunity for personalized treatments.

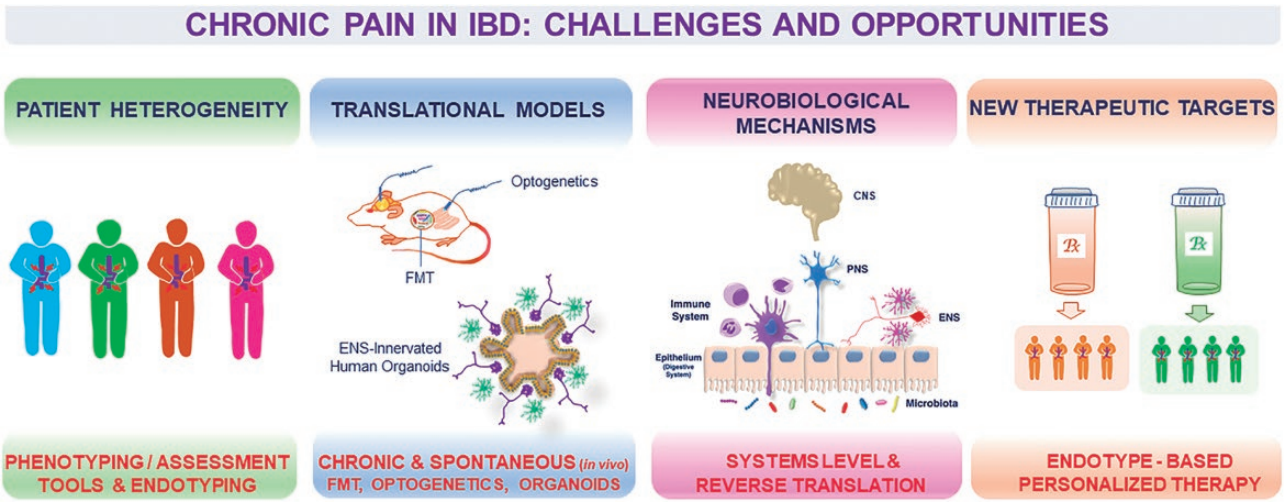

Figure 3. Challenges and opportunities in chronic pain in IBD. Better understanding of the specific physiology and presentation of chronic pain in IBD is necessary to improve patient treatment and outcomes. First, patient heterogeneity requires characterization of different pain phenotypes, matched to their underlying biological drivers or endotypes. Objective assessment measures of pain are also needed. Second, translational and humanized models that reflect spontaneous pain behaviors, chronicity, and comorbidities are required. Technologies like FMT, optogenetics, and ENS-innervated HIOs provide translational modeling opportunities. Third, unraveling mechanism of chronic pain requires a systems-level understanding and a reverse translation approach to generate hypothesis based on clinical observations and samples. Fourth, novel personalized therapies that target endotype-driven variability across chronic pain phenotypes are required. FMT, fecal microbiota transplantation.

compared to IBS, microbial dysbiosis has been extensively shown to associate with IBD pathogenesis[37,38]; so, it is conceivable that gut microbiota may play a role in visceral pain in IBD.[39]

The feasibility of microbiome-based endotyping of individuals with abdominal pain in the general population according to their microbiota profiles, has led to the identification of 3 endotypes linked to the occurrence of abdominal pain, its frequency, duration, and intensity.[40] Thus, microbiome-based endotyping of IBD patients experiencing chronic pain could also lead to the identification of clinically meaningful subgroups of patients, and the identification of microbiome-driven pronociceptive and antinociceptive biological signals. In turn, these studies could support the discovery and development of endotype-tailored probiotic and prebiotic strategies for the treatment of persistent abdominal pain in IBD.

Metabolomics

Intestinal microbiota-derived metabolites play a role in the function of the microbiome–brain–gut axis, nociception, visceral hypersensitivity, and related supraspinal comorbidities like anxiety and depression.[41–43] Experimental evidence supports the role of amino-acid-derived bacterial metabolites (eg, neurotransmitters, kynurenic, and quinolinic acid) as pronociceptive and antinociceptive factors.[42–45] In addition butyrate, bile acids, and lipopeptides have also been reported to have antinociceptive[46–49] and pronociceptive effects.[50–52]

Therefore, given the following evidence: (1) emerging role of microbial-derived metabolites in nociceptive pathways,[42] (2) the improvement in metabolomics analytical platforms,[53] (3) microbial metabolites alone or grouped in pathways related to different pain conditions,[54] and that (4) microbial metabolites may discriminate IBD subtypes,[55] suggest that metabolomics may represent an important approach for the identification of endotypes underlying the phenotypic heterogeneity of visceral pain in IBD and the understanding of their respective biological mechanisms.

Brainomics

The implementation of multimodal structural and functional neuroimaging to identify subtypes of chronic pain is an emerging field that is aiming to provide patient stratification based on the identification of brain signatures reflecting hypertrophic, atrophic, or functional changes in brain regions in patients with pain. This type of analysis can provide another tool for patient endotyping that reflects the pathophysiology of how pain is differentially processed by brain networks between patients.[56,57] Moreover, they can also provide an objective measure of how pain is evaluated, independent of the subjective nature of phenotypic evaluations due to temporal and intrasubject variability[58] and observational bias.[56,59] Importantly, brain signatures can be used to assess whether brain alterations are specific to chronic visceral pain rather than to associated supraspinal processes like anxiety or depression, adding another measure beyond patient-reported outcomes.[60] Taken together, the latest advances in multimodal brain imaging support the notion that it may be useful for a better understanding of the neurobiology underlying the brain–gut axis communication in chronic visceral pain. Moreover, the implementation of a brainomics-based endotyping could have utility to identify chronic pain subtypes in IBD, which are defined by differential alterations in functional brain networks.

To conclude this section, it is important to highlight that for the field of *multi-omics*-based patient endotyping to be successful in the identification of biomarkers with clinical utility and biological signatures for understanding of the pathophysiology of IBD and related chronic pain, access to large cohorts of well phenotyped patients is a requirement.[61,62] In support of this, the Crohn's & Colitis Foundation IBD Plexus biorepository provides a unique collection of baseline and longitudinal biosamples, and *multi-omics* data linked to clinical metadata of well phenotyped patients with IBD. In addition, a large collection of brain images from different pain conditions including visceral pain[63] are available at the

UCLA Pain Repository. The UK IBD Bioresource is another platform which is currently being leveraged by researchers as part of the Crohn's & Colitis UK pain initiative.

Development of Translational Experimental In Vivo and In Vitro Models of Chronic Visceral Pain

In vivo models that recapitulate chronic visceral pain as experienced by patients is a priority, not only for the understanding of the underlying biology but also for the evaluation of the efficacy of novel analgesics with new mechanisms of action linked to the specific biology underlying chronic pain in IBD.

Due to the multifactorial etiology of IBD that involves genetic susceptibility, altered immune responses, microbial dysbiosis, and a plethora of environmental factors, including psychosocial and diet, there is not a single model that can recapitulate all the symptoms and the exact pathophysiology of IBD.[16]

Although more than 500 models of visceral pain have been reported in the literature only very few have demonstrated interlaboratory reproducibility and the ability to mimic in some extent the physiology of chronic pain experienced by patients, or utility for translation to the clinic of drug efficacy studies.[64,65] Most of the work related to chronic visceral pain has been performed by researchers in the IBS field, and the utility, mechanisms and endpoints of these models may also have implications in IBD, as most of the preferred models are those that induce colonic pain, which overlaps with those models used routinely in the IBD field.[66] The primary endpoints required by these models of chronic pain are visceral hypersensitivity and development of pain-like behaviors in response to colonic luminal distention. Secondary endpoints may include gastrointestinal (GI) transit, anxiety-like behaviors, and somatic hypersensitivity.[65] Importantly, in a recent workshop organized by the National Institutes of Health (NIH) the Trinitrobenzenosulfonic acid (TNBS) model of colitis was prioritized as a reproducible model for the assessment of new analgesic therapies.[65] An important feature of this model is that visceral hypersensitivity in response to graded isobaric balloon colonic distension, remains several weeks after the withdrawal of TNBS and the decrease in the associated colonic inflammation,[65] which as mentioned previously, is also a common feature in IBD patients in whom abdominal pain persists even in the absence of inflammation.[1,2] This is a relatively simple model that has been used to successfully predict clinical efficacy of analgesic investigational drugs in human trials[67,68] and has also been evaluated in reverse translation mechanistic studies of colonic hypersensitivity.[69]

According to the widely accepted biopsychosocial theory of pain, pain is a result not only of biological factors but also of psychological and sociological factors,[10,11] this is an important aspect that should be reflected in animal models of pain, and therefore several stress-induced visceral hypersensitivity models have been developed. Examples of these include maternal separation, limited nesting, and odor attachment.[70] However, although these models can be used to understand the mechanistic contribution of psychosocial factors in visceral pain, their use as first-line screening models in pharmacological efficacy studies is not recommended given their cost and labor intensity.[70]

Another in vivo modeling approach includes microbiota-based humanized models[71] (Fig. 3). In support of this, visceral hypersensitivity can be induced in rats by fecal microbiota transplantation from IBS patients,[72] which can be reversed by probiotics in animal models of early life stress-induced pain, and chemical insult mediated inflammation, as well as in IBS clinical studies as previously reviewed.[73]

Overall, gaps remain in available in vivo models regarding the ability to recapitulate the chronicity and heterogeneity of abdominal pain phenotypes in IBD, related to the variable frequency, duration, intensity, and the presence of additional symptoms. Another important deficiency of these models is that the pain response is evoked in response to colonic distention but does not occur spontaneously (Fig. 3).

As mentioned previously, chronic visceral pain integrates a not fully understood circuitry of complex input and output signals at the peripheral, spinal, and supraspinal levels. To better understand these complex nociceptive circuit pathways in IBD, it is critical to implement methods that allow the selective activation or inhibition of neuronal subpopulations in in vivo models. Optogenetics has emerged as a powerful tool that allows regional and cell-type specific neuronal activity modulation[74] (Fig. 3). This is achieved by inducing neuronal expression of light-activated membrane proteins (opsins) to enable either depolarization (eg, by expressing channelrhodopsin-2, ChR2) or hyperpolarization (eg, by expressing halorhodopsin) to directly excite or inhibit neurons, respectively. Tissue-specific promoters are used in optogenetics to target opsins expression to distinct neuronal subsets.[75,76] Although the use of optogenetics to understand visceral pain is still very limited, Johnson et al[77] demonstrated that optogenetics activation of the amygdala induced visceral hypersensitivity in conscious rats, providing a proof of concept that this technology can be used to identify the role of aberrant brain–gut axis signaling in visceral pain processing.

In addition to in vivo models, in vitro models derived from IBD patient's biological material, capable of recapitulating the multifactorial biological mechanisms driving human chronic pain are also needed. In support of this, the successful advancement of the field of inducible pluripotent stem cells (iPSCs) and the ability to grow them in 3-dimensional cultures have provided an excellent tool to generate personalized human intestinal organoids (HIOs)[78] from IBD patients.[79] These HIOs recapitulate several phenotypic features of IBD like inflammation, increased epithelial cell death, and decreased tight junction proteins.[79] While HIOs derived from iPSCs contain an epithelial and mesenchymal layer, they do not contain the neuronal component that innervates the GI tract.[78] However, this deficiency is starting to change with the groundbreaking work of Workman et al[80] who have successfully generated HIOs containing ENS cells by combining HIO with iPSCs derived from neural crestal cells (Fig. 3). Importantly this ENS-innervated HIOs grafted in vivo formed neuroglial structures similar to a myenteric and submucosal plexus. More importantly, neuroglial cells were also functional as peristaltic-like contractions were triggered in response to electric field stimulation. These findings together with the demonstration that HIOs can also be engineered to incorporate microbial and immune compartments, provide a novel humanized model system to understand the neurobiology underlying chronic pain in those patients from whom organoids are derived.[78,81] They can also provide a system for personalized drug screening.[79] Finally, it is tempting to speculate that combination of brain organoids with ENS-

innervated HIOs may also represent a tool to understand the bidirectional gut–brain axis communication and its contribution to pain.

Understanding Translationally Relevant Environmental Factors and Cell–Cell Interactions

At present, a systems-level understanding of interactions between microbiota, epithelial cells, immune cells, and the nervous system is lacking (Fig. 3). Addressing this knowledge gap will be important, as among the different organ systems that can be affected in chronic pain syndromes, the GI system is characterized by an extraordinary range of different cell types involved in maintenance of a homeostatic relationship between the environment and the organism, with the constant need to balance multiple critical functions including peristalsis, nutrient absorption, host defense, immune activation, and response to acute injury. As discussed previously, pain sensitization involves a wide range of signals,[82] including microbial products that may be altered in composition or biodistribution as a part of IBD pathophysiology.[83–85] These signals can drive immune activation of macrophages, neutrophils, T cells, and other immune cells also central to IBD pathogenesis. Nociceptors express multiple cytokine and molecular pattern receptors and can be activated directly by microbial products, by proinflammatory signals originating from immune cells or by other intermediary cells such as spinal microglia[86] or enteric glia.[39,87]

Moreover, recent work, reviewed in this collection by Albers et al, indicates that direct neural–epithelial communication may also be involved in chronic visceral pain. In support of this it has been shown that sensory fibers innervate the epithelium and respond to diffusible signals like ATP, which are released by epithelial cells in response to noxious stimuli.[88] Furthermore, inhibiting these epithelial-derived signals can blunt visceral hypersensitivity in the context of gut inflammation in a preclinical model.[89,90] Serotonergic enterochromaffin cells are another epithelial cell type that has been shown to couple gut signals and primary afferent activation.[91] An important future direction will be to evaluate these mechanisms in a chronic as opposed to acute context.

Within each of these cell types, there are numerous functionally distinct subtypes that express a specific complement of sensory receptors or neuroactive molecules.[90] As described above, understanding of cellular pathogenesis in IBD has significantly advanced with single-cell sequencing, although further progress is needed to expand this knowledge to nonimmune human cell types in chronic visceral pain. In parallel, anatomy and physiology techniques with single-cell or near-single-cell resolution, such as calcium imaging,[92] tract tracing,[93] and optogenetics[75–77,94] have enabled elucidation of causal physiological mechanisms in preclinical models. A challenge moving forward will be to integrate these parallel insights, using omics-based technologies to identify candidate pathways that are altered in patients and translationally relevant models to test causality, in order to define the cell physiology basis of IBD-associated chronic pain in patient subgroups.

Chronic pain in IBD, especially when experienced in the absence of overt intestinal inflammation, can be understood as a maladaptive systems-level change in the relationship between environmental stimuli and neuropsychological responses. Therefore, sensitization processes in the CNS and gut can be potentiated by chronic psychosocial stress, a well-known risk factor for chronic pain in IBD.[15]

It is important to emphasize that all the processes above can, in principle, interact with each other in complex and plastic circuits exhibiting significant functional redundancy, and that the specific drivers of pain in the IBD population are likely to be highly heterogeneous across patients. Thus, there are clearly many opportunities for more effective and targeted interventions, but also challenges in predicting the relative efficacy of a given intervention in each patient.

New Therapeutic Targets and Modalities

Current pharmacological therapies for pain in IBD are not specific for IBD pain and are used across many chronic pain indications.[95] These therapeutics commonly include opioids, nonsteroidal anti-inflammatory drugs, anticonvulsants, antidepressants, and antispasmodics.[95,96] Cannabis may also be used, and may be available via prescription, legal sale or the black market, depending on the legal jurisdiction.[12,97,98] While the level of evidence for efficacy varies across these drug classes, it is clear that none of these approaches is universally effective and that a significant unmet need remains. Patients and physicians will often alter treatment empirically and may employ polypharmacology seeking to improve efficacy and limit side effects. The side effects of these classes of drugs can be significant, and there is some potential for interactions between side effects and IBD disease status (eg, though most patients tolerate nonsteroidal anti-inflammatory drugs, some drugs in this class may exacerbate disease in a subset of patients).[99–101] Given these issues, there are several routes forward for improving treatment. For example, a precision medicine approach matching patient phenotype to therapeutic intervention based on individualized prediction of efficacy and/or safety[62] and tailored to different patient endotypes is likely to be valuable in a heterogeneous disease population such as IBD (Fig. 3). Further, discovery of novel targets linked to the specific biology of pain in IBD could lead to next generation pain therapeutics with significantly improved performance in the clinic. As there may be mechanistic overlap between pain drivers in IBS and IBD in certain patient subsets, progress in this regard could have broader implications for the development of novel interventions for IBS-associated pain as well.

Pain can be influenced by many signaling systems, so a wide variety of novel targets have been proposed. Ion channels represent a commonly cited class of therapeutic targets for pain, with studies linking sodium channels,[102] potassium channels,[103] nonselective cation channels like the transient receptor potential vanilloid 1 (TRPV1),[104,105] GABA A channels,[106] and others to human pain phenotypes. Many other types of cellular receptors including endocannabinoid receptors,[107,108] purinergic receptors,[109–111] neurotrophin receptors,[112] and protease-activated receptors[113] among others are also linked to pain. Some of these receptors may influence nociceptor signaling indirectly, perhaps through effects on inflammation, but many proposed therapeutic targets for pain are thought to exert their effects via direct action on nociceptors. Future therapeutics could move upstream in those same neuronal cells by employing direct neuromodulation.[114–118] Alternatively, future therapeutics could approach pain from a different angle by targeting cells that interact with neurons. Emerging evidence indicates that communication between epithelial cells and neurons may contribute to pain in IBD (see Summary and

path forward).[89] The gut microbiota could also play a key role in pain,[41,119] perhaps via secreted metabolites that impact neuronal function. Related to this, probiotics have been used to treat pain in IBS and this approach could potentially impact pain in IBD as well.[49] Finally, behavioral interventions such as hypnosis, cognitive behavioral therapy, resilience training, and acceptance therapy have all shown promise in improving pain management in certain populations affected by chronic pain, as reviewed by Tillisch and colleagues within this collection.

Regardless of the specific novel target pursued, preclinical modeling of chronic pain is currently challenging (see Challenges and opportunities). In this light, as described above, reverse translational approaches where target discovery and validation are guided by biological data collected from patients, followed by evaluation of efficacy in a translationally relevant animal model that recapitulates the relevant pathogenesis, will remain highly important. Similarly, as patient pain phenotypes and biological endotypes are defined, it will be important for investigators to focus on models that are relevant to specific endotypes and to pursue patient selection/stratification approaches that seek to match target biology to patient population. Finally, significant work is needed to validate and implement assessment methodologies in support of clinical trial endpoints and biomarkers that are appropriate for the patient subpopulation, quantitative and reproducible while taking into consideration patient safety and priorities. Despite the impact of pain on quality of life and morbidity in IBD, collection of pain data from clinicians and patients remains relatively crude and inconsistent across studies, is typically based on language developed with minimal patient input leading to potential miscommunication and variable reporting, and relies on patient recall instead of continuous data collection, despite longstanding consensus recommendations from consortia such as the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[120] Validated instruments should be implemented to collect both patient-reported outcomes[121,122] and clinical-reported outcomes, adapted to the pain phenotypes within the relevant patient population, as well as more general considerations regarding patient priorities and clinical impact.[120,123,124] Preferably, such outcome measures would be coupled with assessment of exploratory molecular and/or imaging markers relevant to the endotype and mechanism of action of the intervention, as potential pharmacodynamic biomarkers to enable more informative exploratory trials.

Summary and Path Forward

Chronic abdominal pain in IBD patients remains a debilitating symptom that dramatically affects their quality of life, including daily activities, social life, work performance; and it is associated with comorbidities like anxiety, depression, sleep disorders, and secondary hyperalgesia. Unfortunately, current treatment options are not fully effective and some of them have adverse side effects.

To address this pressing unmet need, the Crohn's & Colitis Foundation launched the chronic pain in IBD research initiative. This initiative aims to advance research focused on the translational understanding of the neurobiological bases of chronic abdominal pain and a clinical understanding of the ways pain is experienced by IBD patients leading ultimately to improved clinical management and outcomes.

A gap analysis of the field was made during a Foundation convened multidisciplinary workshop gathering chronic pain patients and top scientific and clinical experts in the field. The main thematic challenges identified were: (1) better understanding and subclassification of patient phenotypic heterogeneity and the underlying biological endotypes, which in turn can lead to the discovery of specific neurobiological mechanisms, biomarkers, and translational therapeutic targets, (2) need for translational in vitro and in vivo models reflecting patients biology, clinical manifestations, and comorbidities, (3) unraveling a systems-level understanding of complex cell–cell interactions and environmental factors, and (4) identification of novel and differentiated therapeutic targets reflecting patient's endotype-driven variability across phenotypes (Fig. 3).

This new initiative seeks to address these gaps by providing novel translational and clinical research tools and knowledge to advance the field toward a more personalized, efficacious, and safer way to treat chronic pain and improve patient outcomes.

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