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May the activation of mast cells by IgG- food antigen complexes be the missing piece of irritable bowel syndrome puzzle?

Abstract

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders with multifactorial pathophysiology such as visceral hypersensitivity, intestinal dysmotility, brain-gut axis dysregulation, altered intestinal fluid secretion, impaired permeability, mucosal immune dysregulation, bacterial dysbiosis and psychological stress. Recent studies have suggested that activation of intestinal mast cells may play a role in many of these factors. On the other hand, from the beginning of this century, symptomatic improvements by elimination of foods with increased IgG antibodies have been reported in patients with IBS. These results may be explained by decreased activation of intestinal mast cells due to decreased IgG-food antigen immune complexes. Immune complex mediated mast cell activations occur when they bind to activating IgG receptors (FcγRs). If these antigens belong to some of the commonly consumed foods such as gluten-containing grains, bread yeast, cow's milk and products, chicken egg or food additives like thickening agents, mast cell activations increase and may cause the disease to be treatment resistant. In this article, the role of increased IgG-food antigen complex dependent mast cell activation in the pathogenesis of IBS will be discussed.

Keywords: irritable bowel syndrome, mast cells, food-specific IgG antibodies, food additives

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Abbreviations: IBS, Irritable bowel syndrome; FODMAPs, fermentable oligosaccharidesdisaccharides monosaccharides and polyols; IgG, Immunoglobulin G

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by abdominal pain, bloating, altered bowel habits, flatulence, urgency or straining to stool, and feeling of incomplete evacuation which may differ from patient to patient. Symptom severity also varies in patients, in a way from tolerable to severe which is markedly impairing patients' quality of life.

Irritable bowel syndrome is a multifactorial disease, the pathophysiological mechanisms are complex and have not been completely understood. Visceral hypersensitivity, intestinal dysmotility, impaired gut barrier function, altered intestinal fluid secretion, brain-gut axis dysregulation, mucosal immune alterations, bacterial dysbiosis and genetic, dietary, psychological factors have been suggested.[1,2] Recently, presence of low-grade intestinal mucosal inflammation, rich in mast cells which are mainly activated, has focused the attention to IBS and mast cell association. In a new systematic review, significantly increased mucosal mast cell counts/or density in IBS patients was observed in 30 of the 36 case-control studies evaluated.[3] Many studies have supported that mediators released from the activation of mast cells play an important role for most of the abnormalities seen in IBS such as visceral hypersensitivity,[4-6] altered secretion,[7,8] disturbed motility,[9] increased intestinal permeability.[10–12] Local microenvironment in the gut lumen such as commensal bacteria and products, food antigens, allergens and toxins are able to activate mast cells. Mast cells are also activated by psychologic distress and negative life events.[2]

On the other hand, many patients with IBS have histories of adverse food reactions.[13] Some of them modify their diet by excluding self-identified foods, and a few of them have to feed themselves with a very limited number of foods. Although food related symptoms in IBS are well-known, the underlying mechanisms have not been fully understood. Though, poorly absorbed fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) related luminal distension,[14] IgE-mediated food allergy due to mast cell activation and food intolerances from enzyme deficiencies[13,15] have been known. Recently it has been understood that some patients with IBS may have non-celiac gluten sensitivity.[16]

Since 2004, some studies have been reported symptomatic improvements with the elimination of foods having increased IgG antibody levels (IgG positive foods) in patients with IBS.[17-21] The mechanisms of these results have not been considered to be associated with mast cells. However, some of these improvements can be explained by diminished mast cell activations because of decreased IgG-food antigen immune complexes, due to lack of antigen part of them.[22]

IgG antibody mediated activation of mast cells was shown in 1969 and IgG receptors (FcγRs) were described on these cells in 1971.[23] Because of the most receptors for IgG antibodies in humans are in low affinity, these antibodies can activate mast cells after generating immune complexes with their antigens and later on binding to activating FcγRs.[23] Unfortunately, these type of activations have been overlooked for a long time, IgE antibodies and IgE receptors (FcεRI) have been accepted as the main immunological pathway for mast cell activation.[23,24]

In this paper, the role of increased mast cell activation by immune complexes, formed IgG-food and food additive antigens are

emphasized as one of the pathogenetic factors in IBS.

Mast cells

Mast cells have a widespread distribution and are found predominantly at barrier sites of the body such as the skin, gastrointestinal, respiratory and urinary tracts. Recently, it has been realized that mast cells are multifunctional immune cells implicated in several health and disease conditions.[24] Mast cells are involved in physiological processes and maintain integrity /function in all tissues.[24] They play a pivotal role in innate and adaptive immunity and immune tolerance. They also have an important role in the pathogenesis of several disorders.[23,24]

Many stimuli, such as IgE, IgG, IgA, complements, TLR ligands, cytokines, chemokines and other inflammatory products, certain drugs, physical factors can activate mast cells.[23,24] Substance P, corticotropin releasing hormone (CRH) and estrogens,[25] likewise xenoestrogens which have estrogen-like activities[26] can also activate mast cells. Upon activation, mast cells release preformed mediators stored in the granules (e.g., histamine, heparin, serotonin, tryptase, chymase) and newly synthesised mediators (e.g., prostaglandins, leukotrienes, cytokines, chemokines and growth factors) through classic non-selective degranulation or selective mediator release.[24,25,27] Preformed mediators such as histamine and heparin cause many changes, seen in early-phase allergic reactions and newly synthesized mediators cause inflammation with attracting leukocytes to the inflammatory site.[24,25]

Mast cell-IBS relationship

Mast cells are common residents of the intestine, mainly located in the lamina propria (2–3% of all cells) and slightly less in the submucosa (1% of all cells). They are also found in the intraepithelial, smooth muscle and serosal layers.[28] Mast cells communicate with the adjacent epithelial, neuronal, smooth muscle and other immune cells when they are activated.[1,2,29] There are close proximity and crosstalk between neuronal units (enteric nerves and extrinsic nerve fibers) and mast cells.[30,31] Mast cells involve in physiological processes of the intestine such as regulating permeability, secretion, peristalsis, and host defense mechanisms against pathogens.[29,32] These physiological responses are related to the releasing bioactive mediators into adjacent tissues as the result of stimulation of mucosal mast cells both IgE/antigen-dependent and non-IgE-dependent ways.[29]

In many of studies, mast cells have been shown to be increased in number and activation in both small and large bowels in patients with IBS.[1–3] They can be responsible for many of the pathophysiological factors of IBS with their mediators, released by activation. Studies with mast cell mediators (mainly histamine and tryptase) showed increasing excitability of senso-secreto-motor neurons leading to visceral hypersensitivity,[4-6] altering secretion[7,8] and disturbing motility.[9] Increased intestinal permeability[10–12] and tryptase related degradation of the junctional proteins between intestinal epithelial cells were also detected.[12] Activation of intestinal mast cells can cause low grade mucosal inflammation and the inflammation might also be responsible for both visceral hypersensitivity and epithelial barrier dysfunction.[1,2,32]

On the other hand, it is well known that stressful life events are associated with onset or exacerbation of IBS symptoms. CRH which is induced by psychological stress, is one of the factor for mast cell degranulation.[25] Stress enhanced abdominal contractions involving central CRH and intestinal mast cells were shown in rats.[33] In humans, increased intestinal permeability via CRH-mediated mast cell activation due to acute psychological stress was also shown.[34] Finally, ketotifen treatment which prevents mast cell degranulation was found highly effective for the symptomatic improvement in patients with IBS.[35]

Adverse food reactions in IBS related mast cell activation

Food chemicals, such as some additives (e.g., benzoate, sulphite), naturally occurring salicylates and biogenic amines (e.g., histamine) may provoke some symptoms and some of them related to the gastrointestinal system. Several mechanisms have been proposed to explain the pathogeneses of these symptoms, including non-immune direct activation of mast cells.[13] Besides, pesticides, a group of xenoestrogens are very common as environmental pollutants and present in mainly water and foods, can activate mast cells mostly mediated by estrogen receptors α.[26]

Food hypersensitivity (allergy) is an adverse immune response to food and can be classified as IgE-mediated and non-IgE- mediated (delayed or cell-mediated) reactions.[15] IgE- mediated allergy is well-known and associated with mast cells but not common in IBS.[15]

Food sensitivity and IBS

Recently IgG antibody dependent mast cell activation has been classified as allergy and it has been suggested that it is common for food and food additives.[27] IgG-antigen immune complexes can activate mast cells when they bind to activating FcγRs.[23] This type of reaction might observed in patients with IBS. Because from beginning of this century, the number of studies giving symptomatic improvements in patients with IBS by elimination of foods, having higher IgG antibody levels above the cut-off value of healthy people, has reached five.[17–21] The terms such as food sensitivity, food intolerance and even IgG-mediated food hypersensitivity[15] have been used for this type of reaction. Now, two different IgG antibody testings are available, while IgG4 testing measures only the amount of IgG4 antibodies, a subclass of IgG antibodies, IgG testing gives total amount of four subclasses of them. Four of these studies used IgG,[17,19–21] one[18] used IgG4 testings.

Results of these clinical studies suggest the relationship between IBS and IgG positive foods. In case this finding and the growing knowledge for IBS-mast cell association are evaluated together, IgG-food antigen immune complex related mast cell activation can be thought as one of the factors for the pathogenesis of IBS. Consequently, increased IgG antibody titers can help for the selection of eliminated foods. In addition, some kind of food additives, such as thickening agents may be the subject of IgG-mediated mast cell activation. In the light of my experience, almost half of the patients with IBS have increased IgG antibodies for agar (E406), carrageenan (E407), and guar gum (E412).

On the other hand, the relationship between increased food specific IgG antibodies and adverse food reactions has been opposed by some authors. They concluded that the antibodies were present as the result of the physiologic response of the immune system, thereby reflecting exposure to foods and food tolerance.[36] Actually food-specific IgG antibodies are available in healthy individuals.[37] The food tolerance is defined as the specific suppression of humoral and/or cellular immune responses to prevent unnecessary immune reactions to innocuous

dietary antigens.[38] For this reason, presence of the antibodies against the food antigens in low levels may be explained by food tolerance. The increase in the amount of IgG antibodies above normal upper limits for some foods, may be due to loss of tolerance against them.[39] As a result, the immune system may recognize these food antigens as foreign ones and begin to produce antibodies against them. Perhaps their presence in low amounts may be necessary for physiological functions of mast cells.

Some objections have been focused on food specific IgG4 antibody testing.[40] Naturally, food-specific IgG antibodies are detected in healthy people with frequently presence of IgG4 subclass.[37] Currently, IgG4 antibodies have been accepted as "blocking antibodies" especially in the context of allergies.[41] Because IgG4 antibodies have low affinity to activating FcγRs and high affinity to inhibitory FcγRIIb, they can prevent excessive immune responses against sterile antigens.[41] Interestingly, in addition to the IBS study,[18] two Crohn study reaching symptomatic and laboratory improvements with elimination of IgG4 positive foods were reported.[42,43] Their good results can be explained by the presence both IgG and IgG4 positivity for some of the same food antigens especially the ones consumed frequently such as gluten, yeast, milk and products, egg and thickening food additives.[22] These topic needs to be investigated with exclusion diet studies comparing IgG and IgG subclasses.

Furthermore, all IgG positive foods do not cause symptoms. In a Chinese population study, chronic symptoms showed positive correlation with the concentration of some food-specific IgG antibodies, while others did not.[44]. This finding can be explained that some IgG-antigen complexes may not activate mast cells because they can bind inhibiting Fcγ receptors.[23] This possibility can be excluded by provocation for each IgG positive food after the patient become symptomless with elimination diet.

Conclusion

In recent years, numerous studies have revealed that mast cells play a role in both the physiological processes of the intestine and the pathophysiological factors of IBS such as visceral hypersensitivity, dysmotility, mucosal barrier disruption, altered intestinal fluid secretion and mucosal immune dysregulation. Additionally, presence of degranulated mast cell rich low grade intestinal inflammation in patients with IBS has focused the attention to IBS and mast cell association. Since the intestinal mucosa is mainly exposed to food and bacterial antigens, it is natural that food reactions due to mast cell activation may be part of this inflammation.

However, IgE-mediated mast cell activation (food allergy) is not common in IBS, symptomatic improvements with the elimination of foods having increased IgG levels suggest the activation of mast cells by IgG-food and addive antigen complexes. This type of activation may be a common factor in the pathogenesis of some IBS patients and can be considered as the missing peace of puzzle. Food-specific IgG antibody levels seem to help in selecting foods to be restricted. Other common mast cell activators are naturally occurring and added food chemicals and xenoestrogens. It should be noted that psychological stress and bacterial antigens and products are also among mast cell stimulants in IBS.

In the future, elimination of dietary and other mast cell activators with using mast cell stabilizers may give more promising results for the treatment of IBS.

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Conflicts of interest

The author has no conflicts to declare.

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