Implications from platelet–leukocyte aggregates in inflammatory bowel disease: Current and future status

Inflammatory bowel disease, which includes Crohn’s disease (CD) and ulcerative colitis (UC), is a chronic autoimmune inflammatory disease. Imbalance caused by immune responses is the benchmark of these two human bowel diseases, which have been traditionally considered as typical examples of T-helper type 1 (Th1) and type 2 (Th2) dominant diseases, respectively. However, the initial concept of Th1/Th2-mediated chronic inflammation must be re-evaluated in light of the discovery of an interleukin-12-related cytokine (interleukin-23). Interleukin-23 is known for its involvement in the establishment of chronic inflammation and in the development of a T-helper cell subset producing interleukin-17 (Th17). This distinct subset of T-helper cells, Th17 cells, has been shown to be capable of converting into Th1-producing cells after stimulation. Th17-related cytokines are regarded as new players in the control of chronic intestinal inflammation and homeostasis. Therefore, Th1/Th2/Th17 cell populations are potential targets of pharmacological manipulation and novel paradigms open up new avenues for the development of therapeutic strategies in the treatment of inflammatory bowel disease.

Inflammation and thrombosis are closely associated processes that may play important roles in the pathogenesis of inflammatory bowel disease and its complications. Apart from playing a pivotal role in the Th1/Th2/Th17 axis of the CD7 helper cells, platelets also participate in inflammatory and thrombotic responses. Furthermore, microparticles budding from cellular elements during inflammation are related to vascular dysfunction. Previous studies have shown that the levels of microparticles derived from leukocytes or platelets are increased in human inflammatory bowel disease, type 2 diabetes mellitus, and rheumatoid arthritis. Restoration of glycemic control in patients with type 2 diabetes mellitus has been reported to be correlated to the reduction in monocytic-derived microparticles after either gastric bypass or sleeve gastrectomy.

Moreover, a recent study also identified the collagen receptor glycoprotein VI as a key trigger for the generation of platelet-derived microparticles in human rheumatoid arthritis, which leads to the release of cytokine from synovial fibroblasts via interleukin-1. Collectively, all of the emerging findings highlight the importance of microparticles derived from endothelium, leukocytes, or platelets in the pathogenesis of human chronic autoimmune inflammatory diseases and their complications.

In this issue of the Journal of the Chinese Medical Association, Tekelioğlu and his colleagues conducted a prospective study to investigate whether the levels of platelet–leukocyte aggregates are increased in inflammatory bowel disease among a Turkish population. Using flow cytometric analysis, they found that the levels of platelet–leukocyte aggregates were indeed elevated in patients with inflammatory bowel disease compared with controls, irrespective of disease activity. This study included four patients with CD and 16 patients with UC. However, the sample size is relatively small compared with a previous study. Other limitations of this study included controls that were not age- and gender-matched, medications that affect the patients were not mentioned, and co-morbidity and complications such as thrombotic events were not described and correlated. The number of platelet–leukocyte aggregates has been found to be higher in patients with inflammatory bowel disease; however, this is lowered by thiopurine medication, suggesting that the use of immunosuppressive agents, and not corticosteroids or aminosalicylates, is linked with the reduced formation of platelet–leukocyte aggregates.

Result of another earlier study demonstrated that fewer leukocytes were found in the blood draining the intestine compared with blood supplying the intestine in CD and UC. In addition, the numbers of circulating platelet aggregates in CD were increased in venous samples than in paired arterial samples. The evidence reflects migration of the leukocytes into extravascular tissues and lumens of the inflamed intestine (such as the lamina propria) in patients with inflammatory bowel disease. This supports the concept that platelet activity is stimulated in the mesenteric microcirculation in CD.

Gut hormones and adipokines are also involved in the regulation of intestinal homeostasis and inflammation. For example, serum levels of ghrelin (anti-inflammatory) are increased, whereas those of leptin (proinflammatory) are decreased in patients with UC and CD. Furthermore, receptors for ghrelin and leptin are detectable on the surface of T lymphocytes, B lymphocytes, monocytes, and neutrophils. Acyl ghrelin has been reported to inhibit leptin-induced increases in tumor necrosis factor-α, interleukin-1β, and interleukin-6 from human T lymphocytes.
The use of nutraceuticals to combat over-nutrition to manipulate acyl ghrelin and leptin concentrations may be applied to affect the Th1/Th2/Th17 axis in human inflammatory bowel disease. In addition, plant extracts and traditional herbs, such as curcumin, guggulsterone, as well as anti-TNF-α therapy with infliximab can modulate the inflammatory status and possibly the mesenteric formation of platelet–leukocyte aggregates. CARD/NOD = caspase recruitment domain/nucleotide oligomerization domain; IL = interleukin; TGF-β = transforming growth factor beta; Th = T-helper cells; TL1a = tumor necrosis factor-like ligand; TNF-α = tumor necrosis factor alpha; Treg = T-regulatory cells.

Fig. 1. Schematic diagram showing the interactions between environmental cues, dendritic cells, leukocytes, hormones, platelets, the endothelium, and Th1/Th2/Th17 cell populations with their related cytokines in the inflammatory bowel disease. Removing the environmental cues and applying nutraceuticals, sairei-to, have been advocated to treat T-helper cell-polarized mucosal immune diseases. Others methods to remove the environmental cues can also be considered, including short-chain fatty acid, probiotics, and antibiotics (Fig. 1). Unfortunately, all of these varied treatment avenues still cannot better elucidate the cause-and-effect relationship between platelet–leukocyte aggregates and inflammatory bowel disease.

Because the incidence rate of UC is trending upwards in Taiwan and thrombotic events significantly contribute to the associated complications, a better recognition of the underlying immune-mediated mechanism of platelet–leukocyte aggregates and adequate treatment for inflammatory bowel disease are warranted to avoid morbidity and mortality. As administration of infliximab has become the mainstream therapy of human CD, and even UC (Fig. 1), the next step should be to investigate whether infliximab treatment with and without azathioprine in patients with CD (or UC) can reduce platelet–leukocyte aggregates, and to correlate platelet–leukocyte aggregates with the disease activity and clinical thrombotic event.

References


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