Enteric Nervous System Abnormalities in Ulcerative Colitis

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1. Introduction

Ulcerative colitis (UC) is a chronic non-specific inflammatory disease affecting the mucosa and the submucosa of the colon, and is characterized by alterations of gut functions which influence the clinical symptoms (Fiocchi, 1998; Reddy et al., 1991; Spriggs et al., 1951). Although reports showed morpho-functional abnormalities of the enteric nervous system in UC patients, the available literature is still heterogeneous and confusing.

UC-related intestinal inflammation causes structural and functional changes to the enteric nervous system and its cellular components (neurons and glial cells), which could be directly related to the development of the disease and its associated symptoms (Geboes & Collins, 1998; Lakhan & Kirchgessner, 2010; Lomax et al., 2005; Villanacci et al., 2008).

UC-related alteration in the enteric nervous system can be categorised into two groups: a) the alterations that occur in the structural morphology of the system, and b) those that occur in the level of enteric transmitters released by neurons and glial cells (Lakhan & Kirchgessner, 2010). Routine pathology of UC reports describe: 1) hypertrophy, hyperplasia and axonal damage of nerve fibres (Cook & Dixon, 1973; Geboes, 1993); 2) a normal aspect, hypertrophy, hyperplasia or damage of neuronal cell bodies (Belai et al., 1997; Siemers & Dobbins, 1974; Strobach et al., 1990); 3) glial cells hyperplasia (Antonius et al., 1960); 4) a variable increase of glial cells number (Geboes et al., 1992; Koretz et al., 1987); and 5) ganglioneuritis (Ohlsson et al., 2007).

Besides structural changes, disruption in the function of neurons and glial cells is reported in patients with UC: defective neuronal control of epithelial secretion, increased excitability of enteric neurons, alteration in synaptic transmission, and variablility in the expression of neuronal and glial-derived factors (vasoactive intestinal peptide, inducible nitric oxide synthase and other mediators in neuronal cell bodies; S100B protein, glial fibrillary acidic protein and other factors in glial cells) (Lomax et al., 2005).

The aim of this chapter is to illustrate the new insights into the pathophysiology of UC, providing an exhaustive overview of the current knowledge of the role of the enteric nervous system during gut inflammation.

Initially, we describe the morphology and the basic physiological functions of the enteric nervous system and its cellular components, neurons and glial cells, respectively. Then, a more extensive part is dedicated to the modifications of the enteric nervous system in UC. Besides the well documented role of enteric neurons, attention is also focused on the

involvement of glial network in the complex scenario of intestinal inflammation, on which there is accumulating evidence in recent years. Finally, the implication of the enteric nervous system in the control of the gut immune system during inflammation is described in the last part of the chapter, as recently hypothesized.

2. The Enteric Nervous System: Morphological and functional features

The Enteric nervous System (ENS) is a collection of neurons in the gastrointestinal (GI) tract, and constitutes the "brain in the gut", since it has the unique ability to control several GI functions, such as exocrine and endocrine secretions, motility, blood flow and immune/inflammatory processes, independent of the central nervous system (Goyal & Hirano, 1996). In the ENS, the nerve-cell bodies are grouped into small ganglia that are connected by nerve bundles forming two major layers embedded in the gut wall, the myenteric plexus (or Auerbach's plexus) and the submucosal plexus (or Meissner's plexus) (Goyal & Hirano, 1996). The myenteric plexus lies between the longitudinal and circular muscle and extends the entire length of the gut. This layer primarily provides motor innervations to the two muscle layers, and secretomotor innervations to the mucosa. The submucosal plexus, located between the mucosa and circular muscle (Furness & Costa 1980; Grundy et al., 2006), is best developed in the small intestine, where it plays an important role in the control of secretion. Both these components contain functionally different neurons (about 100 millions) and four to ten times more glial cells, together organized in ganglia (Goyal & Hirano, 1996; Hoff et al., 2008). Neurons and glial cells of the ENS are derived from stem cells in the neuronal crest, a transient structure present during embryonic development (Dupin et al., 2006).

2.1 Enteric neurons

Although up to eight morphologic forms of neurons have been identified in the ENS, there are two main types: type I neurons, that have many club-shaped processes and a single long process, and type II neurons, that are multipolar and have many long, smooth processes (Furness & Costa, 1980). Functionally, enteric neurons can be classified into primary afferent neurons, interneurons and motor neurons, synaptically linked to each other in microcircuits (Furness & Costa, 1980). Moreover, there is a general classification between neurons of the submucosal plexus and neurons of the myenteric plexus: while the first ones predominantly innervate the mucosa and regulate secretion, absorption and blood flow, the second ones are primarily involved in the control of intestinal motility (Brookes, 2001). Enteric neurons are also known to control mucosal development and function as well as some aspects of the local immune system within the gut. This fine regulation of several and different functions is possible because enteric neurons are in close proximity to other cells present in the gut wall (mucosal immune cells and epithelial cells) and also secrete a wide range of neurotransmitters.

The chemical neuro-mediators of the ENS were initially thought to be limited to neurotransmitters such as acetylcholine and serotonin, but, subsequently, purines, such as ATP, amino acids, such as γ-aminobutyric acid, and peptides, such as vasoactive intestinal polypeptide (VIP) and neuropeptide Y (NPY), were identified (Gershon et al., 1994). More recently, nitric oxide (NO) has emerged as an important neurotransmitter in the ENS (Bogers et al., 1994). Overall, more than 20 candidate neurotransmitters have now been

identified in enteric neurons, and most neurons contain several of them (Gershon et al., 1994). Distinctive patterns of co-localization of mediators appear to identify sets of neurons that perform distinct functions (Costa & Brookes, 1994; Gershon et al., 1994). Although neurotransmitter functions have been clearly defined for only a few of these mediators such acetylcholine, substance P (SP), VIP, NPY and NO, it is well known that a wide variety of neurons that perform different functions may use the same neurotransmitter.

2.2 Enteric Glial Cells (EGC)

Morphologically, EGC are small cells with a 'star-like' appearance (Hoff et al., 2008) containing intracellular arrays of 10 nm filaments made up of glial fibrillary acidic protein (GFAP) (Bjorklund et al., 1984; Endo & Kobayashi, 1987; Hoff et al., 2008; Mestres et al., 1992). These cells envelop enteric neuronal cell bodies and axon bundles (Gershon & Rothman, 1991), as well as intestinal blood vessels (Bjorklund et al., 1984; Geboes et al., 1992), and extend their processes into the intestinal mucosa (Bush et al., 1998; Jessen & Mirsky, 1980). Though, phenotypically comparable to the astrocytes in the central nervous system, EGC account for other similiar functions, such as the regulation of gut homeostasis, as well as inflammatory responses (Broussard et al., 1993; Gershon & Rothman, 1991). Since their first description by Dogiel in 1899, EGC have been assumed to be the most abundant cell type in the ENS (Gabella, 1981). At present, the S100B protein and GFAP, together with more recently identified markers such as Sox 10, are commonly used to identify EGC in the human gut (Bjorklund et al., 1984; Cirillo et al., 2009a; Esposito et al., 2007; Ferri et al., 1982; Hoff et al., 2008). Functionally, EGC have been traditionally considered as a mechanical support for enteric neurons since they release a wide range of factors responsible for the development, survival and differentiation of peripheral neurons (Laranjeira & Pachnis, 2009). Like their counterpart in the brain, EGC, in physiological conditions, constitutively express major histocompatibility complex (MHC) class I molecules, whereas MHC class II expression is sparsely detectable (Geboes et al., 1992; Koretz et al., 1987). In recent years, this restrictive view has been changed to one of a more articulate and complex nature, since EGC are involved in the maintenance of intestinal homeostasis (Bassotti et al., 2007; Van Landeghem et al., 2009). Indeed, these cells control intestinal epithelial barrier functions, such as permeability, via the release of GSNO (S-nitrosoglutathione) as well as the regulation of expression of zonulin-1 and occludin (Neunlist et al., 2008; Savidge et al., 2007a).

Besides the well documented 'protective role', EGC are also activated by means of inflammatory insults and they directly contribute to an inflammatory condition by antigen presentation and by promoting the release of pro-inflammatory cytokines in the gut milieu, thus making them the initiators of immune responses (Cabarrocas, 2003; Cirillo et al., 2009a; Esposito et al., 2007; Neunlist et al., 2008; Savidge et al., 2007b). This ability of EGC to be atigen presenting cell is due to the expression of MHC class II molecule, in the presence of pro-inflammatory stimuli, as recently demonstrated (Cirillo et al., 2009a). Therefore, EGC act as 'receptors' for cytokines and may themselves produce cytokines, such as interleukin-6 and interleukin-1-beta (Murakami et al., 2009; Ruhl et al., 2001). In addition, EGC express the inducible form of nitric oxide synthase (iNOS) and L-arginine, the machinery required for the time-delayed and micromolar release of nitric oxide (NO), one of the most important pro-inflammatory mediators within the gut (Aoki et al., 1991; Cirillo et al., 2009b; Nagahama et al., 2001).

2.2.1 EGC markers: GFAP and S100B protein

Mature EGC are rich in the intermediate filament protein GFAP (Eng et al., 2000; Jessen & Mirsky, 1980). In animals, two classes of EGC can be distinguished, namely the GFAP positive and GFAP negative groups and this ratio is under control of pro-inflammatory cytokines (von Boyen et al., 2004). GFAP expression is modulated by cell differentiation, inflammation and injury (Eng et al., 2000), indicating that the level of this filament matches with the functional state of EGC. Increased GFAP expression has been observed in inflammation or inflammatory diseases of the gut, such as UC (Bradley et al., 1997; Cornet et al., 2001).

S100B is an easily diffusible protein that is a homodimer of β subunit (Baudier et al., 1986). It belongs to the S100 protein family that includes more than 20 EF-hand Ca^{2+}/Zn^{2+}-binding proteins (Haimoto et al., 1987; Sugimura et al., 1989; Zimmer & Van Eldik, 1987). In the human gut, among S100 proteins, only the S100B protein is specifically and physiologically expressed by EGC (Cirillo et al., 2009a; Cirillo et al., 2009b; Esposito et al., 2007), while other members, such as S100A8, S100A9 and S100A12 are found in phagocytes and in intestinal epithelial cells in patients affected by inflammatory bowel disease (Leach et al., 2007; Pietzsch & Hoppmann, 2009). Recent findings have demonstrated that aberrant expression of S100B correlates with the degree of the gut inflammation (Cirillo et al., 2009b; Esposito et al., 2007). The search for a specific S100B signalling receptor has demonstrated that, in micromolar concentrations, this protein may accumulate at the RAGE (receptor for advanced glycation endproducts) site on target cells, such as immune cells (Adami et al., 2004; Hofmann et al., 1999; Schmidt et al., 2001). Such interaction leads to the activation of a signalling cascade resulting in the transcription of different pro-inflammatory cytokines and iNOS protein. S100B can, thus, be considered as a diffusible pro-inflammatory cytokine which gains access to the extracellular space especially at immune-inflammatory reaction sites in the gut (Adami et al., 2001; Cirillo et al., 2009a; Cirillo et al., 2009b; Esposito et al., 2007; Petrova et al., 2000).

3. Role of enteric neurons in UC

Inflammation is well known to affect gut functions, since it leads to persistent changes in enteric nerves thus resulting in dismotility, hypersensitivity and dysfunction. Data obtained from intestinal biopsies from UC patients, or on animal models of UC, have consistently suggested a role of neuro-inflammation in the generation of symptoms associated with the disease (Beyak & Vanner, 2005; Geboes & Collins, 1998). Neuronal abnormalities strongly illustrate the impact of inflammatory signals generated within the gut mucosa on the ENS. In this context, the neuronal regeneration represents a challenging concept and studies aiming to the identification of progenitor-like cells in the ENS are crucial (Kruger et al., 2002).

3.1 Structural changes

To understand the relationship between the intestinal inflammation that characterizes UC and structural abnormalities to the enteric neurons, animal models of colitis are routinely used. This enables us to elucidate the mechanisms underlying gut dysfuctions, which would be rather difficult to observe in humans. The most commonly used models to induce colitis are characterized by intracolonic administration of 1) trinitrobenzene sulfonic acid (TNBS)

or 2) 2,4-dinitrobenzene-sulfonic acid (DNBS) or 3) *Trichinella spiralis* (T. Spiralis) infection in the animal.

In guinea pigs, it has been described that the number of myenteric neurons per ganglion is significantly decreased in TNBS-induced colitis (Linden et al., 2005). In this experimental model, the observed decrease in myenteric neurons was not associated with a decrease in any particular subpopulation of neurons, suggesting a severe loss of neurons that occur during the onset of colitis. In addition, the neurotoxic insult is followed by a rapid regeneration of the axons from the surviving neurons. These data are confirmed in a rat model of TNBS-induced colitis, in which there is a significant loss of myenteric neurons as a result of an increased rate of apoptosis (Sarnelli et al., 2009). Similar changes are reported in another model of chemically-induced colitis in rats, with DNBS administration, which is characterized by a significant decrease of neuronal cells in the myenteric plexus of the ENS (Sanovic et al., 1999; Hawkins et al., 1997). As confirmed by histopathological assessment, in this model, compared to the TNBS-induced model, the neuronal damages are more similar to those observed in UC patients. Significant neuronal death is also observed in T. spiralis induced colitis in mice and rats (Auli et al., 2008). Intracolonic administration of T. spiralis larvae in rats causes colitis with features similar to UC, notably with inflammation predominantly limited to the colonic mucosa (Auli et al., 2008). Interestingly, in this animal model of colitis, the authors also provide information about the subpopulation of neurons affected by inflammation, describing that there is a significant decrease especially in the number of nitric oxide synthase (NOS)-immunoreactive neurons in the myenteric plexus of infected rats, with consequent changes in intestinal motility.

In humans, abnormalities of the neuronal components of the ENS reported in UC patients include hyperplasia or increased number of neuronal cell bodies, mainly in the ganglia of the submucosal plexus, neuronal cell damage, and neuronal hypertrophy. In addition, hypertrophy of the neuronal cell bodies in the submucosal plexus seems to be common in UC patients (Mottet, 1971; Van Patter et al., 1954). Neuronal hyperplasia of the myenteric plexus is also reported for UC but the data available in the literature is rare and may have been complicated by difficulties in the differential diagnosis between granulomatous colitis and genuine UC (Okamoto, 1964; Storsteen et al., 1953). Neuronal cell hyperplasia is certainly more frequently reported for Crohn's disease and seems more common with a significant, statistical difference when compared with UC. In addition to hypertrophy and hyperplasia of neuronal cell bodies, signs of degeneration have been described occasionally in areas of the inflamed gut in UC patients (Oehmichen & Reiffersscheid, 1977; Rienmann & Schmidt, 1982).

Also neuronal synapses appear to be altered in patients with UC. This is because of an increased synaptophysin (a synaptic vesicle protein involved in synapse formation but without a well defined functional role) immunoreactivity, compared to samples from normal mucosa and from cases with non-specific colitis, in which mucosal fibres are rare and usually small (Strobach et al., 1990). Submucosal and myenteric nerve fibre hypertrophy is uncommon in UC patients. Ultra-structural studies of UC and control samples have shown that, in both submucosal and myenteric layers, the nerve fibres or axons appear as swollen, empty, lucent structures, with large membrane-bound vacuoles, swollen mitochondria and concentrated neurofibrils (Dvorak et al., 1980). These changes can be focal or diffuse and can affect all axons in one nerve bundle or just few of them. This data supports the hypothesis of a correlation between the neural hyperplasia and the

inflammatory reaction in UC patients. It appears, thus, that UC is characterized by two types of structural neuronal abnormalities: damage and hyperplasia of neurons in all parts of the ENS, related to inflammation.

Changes in the chemical coding of myenteric neurons are described in UC patients (Neunlist et al., 2003). Immunohistochemical characterization of neurons in the myenteric plexus revealed that alterations occur in the proportion of choline acetyltransferase (ChAT)/negative (-ve), ChAT/SP-ve, and SP-ve populations in UC patients compared to the intestinal tissues from control subjects. These changes have similar features in inflamed and non-inflamed areas of the gut in UC patients. The use of a combination of antibodies against ChAT, VIP and SP enabled the identification of transmitter co-localisation in colonic myenteric neurons, showing five distinct subpopulations (ChAT-ve, ChAT/SP-ve, ChAT/VIP-ve, VIP-ve, and SP-ve). The largest neuronal population identified in the myenteric plexus of UC patients is ChAT immunoreactive and hence of cholinergic nature. VIP formed 9% of the total neuronal population. Most of the SP+ve neurons co-localize with ChAT. In UC patients, there is a threefold increase in the proportion of myenteric neurons immunoreactive for SP, compared to control subjects, whereas the proportion of ChAT+ve and VIP+ve neurons was not affected. The increase in SP observed in the inflamed gut of UC patients is a hallmark of the disease pathology. Moreover, an increase in the density of SP immunoreactive fibres and SP content in UC patients, especially in the lamina propria has been reported (Goldin et al., 1989; Keranen et al., 1995; Vento et al., 2001). At present, no data are available to address the questions of whether the changes in SP observed in myenteric neurons of UC patients are the result of transductional, post-transductional, or even alterations in peptide transport. In this context, changes in mRNA levels for SP receptors are observed in UC patients (Goede et al., 2000) but it is not known whether SP mRNA is increased in myenteric neurons or whether degradation of SP is altered in this inflammatory disease. The increase in SP+ve neurons observed in UC patients occurs primarily in the population of ChAT-ve neurons detected in control subjects. In fact, the total proportion of ChAT+ve neurons is not modified in UC patients compared with control subjects, and the increase in the proportion of ChAT/SP-ve neurons is equivalent to the decrease in the proportion of the ChAT-ve population observed in UC patients. What might be the clinical relevance of the SP increase in UC? Firstly, SP may play an important role in the pathophysiology of UC (Holzer, 1998). In fact, there is increased expression of SP binding sites in UC as well as an increase in neurokinin 1 (NK-1) receptor mRNA (Goede et al., 2000; Mantyh et al., 1995). Confirming the involvement of NK-1 in the modulation of gut inflammation, in an animal model of colitis, the administration of NK-1 antagonist reduced colonic inflammation (Stucchi et al., 2000). In the same animal model, inflammation induced an increase in SP synthesis in myenteric neurons. Moreover, a decrease in neutral endopeptidase activity (the enzyme which degrades SP) was observed in T. spiralis-infected intestine in conjunction with increased SP levels (Hwang et al., 1993). These combined effects result in an increased SP levels and down-regulation of endopeptidase activity, which could significantly increase SP that might contribute to uncontrolled intestinal inflammation in UC. A surprising finding is that alterations in the neurochemical code of myenteric neurons occur in similar proportions in inflamed and non-inflamed areas of UC patients, as mentioned above. SP induction during UC in non-inflamed and inflamed areas could be due to an increase in inflammatory cytokines such as interleukin-1beta, which have

been observed during UC in the intestine (Fiocchi, 1998). In fact, interleukin-1beta induces increased SP expression in rat myenteric fibres (Hurst et al., 1993). In summary, marked changes in the neurochemical coding of myenteric neurons characterize UC. ChAT-ve neurons can be considered as the putative neuronal population exhibiting neural plasticity by expressing different levels of SP. Therefore, this remodelling in UC occurs as a shift from mainly cholinergic to more peptidergic innervation. Similar changes in neurochemical coding were also observed in the least affected sites of inflammation. This effect may constitute part of the neuronal basis for the altered motility observed during UC.

Another important neuropeptide, calcitonin gene-related peptide (CGRP), is involved in inflammatory processes and is regulated by nerve growth factor (NGF) (Linsday & Harmar, 1989). In inflammatory bowel disease, NGF and its high affinity receptor (trkA) are highly over-expressed in the inflamed tissues (Di Mola et al., 2000). Studies have shown that neuropeptides, like CGRP (Reinshagen et al., 1998), are protective in acute (Reinshagen et al., 1994) and chronic (Reinshagen et al., 1996) models of experimental colitis. As a result, the protective effect of neurotrophic factors can partly be explained by a specific modulation of neuropeptide expression during inflammation. Therefore, in an experimental model of inflammation of the rat gut, NGF and neurotrophin-3 seem to have a protective effect. When these neurotrophic factors are experimentally and selectively blocked during colitis, this leads to a significant increase in inflammation (Reinshagen et al., 2000).

3.2 Functional changes

Abnormalities of the enteric neurons during the course of inflammation leads to altered intestinal functions. Three major groups of functional neuronal changes are observed in UC patients: 1) defects in the neuronal control of epithelial secretion, 2) increased excitability of enteric neurons and 3) alteration in synaptic transmission (Lomax et al., 2005). Due to their localization within the intestine, changes in enteric neurons reflect in the alterations of a broad range of functions that are orchestrated by the other cell types (epithelial, immune, endocrine cells) residing the gut wall. Specifically, the five primary targets of the enteric neurons are 1) smooth muscle cells responsible for motility; 2) mucosal secretory cells; 3) endocrine cells; 4) the microvasculature that maintains mucosal blood flow during intestinal secretion and 5) the immunomodulatory and inflammatory cells that are involved in mucosal immunologic, allergic and inflammatory responses (Goyal & Hirano, 1996).

A number of electrophysiological studies have been performed in animal models of colitis in order to elucidate the mechanisms underlying inflammation-induced changes in enteric neuronal functions in UC patients (Lakhan & Kirchgessner, 2010). Independent of the method used to induce colitis, the type of enteric neurons most dramatically affected by inflammation is the after-hyperpolarizing (AH) neurons. The AH neurons physiologically work as intrinsic primary afferent neurons in the myenteric plexus and control intestinal peristalsis, mucosal secretion and vasodilatation. While in normal conditions these neurons very rarely receive fast synaptic inputs, in course of inflammation more AH neurons receive fast synaptic inputs, exhibit increased excitability, depolarized membrane potential, reduced AH potential amplitude and duration along with increased input resistance (Lennon et al., 1991; Yoshida et al., 1988). AH neurons characteristically receive slow excitatory postsynaptic potentials in the normal non inflamed intestine, but increased excitation (long-term hyperexcitability) occurs in AH neurons during the course of inflammation (Qualman et al., 1984). This pathological phenomenon indicates that a brief synaptic activation can

trigger a long period of hyperexcitability in AH neurons after they have been exposed to an inflamed environment, thus suggesting that perturbation of the sensory component of intrinsic motor reflexes may occur during inflammation and that increased neuronal excitation may contribute to the altered motility, pain and discomfort associated with intestinal inflammation in UC patients. The mechanisms responsible for the changes in excitability are not yet understood, but it is postulated that they involve a persistent alteration in channel expression and/or a continuous release of inflammatory mediators in the intestinal milieu.

Together with neuronal hyperexcitability, alterations in sympathetic neural activity, with consequent impact on the functions of the ENS, are reported in UC patients (May & Goyal, 1994). In animal models of colitis, the decrease in the release of noradrenaline from sympathetic varicosities due to inhibition of N-type voltage-gated Ca^{2+} current in postganglionic sympathetic neurons, has been reported in both inflamed and un-inflamed regions of the gut (Ikeda et al., 1982). However, at present, how an alteration of sympathetic function contributes to the pathogenesis of UC has not yet been fully understood.

As described above, UC is also characterized by nerve fibre hypertrophy and hyperplasia, but it is not clear whether these alterations have functional consequences or which functional changes they might induce in the inflamed gut of UC patients. Some of the fibres with a prominent appearance on routinely stained slides may indeed not be functional. The swollen aspect of the axons observed with ultra structural studies might correspond with the thickened appearance of the fibres reported in some immunohistochemical studies while in fact these fibres are damaged and hence not functional.

4. Role of Enteric Glial Cells in UC

It is widely known that EGC display many morphological and functional similarities with astrocytes in the brain, which are essential to maintain homeostasis in the central nervous system. Emerging reports indicate a regulatory role of EGC in the gut (Bassotti et al., 2007; Neunlist et al., 2008; Van Landeghem et al., 2009). From *in vivo* studies, we now know that the selective ablation of the glial network, carried out by using chemical methods, leading to intestinal inflammation that is associated with the alteration of mucosal barrier integrity (Bush et al., 1998; Savidge et al., 2007). Moreover, animal models in which the ablation of EGCs was auto-immune mediated, demonstrated that these cells are also capable of immune functions *in vivo* (Cornet et al., 2001). Additional studies have demonstrated that EGC directly affect intestinal epithelial barrier integrity via the release of factors such as transforming growth factor-beta, S-nitrosogluthatione and glial-derived neurotrophic factor (GDNF) (Neunlist et al., 2007; Savidge et al., 2007; von Boyen et al., 2011), thus confirming the crucial role played by EGC in the regulation of gut homeostasis. Given the ability of EGC to modulate the intestinal barrier functions and to mediate immune responses *in vivo*, it has also been claimed that these cells are involved in inflammatory bowel disease (Cirillo et al., 2009b; Cornet et al., 2001; Neunlist et al., 2007; Neunlist et al., 2008). Several studies have underlined the involvement of EGC in intestinal inflammation during which both mucosal and motor functions are altered (Cirillo et al., 2009b; Cornet et al., 2001; Sethi & Sarna, 1991). Indeed, changes in EGC architecture, together with impaired expression of EGC-derived factors, are reported in UC patients. Among the glial-derived mediators, GFAP, S100B protein and GDNF are up-regulated in UC patients (Cirillo et al., 2009; Cornet et al., 2001; Steinkamp et al., 2003; von Boyen et al., 2011).

Confirming the involvement of EGC in the intestinal inflammatory scenario, immunohistochemical studies also revealed an increase in MHC class II membranous expression on EGC and glial sheaths of nerve fibres in the mucosa and submucosa of UC patients. This increased and aberrant expression is present in both macroscopically involved and uninvolved areas, in the colon and ileum, and correlates with the increased MHC class II expression on epithelial cells. The enhanced MHC class II expression on the EGC is positively correlated with the local intensity of the cellular inflammatory infiltrate, especially with the increased infiltration of T lymphocytes.

4.1 Neuro-glial crosstalk in UC

Morpho-functional changes in EGC observed in UC patients could also be a major link between the alterations in neuronal functions described above. Indeed, EGC have been shown to control neuronal functions which alter the course of gut inflammation.

Various observations indicate that EGC may promote neuronal survival by directly regulating substrate supply (Cabarrocas et al., 2003; Nagahama et al., 2001). They also appear to regulate perineuronal homeostasis (Cabarrocas et al., 2004). For example, EGC are the only cell type in the ENS that express glutamine synthetase, which might be involved in the detoxification of glutamate and γ-aminobutyric acid. Selective ablation of cycling EGC is also associated with a moderate degeneration of myenteric neurons but not in neuronal content of SP. Changes in enteric neuron phenotype and intestinal functions are described in a transgenic mouse model of EGC disruption. In this experimental model, in which immune alteration of EGC was induced in adult animals, EGC abnormalities induce changes in both the neurochemical coding of enteric neurons and in intestinal motor and mucosal functions. In this adoptive transfer model, however no overt clinical signs were observed. This minor disruption of EGC is characterized by a decrease in GFAP expression both at the protein and mRNA level. Alteration of GFAP expression is not associated with intestinal inflammation, as detected by histological assessment. While it has been reported that acute intestinal inflammation is usually associated with an increase in GFAP expression, as well as proliferation of EGC (Bradley et al., 1997, von Boyen et al., 2004), the absence of intestinal inflammation reported in the mentioned study could be due to the fact that EGC disruption was not profound enough to cause severe inflammation as the number of GFAP structures was not affected. In addition, in this mouse model of EGC disruption, the number of enteric neurons per ganglion from the submucosal and myenteric layers is not modified compared to the control animals, suggesting that neuronal cell loss did not occur at this stage. In contrast, the neurochemical coding in both enteric layers is altered and these changes in the phenotype affect different cell populations of the ENS. The mechanism responsible for these modifications however remains to be explored. Similar to the central nervous system, astrocytes are well known synthesizers of various neurotrophic factors (NT-3, GDNF, NGF) that are involved in the regulation of enteric neuromediator expression (De Giorgio et al., 2000; Saffrey et al., 2000). In the same way, enteric neurons have also been shown to express neurotrophin receptors (De Giorgio et al., 2000). Therefore, alterations in EGC could result from altered neurotrophic factor synthesis.

Apart from the involvement of other neurotrophic factors, alterations in EGC induce motor changes both *in vivo* and *in vitro*, with a corresponding decrease in intestinal motility. These changes in motility could be correlated with the decrease in NOS immunoreactivity in myenteric neurons, which are notoriously recognized to be inhibitory motor neurons

(Kunze & Furness, 1999). Together with changes in NO expression, the delayed transit observed in transgenic mice may be the result of the alterations in neurotrophic factors, such as neurotrophins or from modifications in EGC of the spinal cord as extrinsic neuronal pathways can modulate GI functions (Cabarrocas et al., 2003; Coulie et al., 2000; Parkman et al., 2003). As mentioned above, EGC are also involved in the regulation of intestinal paracellular permeability. It is conceivable that the decrease in VIPergic submucosal neurons observed when EGC are ablated could be partly responsible for the increased permeability, since the activation of VIPergic neurons decreases paracellular permeability (Neunlist et al., 2003). In summary, EGC are involved in the regulation of GI functions, such as intestinal motility and permeability, and participate in the control of the neurochemical phenotype of enteric neurons.

4.2 S100B expression in UC

It is clear that EGC directly participate in the chronic mucosal inflammation in UC. EGC perform this role via the release of several mediators. Among these, S100B protein plays a crucial role in UC (Cirillo et al., 2009b). More specifically, a study performed in both UC patients and control subjects demonstrates that in the rectal mucosa of UC patients there is an increased S100B immunoreactivity, together with a significant increase in S100B mRNA, protein expression and secretion. This up-regulation is associated with enhanced NO production through the specific induction of iNOS protein. This correlation is very interesting, since a growing body of evidence indicates that UC is characterized by abnormal mucosal NO production in response to iNOS induction by pro-inflammatory cytokines (Linehan et al., 2005; Menchen et al., 2004). Within the human gut, the ability of EGC to specifically modulate NO production through S100B protein seems to play a pivotal role. In fact, it is described that the application of exogenous S100B, in micromolar concentrations, induces a significant and concentration-dependent increase in NO production, through the induction of iNOS expression, in the human non-inflamed rectal mucosa of control subjects. It's interesting that micromolar concentrations of S100B mediate a significant NO increase in UC patients, as well as in the rectal mucosa of control subjects. This finding suggests that EGC are able to mediate mucosal NO-dependent inflammatory responses by increasing S100B protein level within the intestinal milieu. Once released, S100B acts as extracellular ligand for cell surface receptor RAGE (receptor for advanced glycation endproducts) on targeted cells, by triggering pro-inflammatory signals that lead to NO production. It has been previously demonstrated that other members of S100 proteins family (i.e. S100A12) play a role during intestinal inflammation via RAGE interaction (Foell et al., 2003). More specifically, the S100A12/RAGE-mediated pathway affect immune cell-derived NO production. The specificity of EGC activation induced by inflammation is confirmed by the fact that, in an *in vitro* model of gut inflammation, S100B mRNA, protein expression and release are significantly increased, simultaneously with an enhanced NO production. These findings indicate that EGC are able to recognize inflammatory stimuli and that, once activated, they produce and release S100B contributing to the induction of iNOS. In addition, EGC activation observed in the inflamed gut mucosa of UC patients is not reduced by the administration of cortisone suggesting that this phenomenon occurs via a steroid-insensitive mechanism and that it is not secondary to immune system activation. These findings, together with the recent demonstration that EGC express MHC class II molecule when stimulated (Cirillo et al., 2009) pave the way to look at this cell population as

primary effectors and not as secondary targets during inflammatory responses within the gut.

5. ENS-immune system cross-talk in UC

The gut is also home to the largest component of the immune system. The interaction between ENS and immune system remains an important topic and considerable progress has been achieved to shed some light on the neuro-immune axis in the human gut. Although the immunomodulatory role of the ENS remains to be clarified, it is conceivable that chronic gut inflammation is characterized by altered ENS-immune system cross-talk. It has been known for some time that the ENS and mucosal immune systems have the ability to regulate one another's functions. For example, in experimental animal models of colitis it has been reported that the vagal anti-inflammatory pathway plays a crucial role in the control of gut inflammation and that the ENS is probably involved in this phenomenon as a player in the 'final step' (Ghia et al., 2006; Tracey, 2007).

Neurons in the ENS are found in close proximity to immune cells in the mucosa. The two systems even share several chemical mediators, such as SP. Neuronal activation can lead to degranulation of mast cells and influx of neutrophils, thereby recruiting elements of innate immunity to the area. Lymphocytes express receptors for neuropeptides released by enteric nerves, and stimulation of these cells with SP or VIP can induce their differentiation and alter their production of immunoglobulins. SP receptor antagonists therefore reduce inflammation and gut infiltration with neutrophils. As enteric neurons are closely co-localized to macrophages, as well as B- and T-lymphocytes in the gut wall, these neurons seem to exacerbate inflammation by stimulating the release of cytokines in the latter directly by releasing VIP (Goyal & Hirano, 1996) from their terminals. Similarly, VIP secretion of neurons can influence IgA synthesis, by stimulating B-lymphocytes, and increase secretion in enterocytes directly by releasing VIP from varicosities close to epithelial crypt cells (Pascual et al., 1994). After stimulation, primary afferent neurons, originating from the dorsal root ganglia, cause submucosal vasodilatation by releasing CGRP (Holzer et al., 1995). The vasodilatation enhances the recruitment of neutrophils from blood into the gut tissue. Additionally, the ENS modulates vasodilatation indirectly by degranulation of mast cells, whose mediators contribute to vasodilatation. As several non-neuronal cells, including epithelial and immune cells, express neurotrophin high and low affinity receptors (Levi Montalcini et al., 1996), there must be additional pathways for neurotrophic factors to modulate gut inflammation.

Signalling between immune cells and enteric neurons can also evoke alterations in gut functions. Linden et al. indicated that the hyperexcitability of intrinsic primary afferent neurons of inflamed guinea pig colon may be secondary to the activation of cyclooxygenase-2 and also for the production of prostaglandins (Linden et al., 2004). This increase in prostaglandins may be underlying factor responsible for some of the changes in neuronal properties observed at sites of gut inflammation. These changes can occur in non-involved regions during episodes of intestinal inflammation. Several studies indicate that the loss of neurons is associated with the appearance of eosinophilic and neutrophilic infiltrates into myenteric ganglia, suggesting that it might be mediated by interactions with the mucosal immune system (Sanovic et al., 199). Myenteric ganglionitis, associated with infiltrates of lymphocytes, such as plasma cells and mast cells, is frequently observed in UC patients and in experimental models of colitis (De Giorgio & Camilleri 2004; Tornblom et al., 2002).

Following TNBS colitis, eosinophils and T cells are commonly found adjacent to myenteric ganglia. This indicates a specific targeting of enteric ganglia by immune components (Pontell et al., 2009). Eosinophils are first observed adjacent to myenteric ganglia at six hours, and T cells are observed at twenty-four hours. Interestingly, no eosinophils and T lymphocytes are associated with myenteric ganglia in normal intestine. Thus, their presence in elevated numbers is an indication of ganglionitis and suggestive of neuropathology.

Recently, it has been demonstrated that NPY, which is produced by enteric neurons, plays an important role in initiating and modulating gut inflammation and in regulating immune system functions (Chandrasekharan et al., 2008; Hassani et al., 2005; Wheway et al., 2007). NPY has been shown to have the capacity to activate macrophages, stimulate the production of various cytokines such as tumor necrosis factor-α, and affect T-helper1 function (Chandrasekharan et al., 2008; Dimitrijevic et al., 2005; Sung et al., 1991; Wheway et al., 2007). Confirming the role played by NPY, a marked increase in both the mucosal NPY expression in experimental colitis and plasma levels of NPY in UC patients has been observed (Chandrasekharan et al., 2008). These results indicate that NPY can promote inflammation and is related to the pathogenesis of UC. Therefore, it has been postulated that, targeting or blocking NPY may be beneficial for the treatment of UC. In this context, recently, it has been demonstrated that the administration of NPY antisense oligodeoxynucleotides ameliorates the significantly established experimental colitis, suggesting that antisense oligodeoxynucleotides may be a useful therapeutic approach for the treatment of UC.

6. Conclusion

In the recent years, there is increasing evidence highlighting the crucial role played by ENS in intestinal inflammation, as demonstrated by the growing numbers of studies looking at both morphological and functional alterations in the ENS and its cellular elements, neurons and glial cells. These observations are the results of investigations carried out in both experimental animal models and in intestinal tissues of patients with inflammatory bowel disease. Although morpho-functional abnormalities of the ENS of UC patients have been consistently reported, additional studies are necessary to better understand the changes in the enteric cells, including neurons (of both submucosal and myenteric layers) and glial cells, which control gut functions, such as colonic motility and secretion, in the inflamed gut. This approach will help to prevent enteric neuropathies associated with inflammation and pave the way to future therapeutic options. Targeting neuronal and/or glial alterations during the course of inflammation may represent a novel approach to diminish the entity of tissue damage as well as the lack of long-term effectiveness of classical immunosuppressant agents used in the treatment of UC. Moreover, additional studies investigating the relationship between ENS and immune cells are warranted in order to carry out an in-depth assessment of the role of neurons, glial cells and their derived factors in the modulation of immune/inflammatory responses in the human gut, in light of establishment of new therapeutic approaches towards the treatment of gut inflammatory diseases.

One of the main questions that still need to be addressed to is whether the alterations of the ENS precede or are secondary to the inflammatory process within the gut. This will hopefully help to predict the disease outcome in UC, that until now remains a challenge, and for better understanding of the pathogenesis of this disease.

In conclusion, the complex interactions of the ENS and the other systems during gut inflammation require a broad perspective from neurophysiology, biochemistry and immunology to completely understand the regulation of inflammatory processes involved in UC. Therefore, important progress in this field can only be achieved by interdisciplinary approaches. Further research in this direction needs to be done for the discovery of long-lasting, effective treatment for inflammatory diseases of the gut.

7. References

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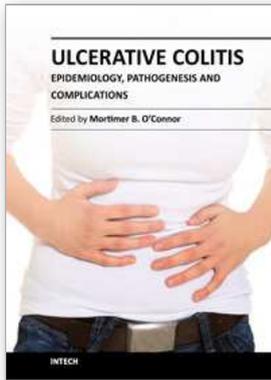
Ulcerative Colitis - Epidemiology, Pathogenesis and Complications

Edited by Dr Mortimer O'Connor

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