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REVIEW

Cytokine-induced alterations of gastrointestinal motility in gastrointestinal disorders

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Abstract

Inflammation and immune activation in the gut are usually accompanied by alteration of gastrointestinal (GI) motility. In infection, changes in motor function have been linked to host defense by enhancing the expulsion of the infectious agents. In this review, we describe the evidence for inflammation and immune activation in GI infection, inflammatory bowel disease, ileus, achalasia, eosinophilic esophagitis, microscopic colitis, celiac disease, pseudo-obstruction and functional GI disorders. We also describe the possible mechanisms by which inflammation and immune activation in the gut affect GI motility. GI motility disorder is a broad spectrum disturbance of GI physiology. Although several systems including central nerves, enteric nerves, interstitial cells of Cajal and smooth muscles contribute to a coordinated regulation of GI motility, smooth muscle probably plays the most important role. Thus, we focus on the relationship between activation of cytokines induced by adaptive immune response and alteration of GI smooth muscle contractility. Accumulated evidence has shown that Th1 and Th2 cytokines cause hypocontractility and hypercontractility of inflamed intestinal smooth muscle. Th1 cytokines downregulate CPI-17 and L-type Ca^{2+} channels and upregulate regulators of G protein signaling 4, which contributes to hypocontractility of inflamed intestinal smooth muscle. Conversely, Th2 cytokines cause hypercontractilty *via* signal transducer and activator of transcription 6 or mitogen-activated protein kinase signaling pathways. Th1 and Th2 cytokines have opposing effects on intestinal smooth muscle contraction *via* 5-hydroxytryptamine signaling. Understanding the immunological basis of altered GI motor function could lead to new therapeutic strategies for GI functional and inflammatory disorders.

Key words: Cytokine; Motility; Inflammation; Immunology

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INTRODUCTION

Intestinal inflammation and immune activation are accompanied by alteration of gastrointestinal (GI) motility, associated with altered function of enteric nerves, intestinal cell of Cajal (ICCs) or smooth muscles. Changes in motor function have been described in experimental

models following a variety of inflammatory stimuli, including infection[1,2], chemical irritation[3,4] and immune activation[5,6]. In the context of infection, changes in motor function have been linked to host defense by enhancing the expulsion of the infectious agent. Also, evidence has emerged in animal studies that low-grade inflammation in the gut could alter GI motor function[6,7].

From a clinical viewpoint, some motility disorders have been associated with evidence of immune activation, such as inflammatory bowel disease (IBD), ileus, achalasia, functional GI disease (FGID), or life-threatening intestinal pseudo-obstruction[8]. An understanding of the mechanisms that underlie immune-mediated changes in gut motor function is therefore critical, not only in understanding the pathophysiology of, but also in devising new therapeutic strategies for, these disorders.

This review describes the evidence for immune activation in GI inflammation, infection and FGID, with a particular focus on cytokine-induced alteration of GI motility.

CLINICAL POINT OF VIEW

Common symptoms of GI diseases are abdominal pain or discomfort, diarrhea, constipation, fullness and bloating. A mechanical approach to constipation consists of poor intake of fluid or fiber, slow colonic transit, and outlet dysfunction in the anorectal area. Diarrhea is an increase in the volume of stool or frequency of defecation, and is categorized into osmotic, secretory, exudative, and altered intestinal motility. Acute diarrhea that lasts for < 14 d is usually related to a bacterial, viral, or parasitic infection and poses the risk of dehydration. Chronic diarrhea that lasts at least 4 wk is more likely to be due to alterations in GI motility and rapid transit than to a secretory component[9]. The symptoms of GI disorders reflect a broad spectrum of disturbance of GI physiology, including altered epithelial, muscle, intestinal and enteric neural function and are also, at least in part, due to immune activation.

Infections

Several types of bacteria, including: *Campylobacter*, *Salmonella*, *Shigella* and *Escherichia coli*; viruses, including: *Rotavirus*, *Norwalk virus*, *Cytomegalovirus* and *herpes simplex virus* (HSV); and parasites, including: *Giardia lamblia*, *Entamoeba histolytica* and *Cryptosporidium* cause diarrhea. Different pathogens such as enterotoxin invade the host and cause infectious diarrhea.

In bacterial infection, *Salmonella* is a leading cause of GI disease worldwide. Ma *et al*[10] have reported that tumor necrosis factor (TNF)-α modulates the expression of *Salmonella typhimurium* effector proteins and enhances interleukin (IL)-8 secretions in intestinal epithelial cells. Other studies have shown that IL-6 may play an important role in triggering systemic immune response against *Salmonella*[11,12]. *Campylobacter jejuni* infection, which induces a number of cytokines and chemokines including IL-8 and IL-10[13], is also a common cause of human acute bacterial gastroenteritis.

Inflammatory bowel disease

In IBD such as Crohn's disease (CD) and ulcerative colitis (UC), there are longstanding observations of altered motility and intestinal muscle contractility[14,15].

Crohn's disease

Traditionally, CD has been associated with a T helper (Th)1 cytokine profile. Recent studies have indicated that Th17 cells as well as Th1 cells play a major role in the pathogenesis of CD. Th17 cells express the IL-23 receptor (IL-23R) on their surface. Other studies have identified IL-23R and other genes involved in the differentiation of Th17 cells as IBD susceptibility genes[16-20].

Th17 cells produce IL-17, IL-17F and IL-22, thereby inducing a massive tissue reaction, owing to the broad distribution of IL-17R and IL-22R. Th17 cells also secrete IL-21 to communicate with cells of the immune system. Differentiation factors [transforming growth factor (TGF)β plus IL-6 or IL-21], growth and stabilization factor IL-23 and transcription factors [signal transducer and activator of transcription (STAT)3, retinoid-related orphan receptor (ROR)γt and RORα] have recently been identified as involved in the development of Th17 cells[21].

Some studies have shown delays in gastric and intestinal transit that cannot be accounted for on the basis of mechanical obstruction, and are therefore likely due to inflammation-induced alterations in the motility apparatus[22-25]. Conversely, our groups have shown previously that contractility of intestinal smooth muscle strips and cells from the inflamed intestine of CD patients exhibit increased contractility *in vitro* after stimulation by carbachol[14,26]. Although CD is well recognized as having a Th1-dominant cytokine profile, we have demonstrated the dominant expression of the Th2 cytokine IL-4, with little change in the Th1 cytokine interferon (IFN)γ in the muscularis externa of small intestinal segments from CD patients. We have found that Th2 cytokines, IL-4 and IL-13 enhance muscle cell contractility in humans and mice[26,27], and IL-17 enhances muscle cell contractility in mice (unpublished observations), therefore, there is the possibility that Th2 or Th17 immune activation alters muscle contractility in CD patients.

Ulcerative colitis

UC is characterized by an exaggerated Th2-like response as demonstrated by increased production of Th2 cytokines such as IL-4, IL-5 and IL-13[28,29]. TNF-α mRNA is highly expressed in colon biopsy from UC patients correlating with the grade of inflammation[30]. Five genes involved in downstream signaling of IL-23R, IL-12B, Janus kinase 2, STAT3 and IL-2b mediate susceptibility to UC. These findings suggest that Th17 cells are also involved in UC pathogenesis[17-19,31]. Kobayashi *et al*[32] have demonstrated significant upregulation of IL-17A in lamina

propria CD4+ T cells following IL-23 stimulation in UC. It has been reported that high expression levels of the Th17 cytokines IL-17A, IL-22 and IL-26 are found in the inflamed colon of CD patients and in active UC[33-35].

Altered colonic motor function in UC has been well documented[36-38]. Terry *et al*[39] reported that melatonin, which is an important regulator of GI inflammation and motility, might have an ameliorative effect on UC. Ohama *et al*[40,41] have shown that protein kinase C (PKC)-potentiated phosphatase inhibitor protein-17 kDa (CPI-17) expression is decreased in smooth muscle from UC patients. CPI-17 is downregulated by IL-1β and might contribute to the decreased motor function.

Ileus

Ileus occurs as a result of hypomotility of the GI tract in the absence of mechanical bowel obstruction. Presumably, the muscle of the bowel wall is transiently impaired and fails to transport intestinal contents. This lack of coordinated propulsive action leads to the accumulation of gas and fluids within the bowel. Many factors cause ileus, such as sepsis, drugs, trauma and GI inflammation, and most cases of ileus occur after abdominal surgery. The mechanisms underlying the development of postoperative ileus are complex, and involve central neural reflexes, hormonal influences, local molecular inflammatory responses and the recruitment into the intestinal muscularis of activated immune cells[42-46]. Immune activation is involved in ileus as well as IBD. Serum IL-6 and IL-1β are increased in patients with ileus[47].

Bauer's group[48-51] have shown from animal studies that surgical manipulation of the intestine activates the dense network of normally quiescent macrophages, as demonstrated by phosphorylation of mitogen-activated protein kinases (MAPKs) with resultant activation of transcription factors, early growth response gene-1, nuclear factor κB (NF-κB), IL-6 and STAT3. The translocation of the transcription factors to the nucleus ultimately induces the secretion of a complex inflammatory milieu of proinflammatory cytokines: TNF-α, IL-1β and IL-6, and chemokines. Furthermore, NO and prostaglandins have the important role of smooth muscle inhibition in postoperative ileus.

Achalasia

Esophageal achalasia is a motor disorder that is characterized by the absence of esophageal peristalsis and by incomplete relaxation of the lower esophageal sphincter (LES). The failure of LES relaxation is primarily caused by the loss of the inhibitory innervation of the esophageal myenteric plexus[52].

Recent evidence has shown that HSV-1 is involved in the pathogenesis of achalasia[53]. Facco *et al*[54] reported that achalasia patients are characterized by significantly higher esophageal lymphocyte infiltration, mainly represented by CD3+CD8+ T cells than controls. LES-infiltrating lymphocytes recognize HSV-1 antigens specifically. Facco *et al*[54] observed that IL-1β, IFNγ and IL-2 are increased in achalasia patients. Another group has shown that in the immune activation of achalasia patients, TNF-α is significantly increased in the LES[55].

Eosinophilic esophagitis

Eosinophilic esophagitis is an important and established cause of dysphagia, which is caused by exposure to exogenous allergens. Eosinophils and IL-5 produced by Th2 cytokines play a crucial role in this disease. Patients are exposed to food or air allergens. Antigen presenting cells (APCs) process these antigens and present them to Th2 cells. Activated Th2 cells produce IL-5, which is crucial for the terminal differentiation and proliferation of eosinophils. IL-4, also produced by Th2 cells, promotes eosinophilic accumulation and IgE production from B cells. In addition, Th2 cells and activated mast cells release IL-13 and TNF that promote local inflammation. GI epithelial cells produce eotaxins, which have essential chemokine activity for the recruitment of circulating eosinophils to the site of inflammation. As a result, mature eosinophils accumulated in the esophagus, are activated, degranulate and release multiple cytotoxic agents[56].

Microscopic colitis

Microscopic colitis is a common cause of chronic watery diarrhea, especially among older persons. Diagnosis requires histological analysis of colon biopsy samples in the appropriate clinical setting[57]. Microscopic colitis demonstrates a Th1 mucosal cytokine profile with IFNγ as the predominantly upregulated cytokine, with concurrent induction of NO synthase and downregulation of IFNγ-related cell junction proteins[58].

Celiac disease

Celiac disease is a disorder that is characterized by a deregulated immune response to ingested wheat gluten and related cereal proteins in susceptible individuals[59,60]. The characteristic features of celiac disease include nausea, bloating and diarrhea in patients presenting with otherwise typical irritable bowel syndrome (IBS)[61]. Several studies have shown increased concentrations of 5-hydroxytryptamine (5-HT) in the duodenal mucosa[62], increased plasma 5-HT levels[63] and increased urine excretion of the 5-HT metabolite and 5-hydroxyindoleacetic acid[64].

It is considered that the onset of celiac disease is mediated by a skewed Th1 response[65]. In recent literature it has been shown that gliadin-specific Th17 cells are present in the mucosa of celiac disease patients. These Th17 cells have a role in the pathogenesis of the disease as they produce pro-inflammatory cytokines (such as IL-17, IFNγ and IL-21), mucosa-protective IL-22 and regulatory TGFβ, which actively modulates IL-17A production by T cells in the celiac mucosa[66].

Pseudo-obstruction

Chronic idiopathic intestinal pseudo-obstruction (CIIP) is a rare, progressive and life-threatening syndrome that is characterized by severely impaired GI motility. Recurrent

episodes of abdominal pain and distention are accompanied by bloating, nausea and vomiting without evidence of mechanical obstruction[67]. CIIP may occur throughout the GI tract, but usually involves the small bowel. Several neurotropic viruses have the ability to infect the central and enteric nervous systems. Selgrad *et al*[68] and Sanders *et al*[69] have shown that the polyoma virus, JC virus, infects the enteric glia of patients with CIIP[68]. JC virus may infect ICCs and therefore contribute to ICC loss or to redifferentiation to smooth muscle cells. Further investigation is needed.

Functional dyspepsia

FGIDs are common clinical syndromes worldwide. Functional dyspepsia (FD) is characterized by the presence of recurrent or chronic upper abdominal symptoms, such as epigastric pain, early satiety and fullness, without anatomical or biochemical abnormalities[70]. There is increasing evidence for involvement of the immune system in FD. Kindt *et al*[71] have reported that, compared to controls, stimulated lymphocyte expression of IL-5 and IL-13 is enhanced in IBS, FD and non-cardiac chest pain. Conversely, stimulated monocytic IL-12 and lymphocytic IL-10 expression is reduced in IBS and FD, while IFNγ expression is also reduced in FD patients. A shift towards a Th2 cytokine profile is present in FGID, while the cellular immunophenotype remains largely unchanged. Arisawa *et al*[72] have reported that IL-17F 7488T and macrophage migration inhibitory factor -173C alleles are significantly associated with the development of FD, particularly epigastric pain syndrome, a subgroup of FD, in *Helicobacter pylori*-infected subjects.

Futagami *et al*[73] have reported that gastric emptying evaluated by T-max values in post-infectious FD patients is similar to that in controls. However, the degree of histrogical duodenitis in post-infectious FD is significantly greater than that in controls. CCR2/CD68-double positive cell number in post-infectious FD patients is significantly increased.

Irritable bowel syndrome

IBS is characterized by the presence of abdominal pain or discomfort and an alteration in bowel habits[74]. The pathogenesis is considered to be multifactorial and includes psychosocial factors, visceral hypersensitivity, infection, microbiota and immune activation. Several reports have described increased numbers of T cells in various lymphoid compartments of the small or large intestine in IBS patients[75-78]. Pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α in peripheral blood mononuclear cells[79] and IL-6 and IL-8 in serum[80,81] have been reported to be increased in IBS patients.

ROLE OF IMMUNE RESPONSE IN ALTERED INTESTINAL MUSCLE FUNCTION

Innate immune response

Goblet cells: The mucous layer that coats the GI tract is the front line of innate host defense largely because of the secretory products of intestinal goblet cells. In most intestinal infections, induction of goblet cells and mucin synthesis and secretion occur frequently, during the acute phase, to expel antigens[82].

Macrophages: Macrophages perform a key role in innate defense against foreign invaders and produce a number of cytokines such as IL-1β, IL-6 and TNF-α. Macrophages are not crucial for changes in muscle contraction in *Trichinella spiralis*-infected mice[83]. Innate immune response seems not to have a major role in muscle function.

Adaptive immune response: APCs present antigens to CD4+ Th cells. Th cell-dependent immune responses are divided into four subsets: Th1, Th2, Th17 and T regulatory (Treg). Th1 cells produce IFNγ and their primary role is protection against intracellular microbes. Th2 cells produce IL-4, IL-5 and IL-13 and are involved in allergic disorders and protection against extracellular pathogens. Th1 differentiation is mainly driven by IL-12 and IFNγ, while IL-4 drives Th2 differentiation. Treg cells are important in the control of immune responses to self-antigens, prevention of autoimmunity and maintenance of self-tolerance. In contrast, IL-17-producing Th17 cells play a major role in autoimmunity[19] (Figure 1).

Th1/Th2/5-HT: Recent animal studies have shown that Th1 and Th2 immune response is associated with hypocontractility or hypercontractility of inflamed intestinal smooth muscle, respectively.

We have previously shown[7] that Th1 and Th1-related cytokines cause hypocontractility of inflamed intestinal smooth muscle. TNF-α and IL-1β inhibit carbachol-induced contraction *via* downregulation of CPI-17[84] and L-type Ca^{2+} channels[85], respectively. Other groups have shown that surgical manipulation suppresses jejunal contractions with upregulation of IL-6, TNF-α, cyclooxygenase-2 and inducible NO synthase[86]. We also have shown that incubation of IFNγ with intestinal smooth muscle decreases carbachol-induced smooth muscle cell contraction[87]. Wells and Blennerhassett have reported a decrease in muscle contractions in 2,4,6-trinitrobenzene-sulphonic acid (TNBS)-inflamed preparations[88]. In a Th1-dominant, TNBS-induced colitis model, it has been shown that carbachol- and 5-HT-induced contractility of rat colonic circular smooth muscle cells is decreased in the acute phase, and 5-HT-mediated contraction is still impaired by day 36 post-TNBS.

On the contrary, the Th2 cytokines IL-4 and IL-13 acting *via* STAT6 mediate the development of nematode *T. spiralis*-induced intestinal muscle hypercontractility, which contributes to worm expulsion[27,89,90]. A model of *Nippostrongylus brasiliensis* infection supports our finding that Th2 responses mediate muscle contraction[91,92]. Ihara *et al*[93] have shown that MAPK pathways play crucial roles in Th2-cytokine-mediated Ca^{2+} sensitization and

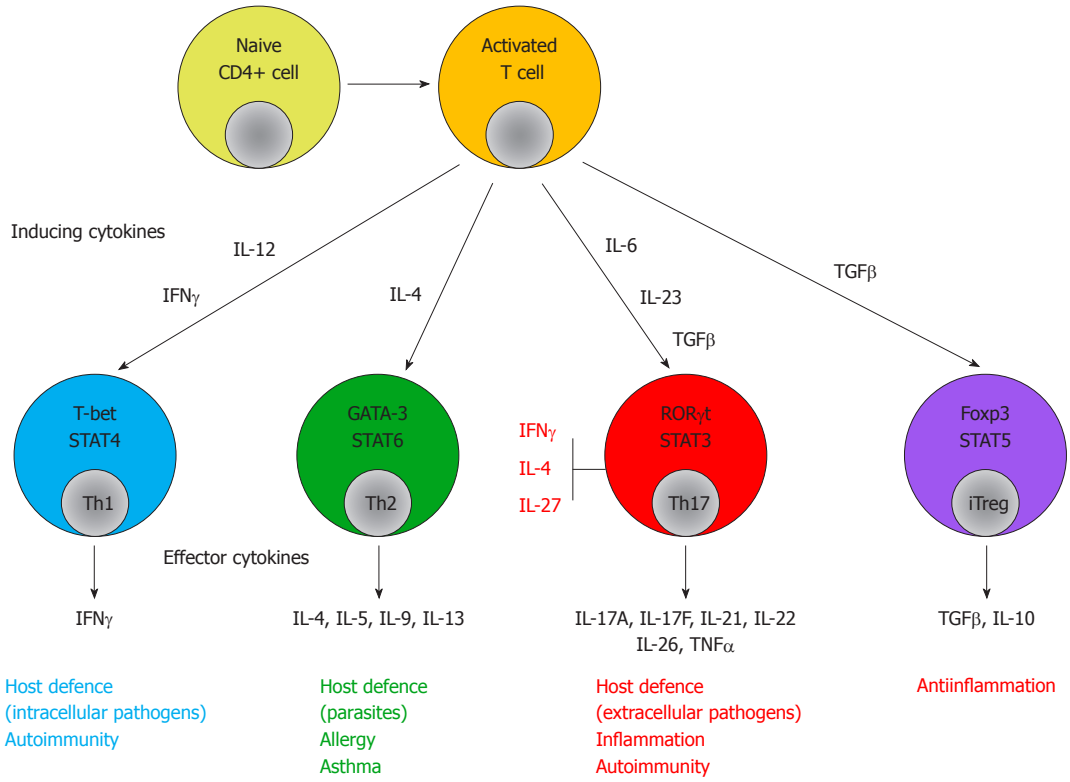

Figure 1 Development of Th1, Th2, Th17 and induced Treg cells from naïve CD4+ T cells. Cytokines that inhibit the development of Th17 cells are marked in red. CD: Crohn's disease; T-bet: T box expressed in T cells; GATA: GATA-binding protein; ROR: Retinoid-related orphan receptor; Foxp3: Forkhead box P3; STAT: Signal transducer and activator of transcription; IL: Interleukin; IFN: Interferon; TGF: Transforming growth factor.

hypercontractility observed in inflamed colonic circular smooth muscle from sodium dextran sulfate-treated mice.

We evaluated the association of 5-HT with Th1/Th2 responses. 5-HT influences intestinal homeostasis by altering gut physiology, and has been implicated in the pathophysiology of various GI disorders such as IBD, IBS and GI infection[94-97]. Using the *Trichuris muris*-infected AKR (susceptible to infection with generation of a Th1 response), BALB/c (resistant to infection, with generation of a Th2 response), STAT4-deficient (impaired in Th1 responses) and STAT6-deficient (impaired in Th2 responses) mice to explore the mechanism of the enterochromaffin (EC) cell and 5-HT responses in Th1/Th2-dominant environments, we found that the EC cell and 5-HT responses to the same infectious agent were influenced by Th1 or Th2 cytokine predominance[98].

Furthermore, we evaluated the 5-HT response and intestinal motility using T cell-induced enteropathy in Th1/Th2-dominant environments[99]. In BALB/c mice, carbachol-induced intestinal smooth muscle cell contraction was significantly increased at day 7 post anti-CD3 antibody injection, when the tissue damage returned to its normal histological appearance. We observed that 5-HT protein in the intestine was significantly increased at day 7. On the other hand, in AKR mice, carbachol-induced muscle cell contraction was significantly decreased and 5-HT protein in the intestine was also decreased at day 7. We showed, in this model, that Th1 and Th2 cytokines had opposing effects on intestinal muscle contraction *via* 5-HT signaling in the post-inflammation phase.

Th17: Several disorders that were originally considered to be Th1-mediated have been reclassified as Th17-mediated inflammation[100,101]. A recent study has shown that Th17 cells are increased during acute infection with *T. spiralis*, and that jejunal smooth muscle strips cultured with IL-17 show enhanced contractions, elicited by acetylcholine, in a concentration-dependent manner[102]. We found that IL-17 protein in the small intestine is upregulated in mice injected with an anti-CD3 antibody[103], and that IL-17 incubation with smooth muscle cells enhances carbachol-induced smooth muscle cell contraction (unpublished observations). IL-17 might be the key cytokine to alter GI muscle function.

HOW DO CYTOKINES AFFECT GI MUSCLE FUNCTION?

As we have mentioned in this review, several cytokines are upregulated in GI diseases, and adaptive immune systems have a key role in altered muscle function of chronic GI diseases such as IBD and FGID.

Signal transduction pathways in smooth muscle cells

Motility disorder is a broad spectrum disturbance of GI physiology, including altered epithelial, smooth muscle, intestinal and enteric neural function and while immune activation may contribute, it plays only a limited role (Figure 2). GI motility depends on activation and coupling of muscarinic receptors at multiple sites including

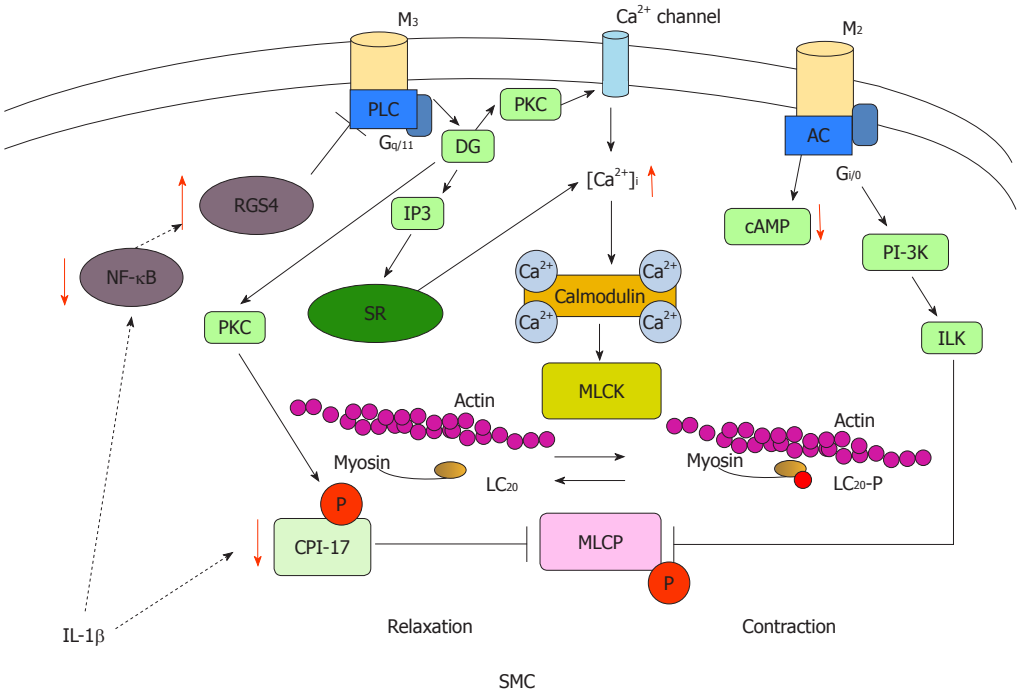

Figure 2 Muscarinic receptor signaling pathways. Gastrointestinal smooth muscle expresses both M2 and M3 muscarinic receptors. The M3 receptors are coupled to Gq/11, which activates phospholipase C (PLC) and produce inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DG). These second messengers elicit the activation of PKC and trigger an increase in $[Ca^{2+}]_i$. M2 receptors are coupled to Gi/o, accompanied by adenylcyclase (AC), which causes a decrease in cAMP level and activation of phosphoinositol 3-kinase (PI3K) and integrin-linked kinase (ILK). Regulators of G protein signaling (RGS4) plays an important role in regulating smooth muscle contraction. To initiate contraction, increases in $[Ca^{2+}]_i$ activate MLCK, a Ca^{2+}/calmodulin-dependent enzyme. MLCK phosphorylates LC20 on Ser-19, which results in contraction of smooth muscle through increases in myosin ATPase activity and cross-bridge cycling. MLCP is responsible for the dephosphorylation of LC20, which results in relaxation of smooth muscle. It is the balance between MLCK and MLCP activities that dictates the contractile activity of smooth muscle. Although MLCK is Ca^{2+}/calmodulin dependent, MLCP functions independently of Ca^{2+}/calmodulin and is regulated directly by phosphorylation of the myosin targeting subunit of MLCP and/or indirectly via phosphorylation of CPI-17. IL-1β upregulates RGS4 expression by inhibiting NF-κB activation. IL-1β also downregulates CPI-17 expression leading to muscle relaxation. PKC: Protein kinase C; MLCK: Myosin light chain kinase; MLCP: Myosin light chain phosphatase; NF-κB: Nuclear factor κB.

enteric neurons, ICCs, and smooth muscle. Cycles (slow waves) of membrane depolarization and repolarization originating in ICCs are transmitted to the smooth muscle cells. Among these, smooth muscle is the most important system because alteration in the contractile process occurs at the level of the GI smooth muscle. The depolarization of smooth muscle cells primarily reflects activation of voltage-gated Ca^{2+} channels, which results in Ca^{2+} entry from the extracellular space. Concurrent stimulation of rhythmic smooth muscle by excitatory neurotransmitters elicits further depolarization and Ca^{2+} entry, and activates intracellular signaling cascades that result in Ca^{2+} release from intracellular stores. GI smooth muscle expresses both M2 and M3 muscarinic receptors. The M3 receptors are coupled to Gq/11, which activates phospholipase C and produce inositol 1,4,5-triphosphate and diacylglycerol. These second messengers elicit the activation of PKC and trigger an increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). On the other hand, M2 receptors are coupled to Gi/o, which regulates adenyl cyclase. Although the inhibition of adenyl cyclase is a classical effect of M2 receptor activation, other possible downstream signaling pathways which contribute to smooth muscle contraction have been proposed, including phosphoinositol 3-kinase and integrin-linked kinase[104]. Alternatively, coupling of M2 and M3 receptors is regulated by G protein receptor kinases and regulators of G protein signaling (RGS) proteins, which also play an important role in regulating smooth muscle contraction[105].

While increased $[Ca^{2+}]_i$ is the paramount signal to initiate smooth muscle contraction, the contractile properties of smooth muscle cells are primarily governed by phosphorylation of the regulatory light chain (LC20) of myosin II[106,107]; this is in turn driven by the balance between myosin light chain kinase (MLCK) and smooth muscle myosin light chain phosphatase (MLCP). To initiate contraction, increases in $[Ca^{2+}]_i$ activate MLCK, a Ca^{2+}/calmodulin-dependent enzyme[108]. MLCK phosphorylates LC20 on Ser-19, which results in contraction of smooth muscle through increases in myosin ATPase activity and cross-bridge cycling. MLCP is responsible for the dephosphorylation of LC20, which results in relaxation of smooth muscle[109]. It is the balance between MLCK and MLCP activities that dictates the contractile activity of smooth muscle. Although MLCK is Ca^{2+}/calmodulin dependent, MLCP functions independently of Ca^{2+}/calmodulin and is mediated by the G protein-coupled process described above; it is regulated directly by phosphorylation of the myosin targeting subunit of MLCP (MYPT1)[109] and/or indirectly *via* phosphorylation of CPI-17[110]. Inhibition of MLCP, thus, results in greater LC20 phosophorylation and greater force development at a given $[Ca^{2+}]_i$.

It has been reported that IL-1β plays an important role in decreased GI smooth muscle contractility in Th1 cytokines-dominant colitis. It has been shown that IL-1β downregulates CPI-17 expression, which contributes to decreased GI smooth muscle contractility[40,41,84]. It has also been shown that IL-1β upregulates RGS4 expression by inhibiting NF-κB activation and RGS4 contributes to the inhibitory effect of IL-1β on the GI smooth muscle contraction[111,112]. Th2 cytokines may have opposing mechanisms to downregulate RGS4 expression. The important point is that it has yet to be determined whether the activated cytokines indicated above actually contribute to alteration of GI motility disorder in humans. However, several animal studies have shown that cytokines directly affect GI motility[84,87,89,102]. Further investigations should be undertaken.

CONCLUSION

Understanding the underlying immunological basis of GI disease by considering the time course of the disease, cytokine profile, and motor function may ultimately lead to new therapeutic strategies for GI functional and inflammatory disorders.

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