Review

Glucocorticoid receptor modulates dendritic cell function in ulcerative colitis

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Summary. Ulcerative colitis (UC) is a serious form of inflammatory bowel disease (IBD) occurring worldwide. Although anti-TNF therapy is found to be effective in over 70% of patients with UC, nearly one-third are still deprived of effective treatment. Because glucocorticoids (GC) can effectively inhibit granulocyte-recruitment into the mucosa, cytokine secretion and T cell activation, they are used widely in the treatment of UC. However, remission is observed in only 55% of the patients after one year of steroid use due to a condition known as steroid response. Additionally, it has been noted that 20%-40% of the patients with UC do not respond to GC treatment. Researchers have revealed that the number of dendritic cells (DCs) in patients with UC tends to increase in the colonic mucosa. Many studies have determined that the removal of peripheral DCs through the adsorption and separation of granulocytes and monocytes could improve tolerance of the intestine to its symbiotic flora. Based on these results, further insights regarding the beneficial effects of Adacolumn apheresis in patients subjected to this treatment could be revealed. GC can effectively inhibit the activation of DCs by reducing the levels of major histocompatibility complex class II (MHC II) molecules, which is critical for controlling the recruitment of granulocytes. Therefore, alternative biological and new individualized therapies based on these approaches need to be evaluated to counter UC. In this review, progress in research associated with the regulatory effect of glucocorticoid receptors on DCs under conditions of UC is discussed, thus providing insights and identifying potential targets which could be employed in the treatment strategies against UC.

Key words: Glucocorticoid receptors, Dendritic cells, Ulcerative colitis

Introduction

Ulcerative colitis (UC) is a type of chronic crypt-destructive inflammation, in which the mucosa is the main site of injury and is accompanied by clinical relief and exacerbation of bloody diarrhea. UC is a chronic inflammatory disease of the gastrointestinal tract known as inflammatory bowel disease (IBD). IBD is characterized by alternating phases of clinical relapse and remission defined into two major subtypes, Crohn's disease (CD) and UC. Although some pathologies of UC and CD are found to be similar, they can be distinguished based on their risk factors and genetics, clinical manifestations, endoscopy, and histological characteristics (Ordás et al., 2012). In a majority of patients, UC is manifested in the left or lower segment of the colon, with severity ranging from mild to moderate. The majority of patients with UC rely on long-term medication for its remission. Approximately 15% of patients with UC manifest severe acute symptoms and require hospitalization. Although short courses of steroid therapy have been effective in treating many patients with acute severe UC, its status in nearly one-third of the patient population does not improve (Doherty and Cheifetz, 2009). However, researchers

have determined that the levels of DCs in patients with UC are higher than those without, and their removal through the application of other forms of treatment could improve patient condition. GC can suppress the effect of DCs by reducing the levels of MHC II in patients. The correlation between the activities of these components has been described further.

Overview of UC

The highest and lowest rates of incidence and prevalence of IBD have been determined in the populations of Nordic countries, North America, and Asia. UC is the most common form of IBD (Danese et al., 2012). However, an increasing number of epidemiological studies have revealed that the incidence and prevalence of UC in Asia has been increasing annually. We calculated the incidence and prevalence based on the number of 100,000 cases per year. In the 1990s, the incidence of UC in the population of Asian countries such as Japan, China, and South Korea ranged from 0.35 to 1.95. Data has revealed that the rate of incidence of UC in the first decade of the 21st century was comparatively higher, ranging from 2.1 to 5.4. Data of the past 20 years has indicated that the prevalence of UC in these Asian countries has increased from 2.3-30.87 to 26.5-63.6 (Morita et al., 1995; Lok et al., 2008; Yang et al., 2008; Asakura et al., 2009; Chow et al., 2009; Shin et al., 2011; Prideaux et al., 2012). Researchers have elucidated that the increasing impact of westernized lifestyle has contributed to the occurrence and development of IBD and smoking, consumption of high-fat and high-sugar diet, drug use, lifestyle pressures, and an improvement in economic conditions are its major contributors (Dey et al., 2019).

The etiology of UC

The etiology and pathogenesis of UC is still unclear. The most commonly accepted theory is that UC occurs due to the induction of an inappropriate immune response resulting from an intestinal stimulus to unknown environmental factors. Genome-wide association studies have revealed that genetic defects impacting protection of the colonic epithelial barrier may contribute to the pathogenesis of this disease (Ford et al., 2013).

Genetic factors

Recent studies have confirmed that 47 UC-related loci are present in the genome of humans, of which 19 are specific to UC and 28 are associated with CD (Ordás et al., 2012). This association identified in the MHC II region near HLA-DRA is considered to be very significant. The HLA haplotype DRB1* 0103 is closely linked to the susceptibility and spread of the disease and its expression could potentially increase the risk of colectomy (Bouma et al., 1999). Interleukin (IL)-23, IL-

10, and genes of the Janus kinase 2 (Jnk 2) pathway are closely involved in the pathogenesis of UC (Anderson et al., 2011). The regions for hepatocyte nuclear factor 4α (HNFF-4S), CDH1, and laminin β1 have been identified as the risk sites specific to UC, which encode proteins involved in epithelial cell adhesion, and play a key role in the induction of barrier function defects responsible for its pathogenesis (Barrett et al., 2009). Genetic alterations such as MDR1 are related to glucocorticoid failure in UC. MDR1 Polymorphisms increase the Risk for UC, and there was a significant association of SNPs of the CTLA-4 gene and the MDR1 gene with the pathogenesis of UC (Zhao et al., 2015). Mutations of E-cadherin could be a new link correlating the induction of colorectal cancer with UC (Wheeler et al., 2001). Therefore, the main abnormality causing inflammation responsible for UC involves an over-modified atypical Th2 cell response, which leads to an over-reaction in the intestinal mucosa of genetically susceptible hosts against their symbiotic bacteria. Further research on the pathophysiology of UC is important for developing new treatment strategies. Mutations of E-cadherin could prove to be a new link associating colorectal cancer and UC (Lin et al., 2016).

Immune network

The immune system is a biological setup protecting the body from disease. The immune system has several mechanisms by which it can detect multiple pathogens and distinguish them from the healthy tissue of the host. The immune network theory states that the immune system is a network of immune cells and molecules, which are constantly interacting with each other (Gadina et al., 2017). The intestinal immune system consists of innate and adaptive immune components and is the most important element of the mucosal immune system, which is responsible for protecting various mucus membranes of the organism. The intestinal innate and adaptive immune systems have evolved in response to powerful stimuli generated by the presence and activities of the symbiotic flora (Ford et al., 2013).

The innate immune system consists of the epithelial barrier, macrophages, monocytes, neutrophils, DCs, natural killer (NK) cells, eosinophils and basophils. These cells operate together by secreting cytokines, chemokines, and antibacterial components, which trigger inflammation. This promotes the phagocytosis of infected cells and pathogens, triggers antigen presentation, and activates the adaptive branch of the immune system (Niess, 2008). Usually, local immune components are tolerant to the intestinal flora and food antigens. Although imbalances occurring in the intestinal flora might occasionally induce an inflammatory response, the reasons underlying this are not entirely clear (Ford et al., 2013). Defects in the regulation of mucosal immune responses could potentially lead to the development of IBD such as UC and CD (Strober, 2006; Xavier and Podolsky, 2007). Disorders in the epithelial

structures and destruction of tight junctions resulting from mucin deficiency are considered to be the potential causes underlying the occurrence of UC, which lead to the engulfment of normal symbiotic bacteria by the DCs. Then, DCs induce the activation of antigen-presenting cells and cause T cells to drive an abnormal inflammatory response (Hirahara et al., 2016).

Lymphocytes (T and B cells) are the main components of the adaptive immune system, which trigger an immune response (secretion of cytokines and antibodies) upon activation. Compared to the innate immune system, the adaptive immune system is highly specific and has a long lasting immune memory. It has been suggested that the adaptive immune system is mainly responsible for the pathogenesis of IBD and an increase in the levels of pro-inflammatory cytokines driven by the T helper (Th) cell subset may consequently increase those of the anti-inflammatory regulatory T cells (Tregs). Activated naive T cells (Th0) can differentiate into Th1, Th2, or Th17 cells (Ueno et al., 2018). While it has been suggested that the Th1 response drives the onset of CD, UC is mediated by the Th2 response. Recent progress in research has indicated that some cells such as ILCs and Th17 could be important factors driving the pathogenesis of IBD (Niess, 2008).

Clinical manifestations and diagnosis of UC

Since the rectum is inevitably affected during UC, its clinical manifestations usually include rectal bleeding, compression, and tension, and can also cause varying degrees of diarrhea depending on the proximal extent and severity of rectal inflammation (Ford et al., 2013). The standard classification system of UC is based on the severity of symptoms and degree of inflammation (Silverberg et al., 2005). However, during follow-up, this condition may change in 50% of the patients (Langholz et al., 1996). It has been observed that 5% of patients tend to develop primary sclerosing cholangitis and autoimmune liver disease (Vavricka et al., 2011). Joint swelling, saccharitis, and ankylosing spondylitis can be observed in 20% of patients, and eye diseases can occur in about 5%, which include scleritis, episcleritis, and anterior uveitis. Skin conditions including nodular erythema and gangrenous purulent disease is evident in 5% of the diseased population.

Upon manifestation of typical symptoms, patients are usually diagnosed by subjecting them to an endoscopic examination of the lower digestive tract, and the probability of any potential infection is parallelly eliminated by conducting a stool test. Simultaneous detection of colitis and biopsy of the large intestinal epithelial tissues concludes the diagnosis (Ford et al., 2013). Histology of tissues upon the onset of UC has revealed the manifestation of cryptitis, crypt abscess, epithelial loss/ulcer, infiltration of polymorphonuclear cells, and increased numbers of basal plasma cells. It has been observed that during the remission phase crypt abscesses gradually disappear with the simultaneous infiltration of white blood cells, regeneration of the epithelium, and a continuous increase in the number of basal plasma cells. This is accompanied by an increased infiltration of single glandular cells, structural deformation of glands (atrophy, shortening of branches, and appearance of crypts), epithelial metaplasia, and lymphoid hyperplasia. Additionally, an obvious epithelial displacement is also evidenced during chronic healing. Inflammatory cells in the lamina propria are mainly constituted by the lymphocytes, plasma cells, macrophages, mast cells, neutrophils, and eosinophils. These cells will play an important role in the pathogenesis of UC through mucosal damage response and immune reactions (Watanabe et al., 2007). However, few patients are diagnosed for UC during their first consultation. Furthermore, over 40% of patients get diagnosed for uncertain colitis, which is later detected as UC upon subsequent examinations (Henriksen et al., 2006). Contrarily, less than 5% of patients diagnosed initially for UC could later be diagnosed with CD (Henriksen et al., 2006). Because the courses, complications and treatment methods of both diseases are different, accurate diagnosis is very important. The granulocytes are the major population of the inflammatory cells in lamina propria. Dendritic cells are responsible for recruitment of granulocytes but the granulocytes are responsible for tissue damage (Fig. 1).

Therapy

Ulcerative colitis is a chronic, life-long disease. Glucocorticoids remain the first-line induction treatment of choice in moderate to severe UC, glucocorticoid-free remission is an established therapeutic target, and short- and long-term adverse effects should preclude their use as maintenance treatment (Rubin et al., 2019). Approximately 50% of patients affected by this condition undergo remission. However, 90% undergo remission, then relapse (Langholz et al., 1994). Currently, no treatment which can permanently alleviate the symptoms of the disease and prevent its recurrence is available. Although traditional research goals have focused on alleviating and curing the symptoms, in the past decade, there is increasing evidence to suggest that healing may be associated with the recurrence of the disease or colectomy. Therefore, in increasingly randomized experiments such as RCTs, healing of the mucosa during endoscopy is considered as the end point of the treatment (Ford et al., 2013). Abundant data derived through RCTs on the treatment methods, which induce and sustain the conditions of remission in UC is available. However, there is little data on overall disease management (Talley et al., 2011). Patients consuming 5-aminosalicylates for a long time to maintain good physiological state could be allowed back to the community with continued treatment. However, it is recommended for the patient to timely consult a specialist if worsening of conditions is observed (Kennedy et al., 2004). Patients with frequent relapses

(over once a year) should be treated or upgraded to the use of immunosuppressive or biological therapies under the supervision of an expert (Bernstein et al., 2010; Mowat et al., 2011). The surgical rates for patients with UC are declining due to the active cooperation of patients with frequent relapses (Targownik et al., 2012). Evaluating the duration of use of biologics in patients with UC is currently underway. For example, the efficacy of alternative medicines against TNF-α and other biologics is being evaluated (Van Assche et al., 2011). Adalimumab is an antibody different from anti-TNF-α, which has been reported to induce relief against the clinical symptoms of UT (Reinisch et al., 2011). Antibodies such as MLN0002 and pf-00547659 are also known to prevent the homing of white blood cells in the intestine, the preliminary effect of which is active inflammation and an ulcerative colon (Feagan et al., 2005; Vermeire et al., 2011). Since IL-13 is a potent cytokine secreted under conditions of UC, the development of IL-13 blockers is also necessary for its control. A recent study has confirmed that the interferon beta-1α can inhibit the production of IL-13 in patients experiencing UC (Mannon et al., 2011). The report has revealed that the conditions were exacerbated in patients with UC after clinical administration of the rituximab mAb, which consumes B cells, suggesting that it is important to carefully evaluate new individualized treatments prior to implementation (Goetz et al., 2010).

Interestingly, some studies have reported that the removal of peripheral DCs through the adsorption of granulocytes and monocytes may help improve the tolerance of the intestine for its symbiotic flora. These results further suggested that this method of adsorption-separation was efficacious in patients experiencing UC (Waitz et al., 2008; Thanaraj et al., 2010; Yoshino et al., 2011). Whether stem cells or combined immuno-suppressive therapies can be used to treat UC during its early stages is still an open question (Goetz et al., 2010).

DCs and UC

DCs

DC is the most important antigen-presenting cell which initiates the primary immune response against protein antigens. In the intestine, DCs are commonly present in the lamina propria, intestinal-associated lymphoid tissues (including lymphoid follicles and Peyer's patches), and mesenteric lymph nodes. In the Peyer's patches, DCs are located in the T cell area between the subepithelial dome and vesicles, while some occur in the lamina propria below the epithelial cells, which is convex in structure and used for intraluminal sampling (Wang et al., 2015). Functional studies have identified two major subgroups of DCs, which are characterized by the presence or absence of CD103. Some DCs produce effects through the formation of TNF-α and IL-12, while others promote the proliferation of Th17 cells. Additionally, anti-inflammatory responses are mediated by IL-10 or Tregs (Rescigno, 2010 Fig. 2).

DCs are antigen-presenting cells, which act as sentinels by acquiring antigens and transporting them to the lymphatic tissues, where they have the unique ability to activate naive T cells (Magnusson et al., 2016). DCs are involved in many activities of the innate and adaptive immune responses. They can determine
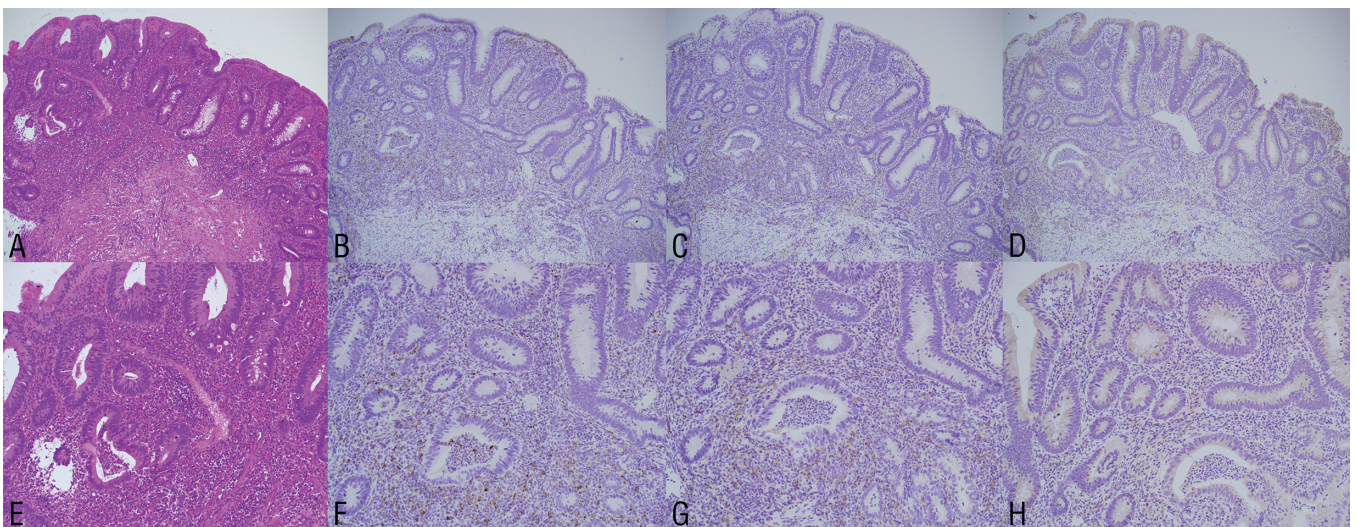
Fig. 1. Representative histopathological findings under conditions of UC. **A, H and E** show the histopathological features of UC such as cryptitis, crypt abscess, infiltration of polymorphonuclear cells, and increased basal plasma cells upon staining. The inflammatory cells in the lamina propria mainly constitute the macrophages and granulocytes (**B**, CD68 staining and **C**, CD163 staining) and DCs (**D**, DEC205 staining). **E and F** present images of the histopathological features of UC and CD68 staining, respectively, observed under magnifications of 200x. **G and H** present high magnifications of CD163 and DEC205 staining. A-D, x 100; E-H, x 200.

whether the induced immune response should be non-reactive or active or to be carried out by Th1 or Th2 cells. DCs can also control the tissue-specific homing of antigen-specific effector cells.

In our previous study, we evaluated the histological localization and phenotypic characteristics of infiltrating DCs and examined the relationship between the degree of DC infiltration and severity of inflammation in the colonic mucosa under conditions of UC. We also studied the expressions of macrophage inflammatory protein-3α (MIP-3α) and CC chemokine receptor 6 (CCR6) to evaluate the significance of immature DCs in crypt inflammation evidenced in UC (Ramamourthy et al., 2019). A significant positive correlation between the number of infiltrating DCs and the degree of crypt inflammation, mononuclear cell infiltration, crypt atrophy, and comprehensive active inflammation was observed. No significant correlation between the number of cells expressing the S-100 protein and the severity of crypt atrophy was determined. Cells positive for the S-100 protein, MIP-3α, and CCR6 were found to be frequently localized in or around the inflamed crypts. Neutrophils and cells exhibiting a dendritic morphology, which were positive for MIP-3α, and the S-100 protein and CCR6, respectively, were detected in or around the site of crypt inflammation. DCs and cells expressing the S-100 protein and CCR6 were found to be frequently clustered on the mucosal surface beneath that of the epithelium when the crypt was not inflamed. DCs expressing CD1a and the Langerhans cell-type DCs were not detected in any of the examined tissues. These data indicated that DCs had participated not only in the process of chronic inflammation but also in active crypt inflammation (Watanabe et al., 2007).

Mucosal DCs have multiple functions, which involve establishing tolerance and homeostasis of the mucosal immune system. Tolerance to intestinal autoantigens, oral antigens, and symbiotic flora is achieved through the interaction of DCs with Tregs and effector T cells. DCs are also involved in inducing responses against harmful T cells in the endogenous flora, which is the basis of the IBD pathology. Mucosal DCs express integrin αE (CD103) or the fractalkine/CX3CR1 receptor. DCs expressing CX3CR1 and CD103 are involved in intraluminal antigen recognition, and metabolism of vitamin A to retinoic acid as well as conversion of normal T cells to Tregs, respectively. Methods using genetically engineered mouse models and cell cultures will increasingly be used to study the biological connection between DCs expressing CD103 and CX3CR1 with the immune reactions triggered due to the symbiotic flora and their roles in inducing and regulating intestinal inflammation. DCs can maintain a steady state of the intestinal environment and coexist in harmony with the endogenous flora. The discovery of specific DCs involved in intraluminal antigen acquisition and tolerance will help develop targeted antigen acquisitions and design treatments for patients with IBD (Niess, 2008).

The involvement of DCs in the development of UC

Various animal models have provided evidence that mucosal DCs play a key role in the induction of IBD. However, the specific functions of some DCs are not yet clear and need to be determined in future studies to better understand the causes of IBD and develop
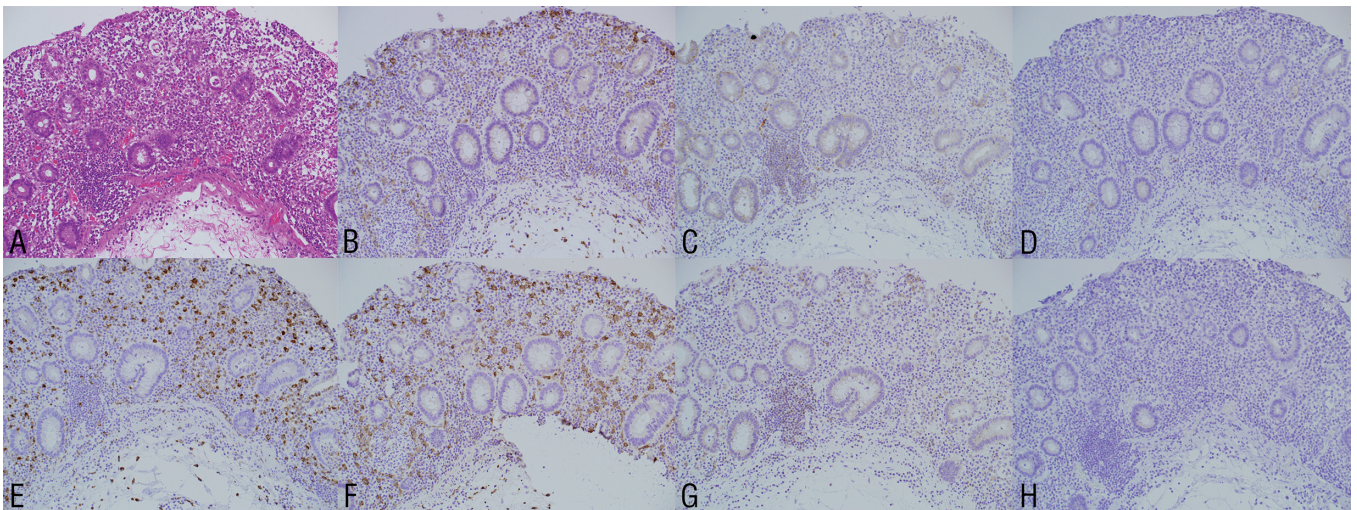
Fig. 2. Representative immunophenotype findings under conditions of UC. **A, H and E** show the histopathological features of UC such as the epithelial ulcer, cryptitis, and infiltration of polymorphonuclear cells upon staining. The inflammatory cells in the lamina propria mainly constitute the DCs (**B**, DC-SIGN staining and **C**, DEC205 staining), plasmacytoid DCs (**D**, CD123 staining), macrophages (**E**, CD68 staining; **F**, CD163 staining; **G**, HO1 staining), and follicular dendritic cells (**H**, CD21 staining). x 100.

mechanisms for protective mucosal immune response through the inhibition of intestinal inflammation. Consistent with the results obtained using animal models, it has been noted that DCs tend to accumulate at the inflamed sites in patients with IBD. Studies have revealed that intestinal DCs in patients with CD could upregulate the expressions of pathogen recognition receptors like TLR-2 and TLR-4, and activated/mature marker CD40 (Hart et al., 2005). Additionally, an increase in the number of monocytes expressing MDC8, which were producing TNF-α (probable precursors of the mucosal DC population) was observed in patients with IBD. As a result, DC activation in patients with CD was found to be reduced upon treatment with the anti-TNF-α antibodies. DCs gradually mature and increase in number in the inflamed tissue (De Baey et al., 2003). The subpopulations of DCs expressing CD83-CD80 and DC-SIGN could produce the cytokines IL-12 and IL-18, thereby promoting the development of Th1 cells (Te Velde et al., 2003). Moreover, in the peripheral blood and lamina propria of patients with CD or UC, the number of DCs expressing CD86 and CD40 was found to increase. Simultaneously, the ability of mononuclear cells present in the peripheral blood of patients with IBD to stimulate an immune response through the involvement of DCs had been enhanced (Yeung et al., 2000). In studies using mice models, DCs from an inflamed colon tissue and those located at the end of the ileum had been sampled continuously, the results revealed that the symbiotic bacteria could frequently produce IL-23 and IL-12 (Becker et al., 2003). IL-10 KO mice developing spontaneous colitis are protected from it upon administration of IL-12p19, which does not occur if the mice are deficient in IL-12 (p35). Constitutive activation of NF-κB in the symbiotic flora in IECs could regulate DCs and prevent tissue inflammation. Thymic stromal lymphopoietin (TSLP) produced by the epithelial cells is involved in the regulation of DCs, which triggers less harmful responses of Th2 and Tregs (Rimoldi et al., 2005; Zaph et al., 2007). However, DCs and their precursors are very sensitive to pro-inflammatory activation signals, an insight which may enable the long-term persistence of local T cell activation under conditions of IBD.

DCs, GR, and UC

What is GR?

Glucocorticoids (GC) are important stress hormones necessary to sustain life, which can regulate a variety of physiological processes and maintain homeostasis of the body. Synthetic derivatives of these hormones have been used for treating inflammatory diseases, autoimmune diseases, and cancers of the blood system. Glucocorticoid-refractoriness is a common phenomenon in UC, and a previous study assessed the mechanism of action related to steroid failure by integrating transcriptomic data from UC patients, highlighting the key role of steroid-induced transcription and the potential implication of ANP32E protein in this phenomenon (Lorén et al., 2019). Vitamin A and its active metabolite, retinoic acid (RA), play a key role in the promotion of the glucocorticoid response (Bonhomme et al., 2019). Other nuclear receptors, such as NF-kB or AP-1, can compete with glucocorticoid response elements (Caraffa et al., 2016). A previous study indicated that endogenous steroid production has a role in the response to glucocorticoids (Hardy et al., 2018). The physiological and pharmacological effects of GC are mediated by the glucocorticoid receptor (GR), which is a factor involved in ligand-dependent transcription and a member of the nuclear receptor superfamily. GR occupied by the ligand binds directly to the response elements of the DNA and physically binds to other transcription factors, inducing or inhibiting the transcription of many genes. The traditional viewpoint, according to which a single GR protein can induce the activity of GC, has changed drastically with the discovery of many isoform receptors with unique expression, gene regulation, and functional properties. GR are expressed in every cell of the body and the global effect of the drug has to be emphasized. GR distribution in isolated hepatocytes and nonparenchymal hepatic stellate cells, kupffer cells, and liver fibroblasts, mediate glucocorticoid action which inhibit chemokine expression (Raddatz et al., 1996, 2005; Sunil et al., 2010). These GR isoforms have been extracted from the individual genes through alternative splicing and selective mechanisms of translation initiation. Post-translational modifications of these GR isomers have further expanded the diversity of GC responses (Oakley et al., 2013).

Our previous study reported the quantitative data of GR spliced variants in lymphoma cell lines created using real-time quantitative reverse transcription-polymerase chain reaction, and documented the subcellular distribution of GRα with GR-P in response to GC administration. Since the hormone-binding domain is present at the C-terminal end, GRα is rendered functional and mediates the transcriptional response of GC. GRβ cannot bind to GC but inhibits the transcriptional signals mediated by GRα. GR-P combined with GRα forms heterodimers, which can translocate to the nucleus and induce the transcription of target genes in ways different than those of the regular GRα homodimers. The GR-P proteins generated abundantly as a result of Dex administration may lead to the relative dominance of the "GRα-GR-P" heterodimers and inhibit normal transcriptional activity of the GRα homodimers in lymphoma cells (Ishida et al. 2011).

DCs and GR

GC stimulates antigen uptake (Piemonti et al., 1999) and can effectively inhibit the activation of DCs by reducing the expressions of MHC II, co-stimulatory molecules, and cytokines (Matyszak et al., 2000). This

has been demonstrated through both *in vivo* and *in vitro* studies. Results of *in vitro* studies have indicated that GC presumably inhibits the activation of DCs by downregulating the expression of CCR7, after which their migration to the lymph nodes is also inhibited (Vizzardelli et al., 2006; Tuckermann et al., 2007). However, in an asthma model, GC treatment *in vivo* did not affect the maturation of DCs during the sensitization phase (Wiley et al., 2004). GC does not simply inhibit the activity of DCs but also induces tolerable DCs and enhances the expression of IL-10 by inhibiting the markers of DC activation, which is accompanied by the upregulation of their phagocytic activity (Rutella et al., 2006). Tolerant DCs induce T cell disability, suppress T cells, and produce Tregs to prevent autoimmune or graft-versus-host responses (Rutella et al., 2006). Glucocorticoids can modify the phenotype of dendritic cells (Chambers et al., 2018). Studies have revealed that GCs are one of the most effective inducers of tolerant DCs (Chamorro et al., 2009). Based on these results, it can be elucidated that a strong mechanism exists, which can produce anti-inflammatory effects through the involvement of GC (Baschant and Tuckermann, 2010).

Interaction of DC and GR in patients with UC

The anti-inflammatory effects of GC are manifested partly due to their influence on the activities of various immune cells. It has been reported that GC inhibits the maturation of DCs (Piemonti et al., 1999). MHC II can also actively induce the maturation of immature DC and apoptosis of matured DC (Lokshin et al., 2002; Leverkus et al., 2003). The addition of GC during DC activation can reduce the expressions of surface MHC II and costimulatory molecules, inhibit the production of pro-inflammatory cytokines, and increase the production of IL-10 (Rozkova et al., 2006). Antigens were also expressed on lamina propria mononuclear cells, which coincided with the distribution of S-100+ dendritic cells. Moreover double staining for S-100 antigen and IL-2R antigen revealed that most of the S-100+ dendritic cells were also IL-2R positive. These findings seem to provide evidence for the important role of lamina propria dendritic cells in the immunological pathogenesis of ulcerative colitis (Watanabe et al., 2007). It was observed that when antigens were pulsed in the presence of GC during their processing, their presentation on the DCs was almost suppressed (Holt and Thomas, 1997). Therefore, it could be suggested that GC had impaired the ability of DCs to stimulate T cells (Bros et al., 2007). Additionally, GC can reduce the number of DCs by inhibiting their migration and increasing DCs apoptosis. However, few reports have suggested that GC does not induce apoptosis in DCs (Rozkova et al., 2006; Bros et al., 2007). It is unclear whether different subgroups of DCs respond differently to GC-induced apoptosis. Both beneficial and deleterious effects of GC are mediated by GR. In previous studies, we have demonstrated that one GR gene encodes multiple isoforms of GR, including

GRα and β, and GRα-A, B, C1, C2, C3, D1, D2 and D3, which are produced by alternative splicing and other mechanisms of translation initiation, respectively (Lu and Cidlowski, 2005). Although various isoforms of GR demonstrate different tissue distribution patterns, it was observed that the level of GRβ was significantly higher than that of GRα. Moreover, GRβ probably does not impact the activity of GC, through which it exerts its effect on DCs (Oakley et al., 1996; Freeman et al., 2005) After activation of GC, GR mainly inhibits expression of the pro-inflammatory genes and induces that of the anti-inflammatory genes at the transcriptional level (Coutinho and Chapman, 2011). Different subtypes of GR have different genomic targets (Lu et al., 2007). Furthermore, all isoforms of GR except GR-D promote apoptosis in the osteoblastic lineage of U-2 OS cells by inducing and inhibiting pro-apoptotic and anti-apoptotic genes, respectively (Lu et al., 2007). Although it has been proven that DCs express GR, the GR isoform located on the DCs has not yet been identified and it is unclear whether the various isoforms of GR specifically regulate the function of DCs (Meindl et al., 2009). TLR activation promotes the induction of effective antimicrobial responses. This is an advantage of TLR activation over the immunosuppressive effects exerted by GC. The immune response, thus induced, can be crucial. Therapeutic manipulation of the TLR pathway using specific agonists may provide new ways of protecting immune cells from harmful immuno-suppression induced by GC. Contrarily, TLR antagonists can be used to restore the sensitivity of GC against inflammation and autoimmune diseases (Lepelletier et al., 2010).

Cao has reported that only mature DCs are sensitive to GC-induced apoptosis and a switch in the isoforms of GR on the DCs is observed during their maturation (Cao et al., 2013). The killing effect of mature DCs can be inhibited by the selective antagonist of GR, RU486, which is effective against the activity of dexamethasone (DEX), an effective agonist of GR. Ectopic expression of the pro-apoptotic subtype of GR in immature DCs can induce GC sensitivity. This suggests that the translation of GR to selectively express its isoforms in immature and mature DCs may have rendered them sensitive to GC during their maturation. We also found that DEX inhibits antigen uptake and production of cytokines by immature and mature DCs, respectively. Therefore, it can be suggested that GC regulates the function of DCs in a DC-specific stage-specific manner through the involvement of selective GR isoforms. These studies, as well as those conducted using other cell types, can provide the basis for developing compounds with higher benefit-risk ratios, which are specific to the GR isoforms (Cao et al., 2013).

Previously, we studied the relationship between the expression of GR in biopsied colonic mucosa and the responsiveness of patients with UC to GC. The results revealed that that the numbers of cells containing GRβ were significantly higher in the GC-resistant group than

those in the GC-sensitive and control groups. The mRNA of GRα was expressed in all patients with UC, while that of GRβ was expressed only in one and 7 patients in the GC-sensitive and GC-resistant groups, respectively. The presence of cells positive for both GRβ and CD4 or CD19 was frequently observed. The count of cells expressing Foxp3 was significantly higher in the GC-sensitive group than that in the GC-resistant group. However, cells expressing both Foxp3 and GRβ cells were not observed. These results indicated that the sensitivity of GC therapy could probably be predicted by immunostaining biopsy specimens for the detection of GRβ and Foxp3 (Fujishima et al., 2009).

GRβ is overexpressed in severe allergic rhinitis. It was found that the extent of expression of GRα and NF-kB was similar in the patients and control subjects, while that of GRβ was significantly higher in the patients, resulting in an increased ratio of GRβ/GRα. Our findings have suggested that GRβ plays an important role in inducing resistance to GC therapy against allergic rhinitis and its expression might be considered as an additional parameter to indicate steroid resistance for this disease (Ishida et al., 2010).

Conclusion

UC is the most common type of IBD, against which anti-TNF treatments such as the use of GC have proven to be efficacious. However, due to a disease called steroid response, only 55% of patients experienced remission after one year of steroid use. GC can effectively inhibit the activation of DCs by reducing the expression of MHC II molecules (Matyszak et al., 2000). Additionally, it was found that 7% of the patients with UC did not respond to GC treatment. Therefore, alternative biological and new individualized therapies need to be evaluated to counter the effects of UC. Furthermore, researchers have determined that the levels of DCs increase in patients with UC. Studies have shown that the removal of peripheral DCs through the adsorption and separation of granulocytes and monocytes could improve tolerance of the intestine to its symbiotic flora (Rutella et al., 2006). DCs are sensitive to apoptosis induced by GC and undergo transition depending upon the GR subtype during maturation. The translation of GR to selectively express isoforms in immature and mature DCs could be the underlying reason for GC sensitivity during DC maturation. Therefore, GC regulates DC function in a stage-specific manner using selective isoforms of GR. Based on these results, further insights regarding the beneficial effects of Adacolumn apheresis in patients subjected to this treatment could be revealed (Waitz et al., 2008; Thanaraj et al., 2010; Yoshino et al., 2011). Some studies can provide the basis for developing compounds specific to the GR subtype with higher benefit-risk ratios. Moreover, researchers have also found that immunostaining of biopsy specimens to detect GRβ and Foxp3 could enable prediction of the sensitivity of GC

treatment (Fujishima et al., 2009). Further studies need to be conducted to determine the regulatory effects of GR on the functions of DCs under conditions of UC, which can provide better solutions and theoretical support for the development of treatment strategies and application of drugs to treat UC.

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