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Research of Immunology Markers of UC

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1. Introduction

Several risk factors are recognized to increase an individual's susceptibility to develop inflammatory bowel disease (IBD) that are related to molecules that play a role in intestinal homeostasis and mucosal immune response to luminal antigens. The hallmark of IBD is a chronic, recurrent inflammation of a particular segment of the gastrointestinal tract, which is presented as a loss and damage of the intestinal epithelial barrier, exposing immune cells to luminal antigens, that might finally trigger the recruitment and activation of other immune cells and unleashing an exaggerated immune response (Abraham and Cho, 2009; Kaser et al., 2010).

Mucosa immune response in general includes different mechanisms of induction, regulation and resolution (Medzhitov, 2010). Different factors participating in these mechanisms will act as inducers, initiating an inflammatory response that will be detected by specialized sensors or sentinel cells. This process will subsequently lead to the production of inflammatory mediators that will affect different tissues; eliciting changes in their functional state that will optimize an adaptation process to the harmful condition associated to the inflammatory response (Medzhitov, 2010).

Due to the chronicity of the inflammatory response, in IBD the mechanisms that regulate and resolve the induction of the inflammatory process are defective. Although the constant induction of the inflammatory process prevents an effective regulation and resolution, making difficult to estimate the key processes involved in the development of IBD.

Since that immune system and cytokines has been linked with the pathogenesis of inflammatory disorders, including IBD, the clinical and pathological significance of IL-33/ST2L system in UC, is consistently supported by *in vitro* and *in vivo* studies. The involvement of the inflammatory mediator IL-33 in the activation the other immune cells might result in a chronic inflammatory response in the colonic mucosa that is reflected at the systemic level. To avoid an exaggerated immune response, the host has developed mechanisms to counteract the resulting inflammation through the release of soluble receptors, such as sST2. These decoy molecules are potential surrogate of immunological markers for UC.

2. Intestinal inflammatory process in ulcerative colitis

IBD is a chronic, relapsing-remitting condition that affects the gastrointestinal tract. The aetiology of IBD has not been fully elucidated, although, it has been described as a multifactorial disease, in which genetics, environmental factors and immune system have a leading role (Abraham and Cho, 2009; Xavier and Podolsky, 2007). IBD is a complex polygenic disease in which many genes, related or not, through their contribution and interaction with environmental factors are involved in the final disease manifestation (Bouma and Strober, 2003; McGovern et al., 2010; Risch and Merikangas, 1996; Thompson and Lees, 2011).

The two major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC), both with unique characteristics that make them different at the clinical, cellular and molecular level (Thompson and Lees, 2011). CD may affect a portion of the intestine in a segmental fashion and present a transmural inflammation that extends the entire intestinal wall; whereas in UC a diffuse and continuous inflammation is confined to the mucosa of the colon (Baumgart and Carding, 2007). Histopathologic features of UC confirm that the inflammatory process is limited to the mucosa and typically consists in an increase of inflammatory cells, such as polymorphonuclear granulocytes (Nishida et al., 2002), that extends through the crypt wall (cryptitis) or inside glands with subsequent formation of cryptic abscesses. Moreover, UC is also characterized by crypt architectural distortion due to epithelial injury, shortening or branching of the glands, goblet cells depletion; and presence of lymphoid aggregates associated to oedematous and congestive lamina propria (Silverberg et al., 2005). According to the features previously described, UC pathogenesis can be explained by a deregulation of the inflammatory response of the intestinal mucosa due to epithelial barrier defects to luminal antigens in genetically susceptible individuals. Thus, those diseases characterized by the presence of a defective epithelial barrier show a deregulation of inflammatory processes (Kaser et al., 2010).

Inflammation in UC is restricted to the most superficial layer of the colonic mucosa. Mechanisms that possible may lead to the epithelial injury are reflected by architectural crypt distortion, an increase in the distance between crypts or a decrease in the crypt number; however they are not fully understood. Nonetheless, these mechanisms are likely responsible for the induction of the distinctive inflammatory process of the disease.

Recently, considerable evidence (murine models, genetic studies, *in vitro* assays, etc) has demonstrated that UC and CD involve an uncontrolled primary response of the innate immune system against intestinal luminal compounds, mainly mediated by macrophages, mast cells and neutrophils (Kaser et al., 2010). This uncontrolled inflammation will redound in a scarcely resolute T and B cells-mediated adaptive immune response. However, in spite of all this information the mechanism involved in the activation of the cellular response is still unknown. This enquiry has highlighted several line of research focused in the study role of the innate immune system in IBD pathogenesis.

2.1 Innate immune receptors in ulcerative colitis pathogenesis

Innate immune response is the first line of defence that protects the host from invasive pathogens and is responsible for their rapid recognition, detection, and elimination. This response initiates and defines the adaptive immunity that is executed by B and T cells. The strategies of recognition in the innate immune system are based on identification of pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors

(PRRs) located on the cell surface or in intracellular compartments, such as endosomes. PRRs are also responsible of the initial recognition of damage-associated molecular pattern (DAMPs) and participate in phagocytosis, activation of pro-inflammatory intracellular pathways, opsonization, complement activation and induction of apoptosis (Medzhitov, 2001). PRRs include Toll-like receptors (TLRs), Nod like receptors (NLRs), RIG-I-like receptor (RLRs), and C-type lectin receptors (CLR) (Kawai and Akira, 2010; Kumagai and Akira, 2010). TLRs are the best characterized family of PRRs that are involved in immune response mechanisms to protect epithelial barrier integrity and invasive microorganisms elimination, contributing to the tolerance and the homeostatic balance of the intestinal mucosa (Podolsky, 2002). TLRs belong to the IL-1 receptor/Toll-like receptor (TLR-IL-1R) superfamily and contain several leucine rich repeats in their extracellular domain and intracellular toll/IL-1 receptor (TIR) domain. TLRs are expressed in both innate immune cells, including macrophages and dendritic cells (DCs) and epithelial cells. The major TLR signalling pathways is the activation of the transcription factors, such as nuclear factor- κ B (NF κ B) and activating protein-1 (AP-1) that direct to the production of pro-inflammatory cytokines, chemokines, and adhesion molecules (Wang et al., 2001). In pathological conditions, such as in IBD, over-activation of TLRs may induce defective signalling, allowing the induction, amplification and perpetuation of harmful immune responses and the development of a chronic inflammation reflected by an impaired function of the epithelial barrier (Cario, 2010; Kamada et al., 2008).

2.1.1 Pathogenic role of TLR2 in ulcerative colitis

In murine models of colitis, Rakoff-Nahoum et al demonstrated that in TLR2 and adaptor MyD88- deficient mice, microflora-dependent TLR2 signalling is required for the homeostasis of the intestinal epithelium and protects gut epithelia (Rakoff-Nahoum et al., 2004). Clinical evidence supports the close relationship between TLR2 over-expression and UC (Cario et al., 2000). Genetic factor involved in UC, some TLR2 polymorphisms have been described, such as SNP Arg753Gly, which affects the recruitment of signalling pathway molecules and influences over inflammation and disease severity in UC patients with no impact on its susceptibility (Pierik et al., 2006). The nucleotide deletion of TLR2 gene at position -196 to -174 might be associated to a higher risk of severe corticoid-dependence in UC (Wang et al., 2007). Intestinal mucosa isolated lamina propria mononuclear cells show a higher expression of TLR2 in IBD patients than in healthy controls (Cario et al., 2000) and submitted data). In addition, peripheral blood monocytes obtained from IBD patients have a high content of TLR2 on the cell surface, which correlate to a high production of TNF- α in response to receptor agonists (Canto et al., 2006). On the other hand, we have recently shown high levels of TLR2 in colonic mucosa of UC patients and that these finding might be related to a higher expression of TLR2 in CD33⁺CX3CR1⁺ macrophage surface in comparison to controls (submitted results). UC patients also presented elevated levels of soluble TLR2 (sTLR2), which has been shown to sequester TLR2 ligands thus, reversing TLR2 pathway activation (LeBouder et al., 2003). At the moment, evidence indicates that sTLR2 generation might be related to post-transduction mechanisms, suggesting that high levels of transmembrane TLR2 in UC intestinal macrophages might be the main cellular source of this decoy receptor. The generation of sTLR2 might be explaining a compensatory mechanism to restrain the exaggerated inflammation triggered by over-activation of TLR2 in intestinal mucosa of UC patients. This inflammatory condition might explain the

participation of sTLR2 to counteract the epithelial damage generated as a consequence of activation of pro-inflammatory signalling pathways, without restabilising the mucosa homeostasis.

2.2 Epithelium in innate immune response

The intestinal epithelial cells (ECs) are continually exposed to bacteria (microbiota and enteric pathogens); however, this interaction does not usually generate a pathological inflammatory response. To maintain integrity and normal function of the intestinal tract, ECs not only constitute a physical barrier that keeps a balance between local homeostatic response and host defence against microbiota and pathogens, but also, provides important functions in the regulation of the mucosal immunity. Recent studies indicate that in response to challenges, intestinal ECs through PRRs drives the expression of critical Th2-driving cytokines, such as IL-25, TSLP and IL-33, which mediate the initiation and interplay between innate and adaptive immunity (Bulek et al., 2010; Schleimer et al., 2007).

IL-33 expression is induced in the intestinal epithelium by exogenous stimuli, including allergens, microbiota, pathogens and pro-inflammatory cytokines (IL-1 and TNF- α), coordinating the immune regulation to maintain homeostasis and drive a protective Th2 phenotype (Schmitz et al., 2005). However, elevated production of these cytokines will be associated with inflammatory Th2 condition in lesions of the mucosa producing pathological changes in the tissue (Schmitz et al., 2005). The IL-33 signalling pathways might exert distinct impact on other inflammatory cells that amplified and perpetuated the immune responses permitting the development of a chronic inflammation (Figure 1).

During inflammatory episodes, different cells, such as lymphocytes, macrophages, neutrophils and mast cells infiltrate the intestinal mucosa, promoting increased production of pro-inflammatory cytokines associated with different immune profiles. In patients diagnosed with UC, Th2 cytokines such as IL-4, IL-5 and IL-13 have been associated (Beltran et al., 2009; Bernstein et al., 2005). In relation to Th2 response that characterized UC, IL-33 is also able to polarize naive T cells into Th2 cells and induce production of IL-4, IL-5 and IL-13 that resulted in pathological changes in the intestinal architecture that includes eosinophilic infiltrates, increased mucus production and epithelial cells hyperplasia and hypertrophy (Figure 1).

2.3 Pathogenic role of the IL-33/ST2 system in ulcerative colitis

Recently, we and others have reported that IL-33 expression is increased in colonic mucosa of UC patients, particularly in those with moderate to severe activity of the disease (Beltran et al., 2010; Kobori et al., 2010; Pastorelli et al., 2010; Seidelin et al., 2010). It has been proposed that in UC, IL-33 may be released by injured epithelial cells to induce pro-inflammatory cytokines production (i.e. IL-1, IL-6, TNF- α , IL-5 and IL-13) through activation of ST2L in mast cells, macrophages, eosinophils and neutrophils (Luthi et al., 2009). Moreover, IL-33 expression is restricted to the epithelial layer of the intestine (Beltran et al., 2010; Pastorelli et al., 2010). In addition, activation of ST2L in dendritic cells may contribute to the polarization to IL-5 and IL-13-producing Th2 cells (Rank et al., 2009) and in basophiles the induction of IL-13-dependent fibrosis (Pecaric-Petkovic et al., 2009). Those cytokines induced by IL-33, mostly IL-13, may have detrimental effects on epithelial barrier function (Heller et al., 2005). Together, the effects induced by IL-33 might amplify the local

inflammatory response, and therefore, contributing to perpetuation of pathogenic inflammatory process that is characteristic of the disease (Palmer and Gabay, 2011).

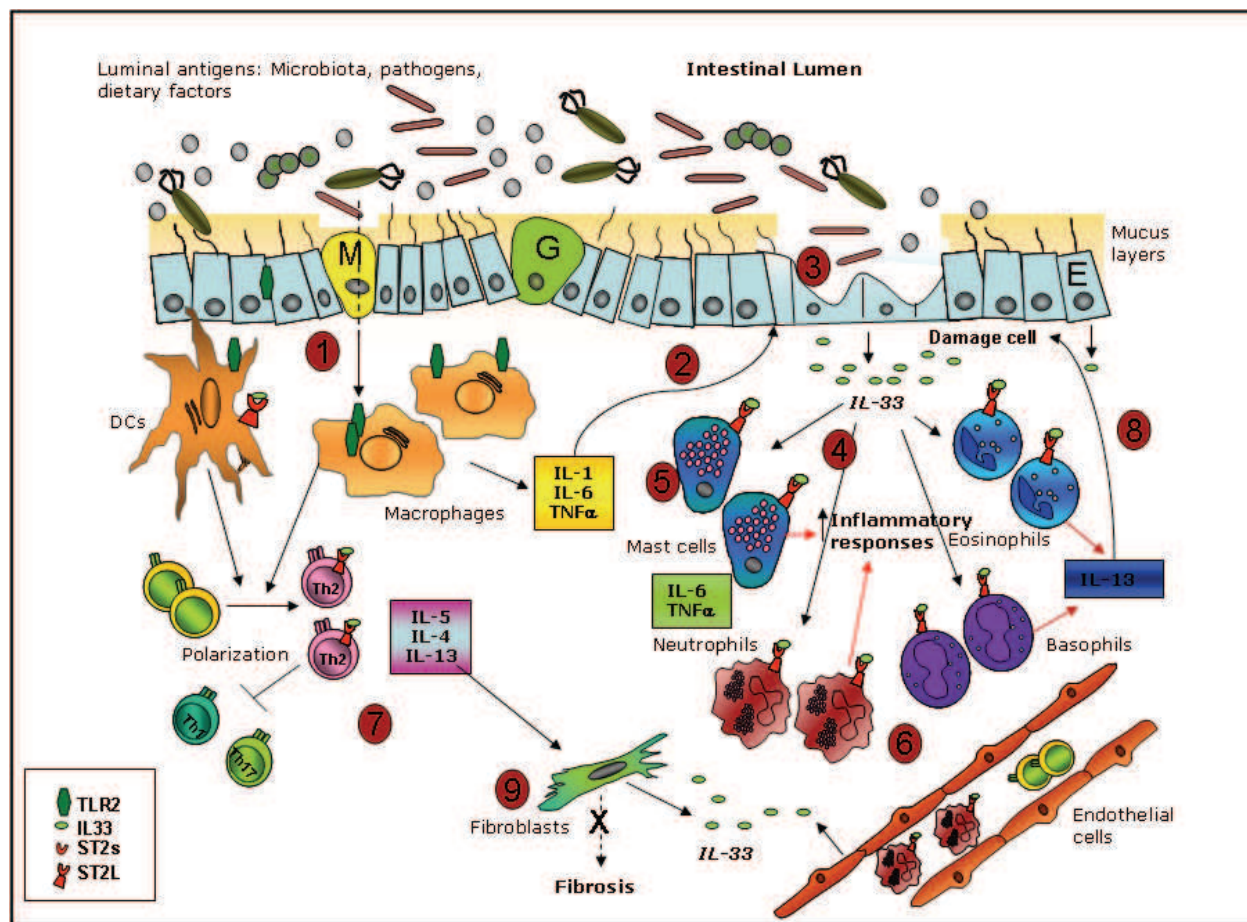


Fig. 1. Role of IL-33/ST2 receptor system in UC. In ulcerative colitis (UC) epithelia is more exposed to pathogens, as mucus layer is deficient to prevent their access to the barrier, with persistent inflammation that also promote epithelial disruption. The tissue injury can be a consequence of infections or the access of the microbiota, which are linked to the development of IBD. The over-activation of TLR2 present in the macrophage cell surface (1) will produce inflammatory cytokines, as well as, tumor necrosis factor (TNF- α) and IL-1 (2), that promote the epithelial injury (3). Tissue damage leads to the release of interleukin-33 (IL-33) from epithelial cells (4), which acts as an early inducer of inflammation. IL-33 induce the expression of pro-inflammatory cytokines in cells that express ST2 receptor (mast cells (5), neutrophils activated, eosinophils and basophils (6)). Moreover, IL-33 may drive antigen sensitization and polarization to T helper 2 (Th2) -mediated inflammation (7) during the development of UC owing to its ability to activate dendritic cells (DCs) and to recruit, polarize and activate Th2 cells that also express ST2 receptor. IL-33 can induce eosinophilia by mast cells through the induction of IL-13 secretion. IL-13 exerts detrimental effects on epithelial barrier function, favoring the effects of IL-33 (8). Mast cell-mediated inflammation may drive a robust proliferation of fibroblast toward fibrosis formation, however high levels of sST2 might counteract this cellular effect of IL-33. (M: M cells; G: Goblet cells and E: Epithelial cells)

2.3.1 Components of the IL-33/ST2 system

Clinical and experimental data have shown that activation of IL-33/ST2 pathway is primarily occurring in diseases that affect epithelial barriers, such as asthma, arthritis and UC (Palmer and Gabay, 2011). ST2 protein (IL1RL1) is encoded by a single gene located on chromosome 2q12 (Tominaga et al., 1991), that is part of the TLR-IL-1R superfamily. Three types of *st2* gene products are generated by alternative splicing: ST2L, which is the complete form of protein, the receptor itself, that has a TIR intracellular domain (similar to Toll/Interleukin-1 receptors domain), a transmembrane and an extracellular domain formed by three immunoglobulin-like domains that binds IL-33; a soluble form of ST2 (sST2) that lacks the transmembrane and intracellular domains, but can also recognize IL-33; and a form bound to the plasma membrane (vST2) that, similar to sST2, lacks the intracellular domain. The production of these isoforms is under the control of two distinct promoters (proximal and distal) which have a differential activity depending on the cell type (Gachter et al., 1996; Iwahana et al., 1999). The differential function of the promoters allows a 3' differential processing of *st2* mRNA to generate the STL2 and sST2 isoforms (Bergers et al., 1994). To date, the cellular and molecular context that might activate a defined promoter it is still uncertain, and the signalling pathways required to produce one protein over the other, is even less clear. Many studies recognized pro-inflammatory properties to ST2L receptor activation and anti-inflammatory effects to the soluble form sST2. However, since there is no an experimental model available where characteristics of one of the protein isoforms are conserved, the attribution of these functional effects to ST2 remains under speculation.

Since IL-33 cytokine was described as the ligand of ST2L receptor, its effect has been associated to a Th2 immune profile (Schmitz et al., 2005). The signalling pathway activated upon ligand binding to ST2L is common to all members of the TLR-IL-1R superfamily, involving recruitment of MyD88, IRAKs and TRAF6 adaptor molecule which leads to phosphorylation of Mitogen-Activated Protein Kinases (MAPK) such as ERK1, ERK2 and p38 pathways and the consequent activation of NF κ B and AP-1 to induce pro-inflammatory gene expression (Palmer et al., 2008; Schmitz et al., 2005).

2.3.2 Cellular sources of IL-33/ST2 system

ST2L receptor expression has been mainly associated to immune cells, such as mast cells, macrophages, dendritic cells, NK cells, eosinophils, basophils, Th2 lymphocytes and activated neutrophils (Allakhverdi et al., 2007; Ho et al., 2007; Komai-Koma et al., 2007; Rank et al., 2009; Suzukawa et al., 2008a) (Figure 1). Polymorphonuclear leukocytes have been also demonstrated to produce the soluble form sST2. However, sST2 has been primarily associated to fibroblasts, epithelial and endothelial cells (Hayakawa et al., 2007). The ligand of ST2, IL-33, was initially described as a nuclear protein, and is constitutively expressed by cells in contact with external surfaces, such as epithelial and endothelial cells (Baekkevold et al., 2003), and is potentially released in response to tissue damage, to rapidly activate the innate immune system (Palmer and Gabay, 2011). Induced expression of IL-33 has been reported in different cell types, in resident as well as in infiltrating inflammatory cells (Oboki et al., 2011). IL-33 is the most recently described member of the IL-1 cytokine family (Schmitz et al., 2005), has been attributed to have similar functions to IL-1 α exerting dual effects as a nuclear factor as well as a pro-inflammatory cytokine (Carriere et al., 2007; Cayrol and Girard, 2009; Roussel et al., 2008; Talabot-Ayer et al., 2009). IL-33 gene does not encode a secretion signal peptide, such as other cytokines, so that its secretion is not

produced by conventional mechanisms (Lamkanfi and Dixit, 2009; Zhao and Hu, 2010). It has been suggested that IL-33 is released during cell necrosis, similar to what was previously described for the alarmins, as an inflammatory response that will produce early activation of innate immune system cells (Haraldsen et al., 2009; Lamkanfi and Dixit, 2009). One of the major cellular sources of the receptor ST2L in the intestinal mucosa is mast cells (Figure 1) which have been demonstrated to have important roles in the distinctive inflammatory process of UC (Allakhverdi et al., 2007; Iikura et al., 2007; Lee et al., 2002; Moritz et al., 1998). Mast cells are considered true sensors of cell injury in tissue exposed to the exterior (Enoksson et al., 2011). These cells might be responsible of orchestrating and enhancing the innate immune response induced by IL-33 in the intestinal mucosa in UC patients, since mast granulatory products have been detected in inflamed areas of the intestine (Bischoff et al., 1996).

2.3.3 Regulation of IL-33/ST2 inflammatory pathway: Role of sST2

One of the hallmarks of UC is chronicity, and periods of active inflammation (flare-ups) and remission. This special feature of UC opens different questions about inflammation regulation. The clinical practice can demonstrate classic endoscopic and histologic patterns of active inflammation in patients, where, mild mucosa inflammation is generally characterized by vascular congestion, erythema, oedema and granularity (Pineton de Chambrun et al., 2010). When inflammation becomes severe in UC, friability, spontaneous bleeding and macroscopic ulcers of different sizes are mainly observed (D'Haens et al., 2007; Fefferman and Farrell, 2005). Therefore, a patient in remission, after a period with lesions, the mucosa might have a reduced inflammatory process, reflected by mucosal healing (MH) and a decrease in cellular infiltrates (Lichtenstein and Rutgeerts, 2010; Rutgeerts et al., 2007). The MH is characterized by restoration of a normal vascular pattern, absence of friability, bleeding, erosions and ulcers in all intestinal segments of the mucosa visualized in the intestine from UC patients (Lichtenstein and Rutgeerts, 2010; Rutgeerts et al., 2007). However, at a cellular level, there is no consensus on the processes leading to MH. Only restoration, proliferation and differentiation of epithelial cells adjacent to the injured area will allow intestinal wound healing (Iizuka and Konno, 2011). Many reports support the evidence that activation of IL-10 signalling pathway may have a leading role in regulation of the inflammatory process (Li and He, 2004; Shih and Targan, 2008). IL-10-deficient mice (IL-10^{-/-}) spontaneously reproduce a colitis phenotype similar to human colitis (Bristol et al., 2000; Kuhn et al., 1993; Rennick et al., 1997). In this mice model, the intestine damage is characterized by the presence of large and thick crypts, and low number of goblet cells, allowing the development of spontaneous colitis (Thompson and Lees, 2011). However, since IL-10 participation might be primarily associated to cellular processes that regulate and resolve the inflammatory response, in chronic inflammation condition, such as UC, its contribution might be relevant to achieve a homeostatic balance (Mosser and Zhang, 2008). Clinical and experimental data have shown sST2 counteractive effect over the activation of IL-33/ST2L pathway and resolution of inflammation (Takezako et al., 2006). Soluble ST2 inhibits IL-33 activity in *in vitro* assays of mast cells stimulated with the cytokine thus blocking the signalling pathway and the release of pro-inflammatory cytokines (Hayakawa et al., 2007; Ho et al., 2007; Palmer et al., 2008; Sanada et al., 2007; Weinberg, 2009). In murine asthma models, pre-treatment with recombinant ST2 reduced IL-13 content in bronchoalveolar lavage fluid induced by intranasal administration of IL-33 (Hayakawa et

al., 2007). Similarly, intraperitoneal administration of sST2 reduced the severity, extent of inflammation and number of affected joints, as well as plasma concentration of pro-inflammatory cytokines in collagen-induced arthritis in mice (Leung et al., 2004). Also, in methylated-BSA induced-rheumatoid arthritis mice model, therapeutic effect of sST2 was also manifested in decrease of neutrophils recruitment to affected joints (Verri et al., 2010). In UC, recent reports have demonstrated that sST2 levels correlate with the severity of the disease (Beltran et al., 2010; Diaz-Jimenez et al., 2011); hence a reduction in protein levels could be used as a biomarker to determine clinical remission. However, although information points to an anti-inflammatory role of sST2, evidence also shows a direct relationship to the disease. Given that UC patients cursing with severe activity have evidently increased plasma levels of sST2, this condition was shown to directly correlate with increased intestinal levels (Diaz-Jimenez et al., 2011). A possible and appealing explanation to this issue is that intestinal increase of sST2 levels reflected in plasma evident a mechanism to prevent an exaggerated immune response; however it might be insufficient to resolve the pathological inflammation distinctive to severe UC (Akhabir and Sandford, 2010).

2.4 IBD genetics

As previously mentioned, IBDs have an important genetic background. Relationship between certain genes and susceptibility to a particular disease has been possible due to molecular characterization made in the past decades (Hardy and Singleton, 2009; Manolio, 2010). Genetic factors relevant in IBD have been demonstrated, through the identification of risk polymorphisms, their loci and genes involved (Barrett et al., 2008; Vermeire et al., 2010). Nevertheless, genetic contributing to disease risk is more profoundly documented in CD than in UC. Many of these risk factors might be related to molecules that participate in the immune response directed to preserve intestinal homeostasis (Carter et al., 2001; Henckaerts et al., 2007). For example, mutations in NOD2/CARD15 gene have acquired great importance as a susceptibility gene for CD. Association between NOD2/CARD15 gene variants and susceptibility and severity of the disease suggest that these mutant alleles may have a prognostic value of an unfavourable outcome and high requirement of surgery (Alvarez-Lobos et al., 2005; Annese et al., 2005; Seiderer et al., 2006). In UC, genes encoding glycoprotein e-cadherin and laminins, such as ECM1, CDH1 and Lamb1, involved in epithelial barrier function and in regulation of inflammatory process, have emerged as significant determinants of susceptibility (Thompson and Lees, 2011). High levels of ST2L protein expression have been described in polygenic and multifactorial diseases recognized to be caused by inflammatory response and with a compromise of the epithelial barrier, such as asthma, atopic dermatitis and systemic lupus erythematosus (Ali et al., 2009; Kuroiwa et al., 2001; Mok et al., 2010; Oshikawa et al., 2001a; Shimizu et al., 2005). These pathologies are also characterized by a high number of local inflammatory infiltrates (mast cells, basophils, neutrophils and eosinophils) and high plasma concentration of sST2, as was also described for UC. Since the physiopathologic role of this protein has been already described, genetic studies have been searching for single nucleotide polymorphism (SNP) in the *st2* gene locus. To date, two case-control studies, one in atopic dermatitis (Shimizu et al., 2005) and another in asthma (Ali et al., 2009), have analyzed the presence of SNPs located in the distal promoter of the *st2* gene. Among these, only the A allele of SNP -26999G/A (rs6543116), could be related to an increase in gene transcription, higher serum levels of

sST2, and a higher risk to develop the disease (Shimizu et al., 2005). Whereas in asthma the presence of the AA genotype was only found in a small fraction of the studied population, it seems to be more often in severe corticoid-dependent asthma patients associated to a worsen course of the disease (Ali et al., 2009).

At the moment, there are no studies to demonstrate a possible association between SNPs present in the *st2* gene and IBD susceptibility. However, our preliminary results seem to not support this association. Recently, two publications related to Genome-Wide Association (GWA) have made possible the detection of risk genes and *loci* associated with complex diseases, such as IBD (Barrett et al., 2008; Hampe et al., 2007; Rioux et al., 2007). In these studies, the *loci* that contains the *st2* gene has not been directly implicated in UC susceptibility. However, the *locus* containing genes for IL1R, IL18R1 and IL18RAP, previously related to UC and with a high linkage disequilibrium (LD) represents an interesting candidate that might be involved in the development and course of the disease (Akhabir and Sandford, 2010). In line with this, a new SNP located in the non-coding region of *st2* gene (rs1420101), has been associated with eosinophilia in asthma and other inflammatory diseases, such as chronic obstructive pulmonary disease (COPD) and myocardial infarction. Gudbjartsson et al. (Gudbjartsson et al., 2009) showed that there is no correlation between this genetic variant and the increased number in eosinophils, or with previously described genetic variants associated to CD (rs917997) (Zhernakova et al., 2008) and celiac disease (rs13015714) (Hunt et al., 2008). Since the IL-33/ST2 signalling pathway has a role in maturation, survival and activation of eosinophils, also in recruitment and regulation of Th2 cell function, the available information is consistent with a greater contribution of this system in eosinophil-mediated inflammation (Stolarski et al., 2010; Suzukawa et al., 2008b). The role of eosinophils in the aetiology and pathogenesis of UC is not completely clear. However, evidence shows a 10-fold higher content of eosinophils in patients with active UC compared to healthy individuals (Kristjansson et al., 2004). In these patients, tissue eosinophilia induced by IL-33 might have a detrimental effect on intestinal structural integrity. As previously mentioned, polymorphonuclear cells constitute an important source of ST2, making an interesting issue the analysis of the presence of these new SNPs in samples of UC patients.

2.5 Soluble ST2 as a biomarker of activity in ulcerative colitis

Many symptoms of UC and CD are similar, but there are some subtle differences. Clinical presentation are rather unspecific, thus further studies are necessary to achieve a differential diagnosis of the diseases. Colonoscopy through biopsy analysis remains the foundation for IBD diagnosis. However, several studies have shown a considerable variability in endoscopic and histological changes of intestinal mucosa (higher inter- and intra-observer variability in determination of the disease activity; low precision and reproducibility of the observations and scarce correlation between endoscopic appearance and clinical indices with treatment response) (D'Haens et al., 2007; Osada et al., 2010; Regueiro et al., 2011). This discrepancy has led physicians and immunologists to search for clinically relevant molecules as biomarkers, non-invasive indicators that objectively assess the damage that is taking place at the intestinal mucosa (Gisbert et al., 2007; Tibble and Bjarnason, 2001; Vermeire et al., 2006). The ideal marker not only might allow for differential diagnosis but also establish prognosis, activity and severity of the disease, risks or complications, relapses,

recurrence and clinical remission, besides evaluation of treatment response (Gisbert and Gomollon, 2007; Gisbert et al., 2007; Tibble and Bjarnason, 2001; Vermeire et al., 2006).

Since intestinal inflammation in IBD patients is associated with acute-phase response and recruitment of immune cells to the site of inflammation, a high production of protein in the mucosa might be detected in serum and/or stool. Among the most commonly used molecules associated with IBD in clinical practice are serological biomarkers, including anti-microbial antibodies (ASCA, ANCA, anti-OmpC, anti-Cbir, anti-I2 and anti-glycans), other plasma proteins (albumin, C-reactive protein (CRP), cytokines, adhesion molecules, among others) and stool proteins (calprotectin, lactoferrin, and neutrophil-elastase) (Li et al., 2008). Most of former serological biomarkers, (mainly ASCA and ANCA) individually have the disadvantage of moderate sensitivity and specificity to predict intestinal inflammation and do not correlate with clinical and disease activity (Papp et al., 2007). C-reactive protein is an objective inflammatory marker and correlates with severe disease activity (Karoui et al., 2007; Rodgers and Cummins, 2007; Solem et al., 2005), however, it is a systemic inflammatory marker elevated in several other inflammatory diseases and with low specificity by diagnosing patients with mild disease activity (Karoui et al., 2007; Rodgers and Cummins, 2007; Solem et al., 2005; Vermeire et al., 2004).

Faecal calprotectin is another biomarker; it is a calcium-binding protein mainly present in neutrophil granules and has the theoretical benefit of having greater specificity for the diagnosis of gastrointestinal diseases. Calprotectin concentration is directly proportional to the migration of neutrophil to the gastrointestinal tract and is not altered by extra-intestinal diseases (Gisbert and McNicholl, 2009; Langhorst et al., 2008; Schoepfer et al., 2010; Sipponen et al., 2008). In addition, calprotectin levels most directly correlate to histological features rather than with endoscopic indexes, suggesting that this marker has a better sensitivity for the evaluation of disease activity than endoscopic procedures (Burns et al., 2003; Poullis et al., 2002). Calprotectin is generally detected in a small sample using simple and low cost methods and is relatively stable in the stool. Although calprotectin has many advantages as a biomarker and is highly sensitive to detect intestinal inflammation (Langhorst et al., 2008), it is not specific for IBD since other gastrointestinal diseases, such as colorectal cancer (Roseth et al., 1993; Tibble et al., 2001) or gastrointestinal infections, were shown to present high levels of this protein (Summerton et al., 2002; Tibble et al., 2002; Pezzilli et al., 2008).

Several clinical studies have reported an increase in plasma levels of sST2 in patients with inflammatory processes, including asthma (Oshikawa et al., 2001b), autoimmune diseases (rheumatoid arthritis, erythematosus systemic lupus and progressive systemic scleroderma) (Kuroiwa et al., 2001), cardiovascular diseases (Weinberg et al., 2003), trauma and sepsis (Brunner et al., 2004). Currently, plasma level of sST2 might work as a biomarker for diagnosis and /or prognosis of several cardiac function conditions directly related to myocardial injury (Diez, 2008; Rehman et al., 2008; Weinberg, 2009; Weinberg et al., 2003). In the context of IBD, we have reported high levels of sST2 that has been proposed as a reliable biomarker of UC activity (Diaz-Jimenez et al., 2011). In UC, serum levels of sST2 grouped by active and inactive, according to endoscopic disease activity index (inactive defined as a Mayo endoscopic score ≥ 1 point), were 33.19 pg/mL and 235.80 pg/mL, respectively. Differences observed in serum concentration were statistically significant ($p < 0.0001$) to discriminate between active and inactive condition. Also, the correlation ROC curve shown a cut-off for sST2 level at 74.87 pg/mL that allow the discrimination between the grade of

disease activity (AUC = 0.92) with a sensitivity and specificity of 83.33%. Additionally, serum sST2 levels directly correlated with the degree of endoscopic activity ($r = 0.76$) according to Mayo endoscopic sub-score classification (0 = normal or inactive state, 1 = mild, 2 = moderate, and 3 = severe disease). According to histopathologic findings (Gomes et al., 1986), levels of sST2 also correlated to the specific index ($r = 0.67$), suggesting that, similar to calprotectin, serum sST2 levels might have a better sensitivity than endoscopic procedure to estimate the activity of UC patients. Furthermore, we demonstrated that serum sST2 levels behave similarly to other serum inflammation marker, such as TNF- α , in relation to endoscopic and histopathologic activity indexes. However, sST2 is potentially a better biomarker as is more stable than the previously reported cytokine (Dieplinger et al., 2010). Finally, we also showed that total levels of ST2 in colonic mucosa of UC patients positively correlated with endoscopic ($r = 0.62$) and histopathologic ($r = 0.60$) UC activity indexes similar to what was described for serum levels. The clear association between intestinal and serum ST2 levels illustrate a valid activity biomarker, unbiased and distinctive of inflammatory process taking place in the intestinal mucosa of UC patients. Thus, ST2 detection might help physicians in the decision making on whether to periodically send patients to colonoscopy, an invasive and expensive test, or use alternative assessment techniques.

3. Conclusion

Current methodology, especially those related to genomics and transcriptomes, will soon allow the improvement in differential diagnosis in patients who show great clinical heterogeneity, with less invasive procedures than colonoscopy and biopsies. Measurement of serum ST2 levels is a reliable, quick and low cost technique for differential diagnosis in IBD and other gastrointestinal diseases, and might allow the assessment of disease activity. Furthermore, in certain subgroups of patients with well-known diagnosis, sST2 has been assigned to have a predictive value to define the course of the disease, ever since genetic analysis of *st2* gene might relate to higher surgery rates, as has been previously shown for NOD2/CARD15 in CD. Here lies the biggest advantage of new biomarkers based on intestinal specific inflammation mechanisms. The future development of molecular classification of IBD, according to molecular biomarkers, may allow a better accuracy in diagnosis, clinical course and response to a determined therapy to induce and sustain remission in IBD.

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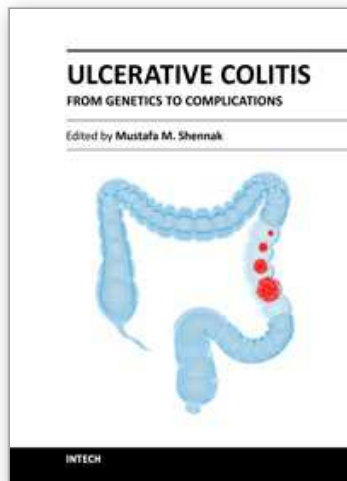
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Ulcerative Colitis (UC) is a rapidly evolving medical field, and will continue to be very exciting in the next few decades. Although the underlying cause of this disease is still unknown, results in research dealing with various issues related to this disease are published every day. Chapters included in this book review the most recent literature on related advancements in regard to this chronic disease, which is controllable but not curable. Aspects like epidemiology, pathophysiology, genetics, incriminated etiologies, clinical aspects, complications, and disease management, including advancements in the diagnostic and therapeutic options, were documented by well known clinicians, researchers, and world wide authorities in their fields. This book on UC will be a valuable addition to each doctor's library interested in this subject, or for physicians dealing with patients suffering from this disease. Authors have also included figures and diagrams to depict their point, and to easily reach the minds of the readers in the simplest way.

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