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Carcinoembryonic antigen (CEACAM) family members and Inflammatory Bowel Disease

Maebh Kelleher[a,b], Raminder Singh[a,c], Caitriona M. O'Driscoll[b], Silvia Melgar[a,*]

[a] APC Microbiome Ireland, University College Cork, Cork, T12YT20, Ireland
[b] Pharmacodelivery Group, School of Pharmacy, University College Cork, Cork, T12YT20, Ireland
[c] Department of Medicine, University College Cork, Cork, T12YT20, Ireland

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ABSTRACT

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic intestinal inflammatory condition with increasing incidence worldwide and whose pathogenesis remains largely unknown. The collected evidence indicates that genetic, environmental and microbial factors and a dysregulated immune response are responsible for the disease. IBD has an early onset and long term sufferers present a higher risk of developing colitis associated cancer (CAC). The carcinoembryonic antigen-related adhesion molecules (CEACAM) are a subgroup of the CEA family, found in a range of different cell types and organs including epithelial cells in the intestine. They can act as intercellular adhesions molecules for e.g. bacteria and soluble antigens. CEACAMs are involved in a number of different processes including cell adhesion, proliferation, differentiation and tumour suppression. Some CEACAMs such as CEACAM1, CEACAM5 and CEACAM6 are highly associated with cancer and are even recognised as valid clinical markers for certain cancer forms. However, their role in IBD pathogenesis is less understood. The purpose of this review is to provide a comprehensive summary of published literature on CEACAMs and intestinal inflammation (IBD). The interactions between CEACAMs and bacteria adhesion in relation to IBD pathophysiology will be addressed and potential new therapeutic and diagnostic opportunities will be identified.

1. Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic intestinal inflammation with unknown aetiology. The collected evidence indicates that genetic, environmental, microbial factors and a dysregulated immune response are responsible for the disease. Long term sufferers present a higher risk of developing colitis associated cancer (CAC) [1]. A high risk of developing IBD is also identified with the consumption of westernised diet (high in fat and sugars), processed food and diets low in fibers. It is widely acknowledged that diets can affect the intestinal microbiota composition resulting in the development of metabolic syndrome, obesity and even IBD, especially in animals exposed to westernised diets or dietary emulsifiers [2]. Changes in microbiota composition with increases in Proteobacteria and reduction in Firmicutes, alterations in epithelial barrier function due to changes in tight junction proteins, reduction of anti-microbial responses and dysregulated immune response are typical features associated with IBD [3].

The carcinoembryonic antigen-related adhesion molecules (CEACAM) are a subgroup of the CEA family, containing 12 human CEACAM genes including CEACAM1, CEACAM3-CEACAM8, CEACAM16 and CEACAM18-21. CEACAM family members are expressed on different cells types including epithelial cells, neutrophils, T cells etc. CEACAMs are heavily glycosylated glycoproteins attached to the plasma membrane of cells where they can act as intercellular adhesions molecules involved in a number of different processes including cell adhesion, proliferation, differentiation and tumour suppression [4]. CEACAMs can also serve as bacterial adhesion molecules for e.g.

Abbreviations: AIEC, Adherent-Invasive *E. coli*; CAC, colitis associated cancer; CD, Crohn's disease; CEACAM, Carcinoembroyonic antigen; CRC, colorectal cancer; DSS, dextran sodium sulphate; ExPEC, extra intestinal pathogenic *E. coli*; GI, gastrointestinal; GPI, glycosylphosphatidylinositol; IBD, Inflammatory Bowel Disease; IECs, Intestinal epithelial cells; NF, κB- nuclear factor kappa-light-chain-enhancer of activated B cells; NiMOS, Nanoparticles-in-microsphere; PCL, poly-epsilin-caprolactone; SAP, 1 - Stomach-cancer–associated protein tyrosine phosphatase 1; Th, T helper cell; TLRs, Toll-like receptors; TNBS, 2,4,6-trinitrobenzene sulfonic acid; UC, ulcerative colitis

* Corresponding author at: APC Microbiome Ireland, Biosciences Institute, 4th Floor, University College Cork, Cork, T12YT20, Ireland.
E-mail addresses: 113507473@umail.ucc.ie (M. Kelleher), s.raminder@umail.ucc.ie (R. Singh), caitriona.odriscoll@ucc.ie (C.M. O'Driscoll), s.melgar@ucc.ie (S. Melgar).

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Escherichia coli, Neisseria spp, Salmonella spp and others, indicating they can play a role in mounting innate immune responses against microbes [5]. Several CEACAMs including CEACAM1, CEACAM5, CEACAM7 are expressed in the luminal intestinal epithelial cells [4]. Upon intestinal inflammation such as IBD, CEACAMs are altered. For example, CEACAM6 is highly increased in patients with CD and has been shown to serve as a receptor to CD-associated bacteria [6–8]. Other CEACAMs such as CEACAM1, normally found on epithelial cells of the gut, is highly reduced in colon cancer. However, conflicting results exist in regards of CEACAM1 and IBD, although a reduction of CEACAM1 in epithelial cells appear to be most consistent finding [9]. To date the role of CEACAM family members and IBD pathology has not been clearly outlined despite their prominent expression in the intestinal epithelium. Thus, the aim of this review is to provide a comprehensive summary on the current knowledge about CEACAM family members and IBD. We will highlight the interactions of CEACAM in bacteria and cell adhesion in relation to IBD pathophysiology and outline potential new therapeutic and diagnostic venues.

1.1. IBD – symptoms, epidemiology and treatment

Inflammatory Bowel Disease is a collective term used to describe Ulcerative Colitis (UC) and Crohn's Disease (CD). IBD is an idiopathic disease causing chronic inflammation throughout the gastrointestinal (GI) tract. Crohn's disease is characterized by deep ulcerations and wall thickening found anywhere within the GI tract from the mouth to the anus, with the terminal ileum and proximal colon being the area most affected. In contrast, continuous superficial inflammation in the mucosa and submucosa of the rectum and colon is observed in UC. The environment, the gut microbiota, the genetic make-up and the immune response are believed to be responsible for the pathogenesis of these diseases [10] (Fig. 1). IBD can occur at any age, but the main onset appears at a young age, between 15 to 30 years of age, although a second onset is seen at 50 to 70 years of age [11]. To date, no definite cure for IBD exists and therefore current goal of therapy is to treat the presenting symptoms and to maintain remission [12]. Furthermore, patients with long-term IBD are at an increased risk of developing colorectal cancer (CRC) [10], with IBD accounting for the third highest risk factor associated with CRC [13,14]. Gastrointestinal manifestations

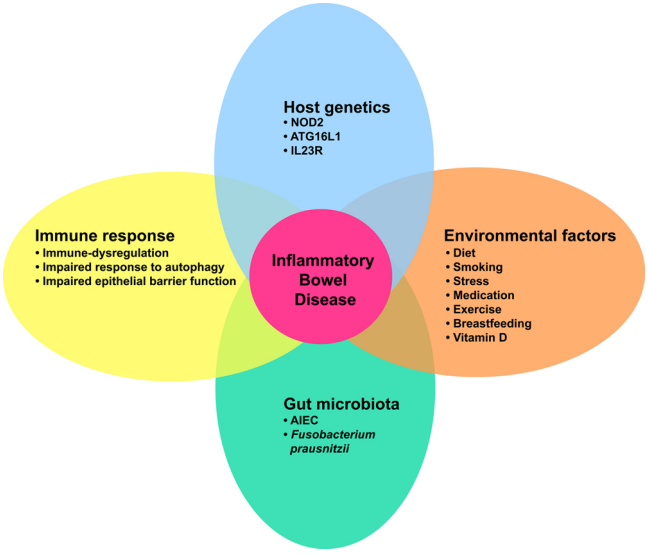

Fig. 1. Schematic of the pathogenesis of IBD. Environmental factors, gut microbiota alteration, host genetics and immune responses are all known to contribute to the onset of the disease. Despite many known causes, the development of the disease varies from patient to patient.

of IBD include abdominal pain, weight loss, recurrent or persistent diarrhoea, constipation, bloody stools, cramping, and fatigue.

A dramatic increase in the incidence and prevalence of IBD has been observed since the middle of the 20th century, which is not only seen in Western countries but worldwide. The highest incidence of IBD occurrence is in North America and Northern Europe [15]. The prevalence of the disease is most common in the age bracket 20–40 years, with equal frequency in women and men. The rate of paediatric IBD is also increasing worldwide, with a greater incidence among Europe and North America [16]. IBD in the elderly is set to increase due to the rise in prevalence of the disease coupled with the ageing population. Approximatively 10–30% patients with IBD fall into this group, either having developed the disease as an adult or having aged with the disease [17]. Late onset of UC is more common than CD, with elderly men at an increased risk in comparison to women [18,19].

Treatment is usually lifelong, with the main goal being to treat the symptoms while inducing and maintaining remission. Treatment include the use of aminosalicylates, corticosteroids, antibiotics, biologics and immunomodulators. The introduction of biological drugs opened up new horizons and has brought ground breaking directional changes in the treatment goals and management of the disease [20]. Among biologicals, anti-TNFs are the most widely used and successful in IBD, although a certain amount of patients does not respond and several adverse effects are accompanied with the treatment [21]. New treatment options, including the development of small molecules against the Janus Kinases and Sphingosine-1-phosphate receptor agonists are currently being evaluated [22].

1.2. IBD and Genetic and environmental factors

To date, genome-wide association studies have identified over 200 IBD-associated genes or loci. The candidate genes within these loci includes genes associated with cytokine and cytokine receptors (e.g. IL-23R) and genes involved in bacterial recognition (e.g. NOD2), autophagy (e.g. ATG16L1), adaptive immunity (Major histocompatibility complex, class II, DQ beta 1), epithelial barrier (e.g. HNF4A), endoplasmic reticulum stress (e.g. XBP1), etc [23]. However, only up to 30% of IBD cases are associated with at least one IBD-gene or loci, indicating that other factors play a role in its pathogenesis [24]. Indeed, an association between genes that control the detection and response to microbes in promoting intestinal inflammation have been identified further supporting a genetic-microbial interaction in IBD [25].

Despite the aetiology of IBD being uncertain, many environmental factors including smoking, diet, breastfeeding, antibiotics, and appendectomy to name a few, appear to contribute to the onset of the disease (Fig. 1). Among these, there is recent preclinical evidence on westernised diet influencing both the development and progression of IBD. Epidemiological data indicate that the risk of CD was increased in patients who consumed a Western diet high in monosaccharides and disaccharides [26]. Diets rich in omega-6 fatty acids have pro-inflammatory effects promoting pathogenesis of many chronic diseases including IBD. Others dietary components such as emulsifiers, sugar and salt have been associated as risk factors for IBD as well as worsening intestinal inflammation [2]. In contrast, a diet high in fibre appears to be beneficial to patients with IBD, by e.g. maintaining intestinal barrier function [27]. Similarly, both fermentable and non-fermentable fibres have anti-inflammatory effects, with fermentable fibres playing a role in the inhibition of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and other pro-inflammatory mediators [28]. Diets containing Omega-3 fatty acids possess anti-inflammatory effects through their suppression of pro-inflammatory cytokines and is therefore considered desirable in an IBD patient diet [29,30].

1.3. IBD and intestinal microbiota

The human microbiome is made up of a vast range of microorganisms including commensal, symbiotic and pathogenic bacteria as well as fungi and viruses. There are over 100 trillion microorganisms residing in the gut, mainly dominated by gram negative Bacteroidetes and gram positive Firmicutes, making it the most colonized organ in the body. Actinobacteria, Proteobacteria and Euryarchaeota are also present in the human gut but to a lesser extent. The intestinal microbiota has many beneficial roles supporting health by symbiotically producing vitamins, aiding digestion, repressing pathogenic organisms, promoting gut epithelial cell renewal all while in contact with the body's immune system [2]. Loss of tolerance to commensal enteric microorganisms is one of the hallmarks of IBD, which can lead to uncontrolled chronic inflammation [31]. The collected evidence to date demonstrate that gut microbiota plays a crucial role in the pathogenesis of IBD [2,25]. This is supported by several studies on animal models of IBD, by findings from germ-free rodents which are protected from intestinal inflammation, and in animals where transfer of the microbiota from mice with colitis to healthy mice result in inflammation [32–34]. In support of these findings, clinical studies show that certain sub groups of IBD patients can respond to antibiotic treatment [35]. Collectively, these studies demonstrate an important role of the gut microbiota in IBD development. A reduction of beneficial bacteria has been reported in patients with IBD. Among these, Firmicutes, including *Clostridium* clusters XIVa and IV, are extensively reduced in these patients. In particular, *Faecalibacterium prausnitzii*, a member of *Clostridium* cluster IV, is less abundant in ileal biopsies, faecal samples and in patients with active IBD [36]. *F. prausnitzii* aids in the promotion of gut health through the secretion of anti-inflammatory bacterial metabolites such as butyrate which is a major energy source for epithelial cells. [37]. Further to the reduced abundance in Firmicutes, an increased abundance of Proteobacteria have been reported in IBD patients. The largest class is the Gammaproteobacteria group which includes pathogenic *Escherichia coli* strains [38,39]. Adherent-Invasive *E. coli* (AIEC) [40] is a so called pathobiont i.e. organisms that can potentially influence pathological processes under certain conditions, and have been isolated from the ileal and colonic mucosa of up to 40% of patients with Crohn's disease [39–42]. They adhere and invade intestinal epithelial cells and macrophages thereby colonizing the gut mucosa resulting in tissue damage and inflammation [42]. In animal models, colonisation of AIEC alone does not induce intestinal inflammation, but it can exacerbate colitis in mice challenged with dextran sodium sulphate (DSS) and in CEABAC10 transgenic mice expressing the human CEACAM6-receptor for AIEC [7]. Other potential pathobionts belong to the Bacteroides genus [43], among which *Bacteroides fragilis* are found in higher abundance in UC patients [44]. Interestingly, mice chronically infected with human commensal *B. fragilis* were found to develop chronic colitis, supporting *B. fragilis* as an IBD pathobiont [45]. Novel approaches aiming to alter and restore microbial balance in the gut as alternative treatment or management of the disease are under investigation. Several strategies are being explored e.g. the use of probiotics, prebiotics, faecal microbiota transplantation, Short Chain Fatty Acids etc. Preclinical studies using these approaches have proven somewhat successful. However, few clinical trials have demonstrated efficacy and future studies will reveal if restoring the microbiome is enough to reduce inflammation in these patients or if a more personalised approach could be more successful treatment for these patients [46]. Bacteria and virus known to bind to CEACAMs in the GI tract are described in Table 1.

1.4. IBD and the host response

The pathogenesis of IBD suggests a defect in one or more elements that are accountable for homeostasis within the GI tract. Intestinal epithelial cells (IECs) form part of the intestinal barrier complex playing a role in mucus production, antigen presentation to the cells of the intestinal immune system as well as controlling antigen trafficking. The intestinal barrier of healthy individuals sustains intestinal homeostasis, supported by IECs and tight junction proteins. These are located at the apical end of the intercellular space, and regulate the permeability of the barrier by hindering entrance of pathogens. IECs, especially goblet cells, play a role in the composition of the mucus layer, which is much thicker in healthy individuals compared to patients with IBD [2,23]. The colonic mucus layer consists of an outer loose mucus layer, where commensal bacteria is usually localised and an inner attached mucus layer where bacteria is totally absent. The thick mucus layer, which is synthesized by goblet cells, traps the presenting microbe preventing pathogen invasion in the cell. In IBD, a thinner mucus layer and an altered barrier i.e. tight junctions thereby increasing the cellular permeability to antigens and luminal bacteria such as AIEC compromising the barrier and leading to an amplified inflammatory response. [47]. Bacteria are recognized by pattern recognition receptors such as Toll-like receptors (TLRs) and NODs. Specific Pathogen Associated Molecular Patterns are recognized by TLRs, activating signal transduction through the NF-κB pathway to initiate the pro-inflammatory cascade. Recognition via TLRs maintains oral tolerance, shutting down the pro-inflammatory response while eliminating the pathogen. However, in IBD an abnormal TLR expression or mutations in NOD2 in IECs and in innate immune cells such as dendritic cells and macrophages, lead to impaired or enhanced microorganism recognition resulting in an amplified immune response [48]. The defective expression of gp-180 on IECs from IBD patients fail to mount a $CD8^+$ suppressor T cell response and instead a T helper 1 (Th1) $CD4^+$ T cells response is mounted [47]. Furthermore, Th17 cells are significantly increased in the inflamed mucosa of patients with both CD and UC and an atypical Th2 cell profile has been demonstrated in patients with UC [41].

1.5. Cancer associated with IBD

As mentioned previously, patients with IBD have an increased risk of developing CAC. The first association between IBD and CAC was made by Crohn and Rosenburg in 1952 [49]. However, patients rarely encounter any form of cancer before 7 years of colitis. Furthermore, IBD patients who have a family history of CRC are twice as likely to develop CAC rather than those without a familial link. Several factors increase the risk of CAC including primary sclerosing cholangitis, severity of histologic inflammation, history of dysplasia, longer duration of colitis. In comparison sporadic colorectal carcinoma arises in patients as a result of genomic instability, mainly chromosomal instability and microsatellite instability. In sporadic colorectal carcinoma, dysplasia lesions arise in one or more focal areas of the colon while CAC arises from dysplasia in the flat mucosa [50]. Furthermore, the onset of CAC occurs in much younger patients (40–50 years) compared to sporadic CRC (60 years) [49]. In addition to colon cancer, patients with IBD and particularly CD, can develop small bowel cancer. Adenocarcinomas usually occur in the terminal ileum and jejunum. Squamous cell carcinoma of the anus is also common in CD patients while a high prevalence of hepatobiliary cancer has been observed in UC patients [51,52].

The genetic events associated with familial CRC i.e. mutations in WNT, RAS, p53, DCC and TGF-β pathways are somewhat different in IBD. For example, mutations in p53 occur as early events in 50% UC patients compared to 10% in non-inflammatory adenomas [53,54]. In contrast, mutations in APC are rarely observed in IBD when compared to non-inflammatory adenomas [53,54]. Furthermore, inflammatory mediators such as reactive oxygen and nitrogen species (ROS and NOS), and cytokines (IL-6, STAT3, TNF-α, IL-10, IL-12 and IL-23) are highly involved in the progression from normal epithelium to indefinite dysplasia [53], further highlighting the inflammatory influence on CAC compared to spontaneous CRC.

Table 1
Bacteria and virus binding to CEACAMs.

Bacterial/ Virus Species	Primary Tissue target	Adhesin	CEACAM1	CEACAM5	CEACAM6	CEACAM7/ CEACAM20	Reference
AIEC	Digestive tract	FimH	–	–	+	N/A	[6]
DAEC	Digestive tract	Afa/Dr-I	+	+	+	N/A	[112]
Salmonella spp	Digestive tract	Uncharacterized Fimbral adhesin	+	+	+	N/A	[113]
Candida albicans	Digestive tract	–	+	+	+	–	[74]

(+) indicates binding to the outlined CEACAM member.
(-) indicates no binding to the outlined CEACAM member.
N/A – not applicable.
Table modified from [114].

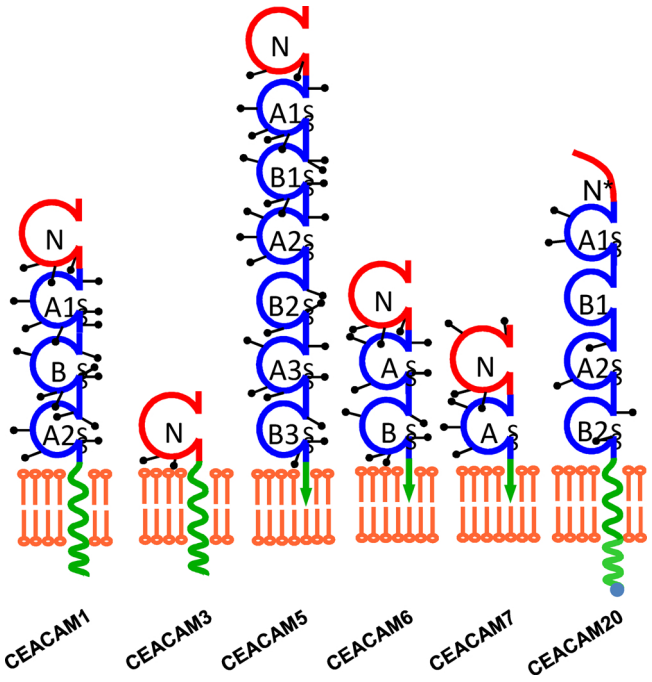

Fig. 2. Schematic depicting six members of the human CEACAMs. The red spheres indicate the IgV like domains, the blue spheres indicate the IgC like domains which are stabilized by disulphide bonds (S—S) The green spiral indicates the transmembrane helices. The green arrow ending in the lipid bilayer in CEACAM5,6,7 is the GPI anchor. CEACAM20 encodes a partial IgV like domain. Diagram modified from www.carcinoembryonic-antigen.de.

2. CEACAM family members

Carcinoembryonic antigen (CEA) is an oncofetal glycoprotein that was first described in 1965 by Gold and Freedman and is clinically used as a tumour marker for colorectal cancer [55,56]. Carcinoembryonic antigen related cell adhesion molecules are members of the glycosylphosphatidylinositol (GPI) – linked immunogloublin (Ig) superfamily. Within this superfamily, more than 17 different genes exist with the gene products being expressed mainly in the cell membrane [4,57]. In humans, 12 different CEACAMs are found; CEACAM1, CEACAM3-CEACAM8, CEACAM16 and CEACAM18-CEACAM21 [57]. CEACAM family members typically exist as cell surface proteins, although the CEACAM family member pregnancy-specific glycoproteins can be secreted by trophoblasts [58]. As seen in Fig. 2, each member of the family is structurally similar and belong to the Immunoglobulin (Ig) family composed of an Ig-variable (V)-like N terminal domain and a variable number of IgC-like A and B domains. In the case of CEACAM5 and CEACAM6, these extracellular domains are attached to the membrane via a GPI anchor [4]. CEACAM1 exists in a transmembrane form. In the case of cell adhesion, this can occur through the N-terminal domain of CEACAMs, following heterodimerization and homodimerization on the same cell (cis-) or across different cells (trans-) [59] or they can function as human pathogen receptors [60].

In the next section the most relevant CEACAM family members i.e. CEACAM1, CEACAM5, CEACAM6, CEACAM7, CEACAM20 and CEACAM3 that are highly present in the GI tract and associated to intestinal inflammation and IBD will be reviewed. Table 2 describe the biological role and Table 3 outlines the protein and gene expression of each CEACAM family member in the GI tract. Fig. 3 summarises the biological functions and expression of CEACAM family members in the healthy and in the inflamed (IBD) intestine.

2.1. CEACAM1

CEACAM1 (Bgp, CD66a), has the broadest tissue distribution of all the CEACAM members. It is expressed in a variety of different cell types including epithelial cells, endothelial cells and myeloid cells but can also be found on leukocytes. Several biological functions have been attributed to CEACAM1 including inhibition of epithelial cell

In the proof - Biological function(s) - an indent on "functions" should be excludedTable 2
Biological functions of CEACAM family members in the Gastrointestinal tract.

	CEACAM1	CEACAM3	CEACAM5	CEACAM6	CEACAM7	CEACAM20
Biological function(s)	- Cell adhesion - Angiogenesis - Apoptosis - Tumour suppression - Modulation of innate and adaptive immune responses - Play a role in tumorigenesis	- Binding site for various pathogens - Innate immune response against pathogens	- Regulate cellular differentiation and apoptosis - Play a role in tumorigenesis	- Immuno-regulator - Receptor for AIEC - Play a role in tumorigenesis	- Proliferation - Differentiation - Play a role in tumorigenesis	- Potentially promoting proliferation or differentiation - Regulated by Gram positive bacteria
References	[61,66,67]	[105,106]	[57]	[6,57,87]	[93,98]	[71,101]

Table 3
Protein and Gene Expression of CEACAM family members in the Gastrointestinal tract.

GI Tract site of expression	CEACAM1	CEACAM3	CEACAM5	CEACAM6	CEACAM7	CEACAM20
Salivary Gland	+	+	+	-/ #	–	–
Oral mucosa	–	–	+	–	–	–
Oesophagus	-/ #	_	+	-/ #	-/ #	–
Stomach	-/ #	+	+	+	–	–
Duodenum	+	–	+	+	–	-/ #
Small Intestine	+	+	+	+	–	-/ #
Colon	+	+	+	+	+	–
Rectum	+	+	+	+	+	–

(+) indicate protein expression.
(-) indicates no protein expression.
(#) indicates RNA expression.
The table is generated from data under www.proteinatlas.org.

proliferation and T lymphocyte activation, promotion of angiogenesis, and regulation of vascular remodelling [61]. CEACAM1 has eleven different splice products, each containing a hydrophobic transmembrane domain and a cytoplasmic domain which are characterized by the length of the cytoplasmic tail, either long (L) or short (S) [62]. The 'L' isoform encodes 71 amino acid residues, including several tyrosine, threonine and serine residues. These play a role in signal transduction and protein-protein interactions as well as acting as phosphorylation targets. The "S" isoform encompasses 10 cytoplasmic residues. Most CEACAM1 expressing tissues express both isoforms [63,64]. The N-domain of CEACAM1 is involved in heterophilic binding with other CEACAM members including CEACAM5 as well as microbial components e.g. *Neisseria* spp. The long isoform of the gene is involved in T cell inhibition dependant on Src homology phosphatase 1 and ITAM domains [65]. Therefore, the loss of CEACAM1 has been linked to increased T cell activation [66]. In addition, the long isoform of CEACAM1 was reported to be a substrate to caspase-3 in apoptotic murine IECs and the caspase-3 cleaved CEACAM1 became a stronger adhesion molecule indicating a potential role of CEACAM1 in apoptosis clearance [67].

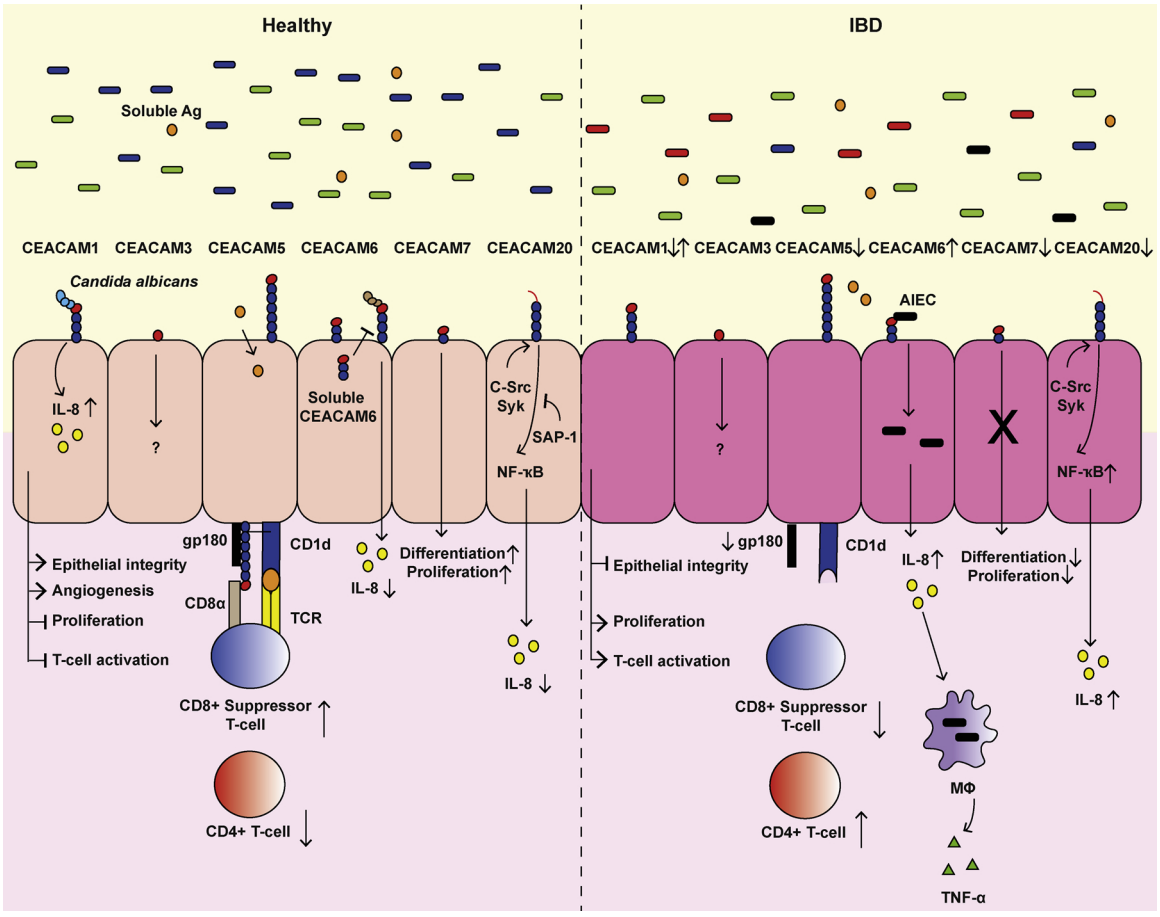

Fig. 3. An schematic outlining the expression and function(s) of CEACAMs in healthy versus inflamed (IBD) intestine.

In healthy individuals CEACAM1 is generally found in the colonic glycocalyx and in columnar IECs and M cells [68–70]. A reduction in CEACAM1 expression in small intestinal IECs was found in germ free mice and in mice treated with antibiotics indicating a regulation of CEACAM1 by the microbiota [71]. However, commensal bacteria challenge did not induce CEACAM1 expression inhuman IECs HT29 and T84 cells [72,73]. In contrast, treatment with the pro-inflammatory cytokine IFNγ induced the expression of CEACAM1 in HT29 and CEACAM1(L) form in T84 cells, while TNFα-activation of T84 cells induced the expression of both CEACAM1(L) and (S) forms. CEACAM1 was recently shown to bind to a fungal pathogen, *Candida albicans,* and induce a CEACAM1-dependent IL-8 response and tighten the barrier in IECs. Interestingly, soluble CEACAM6 inhibited CEACAM1 binding to *C. albicans* indicating a shared fungal epitope by CEACAM1 and a higher CEACAM6 affinity to the fungal pathogen [74]. This paper is the first to describe a role of CEACAMs in maintaining homeostasis to yeast. The relevance of these findings for IBD is important as an increase proportion of *C. albicans* [75] and expression of CEACAM6 has been found in these patients. The implications of these findings in IBD pathology are still yet to be discovered. The expression of CEACAM1 levels in IECs of patients with CD was found to be reduced while no changes were reported in UC [9]. In contrast, transcriptomic analysis of whole colon biopsy and peripheral blood mononuclear cells showed an increased expression of CEACAM1 in patients with UC but not CD [76,77]. Furthermore, immunohistochemistry staining revealed increased CEACAM1 staining on lamina propria immune cells in the colons of patients with CD compared to UC and controls [77]. In addition, inhibition of CEACAM1 on intestinal intraepithelial lymphocytes, present in between IECs, reduced their cytotoxic potential indicating a role of CEACAM1 in regulating T cell responses [78]. To investigate the impact of inhibiting CEACAM1 expression, mice treated with a monoclonal antibody against CEACAM1 reduced 2,4,6-trinitrobenzene sulfonic acid (TNBS)- and Oxazolone-induced colitis by reducing levels of IFNγ [79]. Similarly, in a T cell transfer model of colitis lack of CEACAM1 on T cells resulted in a hyper-inflammatory profile with a reduction in TIM-3 on the cell surface and the reduction in regulatory cytokines resulting in worsening colitis phenotype [80]. Interestingly, overexpression of CEACAM1(L) form reduced colitis by reducing both Th1 and Th2 cytokines in a T cell transfer model of colitis [62]. In other models, overexpression of CEACAM1 in murine colitis reduced disease progression. In mice with TNBS-colitis, the levels of CEACAM1 were reduced in line with human findings. Reintroduction of CEACAM1 by a transrectal injection of a CEACAM1-overexpressing adenovirus construct lead to reduced bowel wall thickening, downregulation of inflammatory cytokines, inhibition of T cell infiltration and a reduction in apoptosis. The latter was associated with increased levels of Bcl-2 (pro-apoptotic) and reduced levels of BAX and cleaved caspase-3 (pro-apoptotic) [81]. The same group also reported protection of dextran sodium sulphate (DSS)-induced colitis, upon overexpression of CEACAM1 which resulted in restored levels of the tight junction proteins claudin-1, occludin and ZO-1 and a decrease in intestinal permeability [82]. In summary, the preclinical data indicate that CEACAM1 in the gut appears to contribute to tissue protection, regulation of epithelial barrier function and inhibition of T cell responses. In colon cancer, it has been reported that the expression of CEACAM1 isoforms is highly dynamic e.g. being downregulated in early phases of solid tumours but increased in advanced stages potentially associated with invasiveness and metastatic spread [61]. It is currently unknown if the contrasting findings in IBD reflect also dynamic changes in CEACAM1 due to e.g. degree or length or type of inflammation or if alterations in CEACAM1 expression is cell type and disease dependent or if one isoform is more relevant to IBD pathogenesis than the other. Future studies on sorted cells and an in-depth analysis of the two CEACAM1 isoforms would address some of these issues.

2.2. CEACAM5

The high molecular weight glycoprotein, CEACAM5 (CEA, CD66e) is a widely used tumour marker in patients with CRC. Beside its function as a cell adhesion molecule, CEACAM5 is also involve in the inhibition of differentiation of cells and inhibition of cell death in colon cells as well as alteration in cell polarisation and tissue structure [57]. In the GI tract CEACAM5 is found in colonic columnar IECs and goblet cells, in the stomach in mucous neck cells and pyloric mucous cells, in the squamous epithelial cells of the tongue and in the oesophagus [83]. The expression of CEACAM5 is more prominent in the proximal colon than the rectum in healthy controls and particularly in the upper third of the crypt and at the free luminal surface [4,83]. In patients with active UC, CEACAM5 was increased [83] while it was decreased in IECs of patients with CD [9]. Interestingly, co-culture of lamina propria lymphocytes with HT29 and T84 IEC lines resulted in an induced CEACAM5 expression on IECs indicating of an immune cell-IEC regulation of this gene [9]. It has been shown that IECs can behave as antigen presenting cells. In a healthy state, IECs can present soluble antigens to T cells thereby activating $CD8^+$ suppressor T cells. Two proteins were identified on these suppressive cell types namely gp180 and CD1d. A sequence homology between the N-terminal domain of CEACAM5 and the glycoprotein gp180 was identified in IECs. Binding of CEACAM5 to CD8α induced Lck phosphorylation and blocking of gp180-CEACAM5 interaction resulted in inhibition of CD8 suppressor cell activation [84,85]. IEC's of patients with IBD were unable to activate $CD8^+$ suppressor T cells leading to a failure in immune suppression of activated $CD4^+$ Th cells which secrete high levels of pro-inflammatory cytokines supporting chronic inflammation [84]. This failure in CD8 suppressor activation was due to the reduced expression gp180 on IECs from CD patients and a reduction and redistribution of gp180 in IECs from UC patients when compared to the surface and crypt expression in IEC of normal controls. Thus, this study confirmed a defect of CEACAM5 in IEC signalling in IBD [86]. In addition, CEACAM5 can also bind to CD1d which can potentially further aid in the activation of $CD8^+$ suppressor T cells or be of importance for MHC class I presentation [84]. Recovery of CEACAM5 and gp180/CD1d interaction to restore suppressor $CD8^+$ T cells activity can be a future approach for CD. For this purpose and similarly to CEACAM1 exogenous addition of CEACAM5 to patients with IBD could be explored in the future.

2.3. CEACAM6

The glycoprotein CEACAM6 (NCA, CD66c) has many functions including undergoing heterotypic binding with integrin receptors (e.g. β1 and β3 integrin) as well as homotypic binding with other CEACAM family members (e.g. CEACAM1, CEACAM5, CEACAM8) on host and bacteria [87], which is an important immune regulatory function. CEACAM6 is expressed on IECs as 1) soluble; or 2) membrane-bound by a GPI anchor on the cell surface or 3) on extracellular vesicles [88]. CEACAM6 can also be expressed on granulocytes and monocytes [4]. In epithelial cell lines, treatment with IFNγ significantly induce the cell surface expression of CEACAM6 [73] but no changes in CEACAM6 were detected when epithelial cells were treated with bacteria [72]. The adhesion and invasion of commensal bacteria into host cells has been strongly associated with the pathogenesis of CD and UC. AIEC are opportunistic bacteria (pathobionts) that have the ability to adhere and invade IECs and colonize the gut mucosa of these patients [39,40]. In 2007, Barnich et al, identified CEACAM6 as a receptor of AIEC. Interestingly, in patients with CD CEACAM6 is expressed abnormally in the ileal mucosa, indicating their potential role in binding AIEC [6]. AIEC adhere to CEACAM6 via FimH, the terminal subunit of type 1 pili. AIECs can also multiply intracellularly in IECs and macrophages resulting in AIEC accumulation and leading to increased secretion of pro-

inflammatory cytokines including TNFα. One of the main features of AIEC is their survival ability in the cells without inducing apoptosis or IFNγ secretion [8]. In an effort to identify a genetic link between CEACAM6 and IBD, Glas and colleagues analysed over 1300 IBD subjects, but no association between CEACAM6 SNPs and haplotypes to neither UC or CD susceptibility was uncovered [89]. As CEACAM6 is not present in the mouse genome, a transgenic CEABAC10 mouse model expressing human CEACAM6 was created and increased levels of pro-inflammatory cytokines IL-6 and IL-17 and decreased levels of anti-inflammatory cytokine IL-10 were observed as well as histopathological damage to the gut mucosa upon AIEC-infection [7]. Similarly, an impact on barrier integrity due to the interaction between AIEC type 1 pili and CEACAM6 before the onset of colitis was reported in the CEACAC10 mice [90]. Feeding CEABAC10 mice a Westernised diet (high fat/high sucrose) resulted in alterations in gut microbiota composition, host homeostasis and promoted AIEC gut colonization without inducing acute inflammation and histological damage, indicating an interaction between AIEC, CEACAM6 and environmental factors [91]. Blocking of CEACAM6 with a monoclonal antibody resulted in a reduction in AIEC colonization and inflammation, indicating that blocking the interaction between type 1 pili and CEACAM6 can be a potential treatment for patients with CD [7]. Another plausible strategy would be to create an adhesion-based vaccine. Promising results were reported in a mouse cystitis model whereby a vaccine containing a recombinant truncated form of FimH adhesin reduced colonization of uropathogenic *E. coli* [92]. A similar approach could be adopted for IBD.

2.4. CEACAM7

Unlike other members of the CEACAM family which are expressed in a variety of different tissues, CEACAM7 (CGM2) is only expressed in pancreatic and colorectal epithelium and specially in the apical surface of differentiated IECs [93]. CEACAM7 is known to play a vital role in the regulation of normal cellular differentiation and proliferation. Based on the number of extracellular immunoglobulin-like domains two splice forms of CEACAM7 exist, CEACAM7-1 and CEACAM7-2 [94]. Currently, there are few reports on the link between CEACAM7 and intestinal inflammation or IBD. Treatment with pro-inflammatory cytokines or whole bacteria to monolayers of T84 and CaCO2 IECs did not induce gene expression of CEACAM7 [72]. A microarray-based gene expression analysis of colon pinch biopsies from IBD patients presented a significant reduction in CEACAM7 in both UC and CD when compared to control biopsies, while no difference between the 2 conditions were observed [95]. A similar profile was observed in a report by Shan et al, who reanalysed meta-analysis of large IBD data sets [96]. The relevance of these findings has not been addressed in IBD. In cancer, a reduction in CEACAM7 has been shown in CRC patients, especially during early oncogenesis [97]. It has been suggested that the downregulation of CEACAM7 has an inhibitory effect against cellular differentiation leading to less well-defined tumours resulting in a poorer prognosis. Throughout tumour development, certain genes are silenced while others require activation. The loss of association of CEACAM7 coupled with the loss of cellular adhesion capability is a necessary step in the early stages of oncogenesis. This promotes the ability of neoplasm to escape the primary tumour bed, invade the lymphatic system and become metastatic [98]. When the relationship between CEACAM7 and rectal cancer was investigated, a reduction in CEACAM7 expression occurs early in the neoplastic process and the expression level is significantly reduced when cancer is developed compared to a healthy rectal tissue. Furthermore, when the relative expression levels of CEACAM7 and reoccurrence in primary rectal cancers was compared, CEACAM7 was identified as a potential predictor of recurrent disease [99]. Since colon cancer is linked to IBD, monitoring CEACAM7 levels in all stages of disease, particularly in early stages, could predict the likelihood of colon cancer development in these patients. This awareness could guide the management of these patients for the early discovery and treatment of CAC.

2.5. CEACAM20

CEACAM20 is a novel member of the CEACAM1 gene family, with an expression profile limited to the lumen of the small intestine, colon, testes, and prostate [100,101]. CEACAM20 is present in the microvilli of the brush boarder in the epithelial cells. The function of CEACAM20 in the gut is less known, although CEACAM20 promotes proliferation or differentiation in prostate epithelial cells [101]. Interestingly, a reduction in CEACAM20 expression in small intestinal IECs was found in germ free mice and in mice treated with antibiotics targeting Gram positive bacteria, indicating a regulation of CEACAM20 by the microbiota [71]. Similarly, organoids treated with butyrate or IFNγ resulted in an induction in CEACAM20 expression, indicating CEACAM20 can be regulated by immune mediators and microbial metabolites [71]. In IBD, no difference in CEACAM20 expression was seen between colon biopsies of UC or CD when compared to controls [95]. In contrast, a reduction in ileal CEACAM20 expression was identified by RNASeq between older (A1b) compared to younger (A1a) paediatric patients with CD [102]. Similarly, a reduction in CEACAM20 expression was found in formalin fix terminal ileum tissue of adult patients with CD compared to controls [103]. An association between CEACAM20 and Stomach-cancer–associated protein tyrosine phosphatase 1 (SAP-1, also known as PTPRH), which is a receptor-type protein tyrosine phosphatase, was identified in mice deficient in both SAP-1 and IL-10. The tyrosine phosphorylation of CEACAM20 was greatly increased in SAP-1 deficient mice, and SAP-1 dephosphorylated CEACAM20 indicating that CEACAM20 is a substrate of SAP-1. CEACAM20 and SAP-1 were also co-localised in the microvilli of IECs suggesting a specific interaction between these proteins. Furthermore, tyrosine phosphorylation of CEACAM20 by c-Src and its association with Syk enhanced the production of IL-8 through the activation of NFκB, indicating CEACAM20 is involved in the promotion of inflammation and contributing to colitis [104]. The discrepancy between the human and murine findings could depend on site of expression (small intestine vs colon) or differences in human vs murine microbiota, as CEACAM20 appears to be regulated by the intestinal microbiota. It is not known either if CEACAM20 might act as a receptor for microbes, which again could be different between healthy and disease state and between mice and human. Further research is necessary to elucidate the role of CEACAM20 in intestinal health and in IBD.

2.6. CEACAM3

Contrary to other CEACAM family members, CEACAM3 (CGM1, CD66d) is not involved in cell–cell adhesion. It has been suggested that CEACAM3 is a neutrophil specific receptor that functions as a decoy in capturing Gram negative pathogens including *Neisseria gonorrhoea* resulting in adherence of the bacteria to the epithelium. In addition, internalisation of the bacteria to neutrophils, dependent on Src family protein tyrosine kinase activity, induces the activation NFκB-dependent genes in neutrophils [105]. The role of CEACAM3 in the gut is less understood. A recent study identified CEACAM3 as a receptor for *Helicobacter pilory* via HopQ, which is the surface-exposed adhesin facilitating the binding [106]. A weak adhesion of DraE, belonging to the Dr family of adhesins of *E. coli* strains associated with diarrhoea and urinary tract infections, to CEACAM3 has been reported [107]. This finding can be of interest for IBD, since AIEC strains share some genetic similarities e.g. phylogenetic origin and virulence genotype, with extra intestinal pathogenic *E. coli* (ExPEC), to which urinary *E. coli* strains

belong [39]. *C. albicans* was also recently shown to bind to CEACAM3, although the relevance of this interaction was not studied in this paper [74]. CEACAM3 protein expression was reported in the stomach, small intestine, colon and rectum (Table 3). No major changes in CEACAM3 expression were noted in IBD biopsies in microarray studies [95,96]. A study in CRC patients reported a decreasing trend of CEACAM3 expression from perioperative to early and late postoperative phase in these patients. This trend was similarly to CEACAM5, although, CEACAM3 expression was in general lower but more specific which explains why the authors suggested that CEACAM3 can be a better marker for circulating cancer cells/micrometastases [108]. Future research will clarify the role of CEACAM3 in the intestine.

3. Conclusion and future perspectives

The incidence of IBD is increasing worldwide and CRC is now a serious health problem across the globe. Both diseases have a complex aetiology and no definite cure exists for either of these conditions. Despite much research carried out on the various CEACAM family members, few studies have explored their potential use as therapeutic agents for IBD and CAC. From the literature we know that certain members are upregulated and can even function as a receptor for pathobionts e.g. CEACAM6, while other CEACAM members are downregulated in the different disease states e.g. CEACAM1. One of the major hurdles in this area is the human contra murine expression of CEACAMs. To date, the only members sharing homologies between humans and rodents are CEACAM1 and CEACAM20 [109]. Therefore, in order to investigate the role of other CEACAMs in IBD disease progression, transgenic mice expressing human CEACAMs have been generated e.g. CEABAC and CEABAC10 mice [7,110]. Once new transgenic mice e.g. expressing human CEACAM7, are generated, their role in disease can be investigated more in-depth and potential new therapies could be evaluated. One interesting approach to target CEACAMs is oral gene therapy whereby Nanoparticles-in-microsphere (NiMOS), in which siRNA is encapsulate by a biodegradable poly-epsilin-caprolactone (PCL) matrix, can be utilised. PCL is degraded in the small and large intestine by lipases, releasing the gelatine NPs over time [111]. Thus, by using this system, siRNA against e.g. CEACAM6 could be created thereby reducing binding of AIEC and resulting in a reduction in Proteobacteria and inflammation. Another approach could be the delivery of overexpression of CEACAM1, CEACAM5 and CEACAM7 to epithelial cells to restore intestinal homeostasis, increase barrier integrity and reduce induction of immune responses [81]. There are however, some limitations with delivery of CEACAMs to the gut, including low delivery efficacy, and safety issues such as immunogenic reactions. Instead of using transgenic mice, *ex vivo* models such as human organoids and human immune cells could be used to model human IBD to test potential new therapies for CEACAMs. Exploring the interaction of CEACAMs and other IBD pathobionts, bar AIEC, could also offer new discoveries on the impact of these adhesion molecules and microbiota recognition on IBD pathophysiology. The potential of using certain CEACAMs such as CEACAM5 and CEACAM7 as diagnostic tools to identify patients with risk of developing CAC is highly advisable and therefore prospective and longitudinal studies should be established to address this question. In conclusion, there is a need to investigate the impact of CEACAMs in intestinal health and disease to identify new functions, new strategies to therapeutic and diagnostic tools for inflammation and cancer progression in IBD patients.

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Conflicts of interest

The authors report no other conflicts of interest in this work.

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Maebh Kelleher, BPharm MPharm, is a registered Pharmacist having received a BSc Pharm (Hons) from University College Cork (UCC) in 2017. Subsequent to this, she obtained a Masters in Pharmacy from The Royal College of Surgeons Dublin in 2018. During her undergraduate studies, Maebh undertook her final year and summer research project under the supervision of Dr Silvia Melgar and Professor Caitriona O'Driscoll, where she investigated the link between Carcinoembryonic antigen family members and Inflammatory Bowel Disease. Other research interests include Novel Drug Delivery, Oncology and Hospital Pharmacy. Maebh currently works as a community Pharmacist in Dublin, Ireland.

Raminder Singh research interests lie in the area of host-microbe interactions and immunology. He received his BSc and MSc (2016) in Biology from Indian Institute of Science Education and Research, Mohali, India. He was the recipient of INSPIRE fellowship (2011–2016) from Department of Science and Technology, India and junior research fellowship (2015) from Council of Scientific and Industrial Research, Ministry of Science and Technology, India. In 2017, he joined APC Microbiome Ireland and UCC as a PhD student under the supervision of Dr Silvia Melgar and Prof Stefan Andersson-Engels.

Caitriona O'Driscoll is Professor and Chair of Pharmaceutics in the School of Pharmacy in UCC. She completed her PhD studies in Pharmaceutical Sciences in Trinity College Dublin (TCD) and undertook a sabbatical in the Department of Pharmaceutical Chemistry at the University of Kansas, USA. She was a senior lecturer in the School of Pharmacy at TCD prior to her appointment to UCC in 2003. She is a Board member of the Health Products Regulatory Authority, and the Critical Path Institute. She is a founding member and Chair of Regulatory Science Ireland. Professor O'Driscoll's research interests are translational in nature and include formulation of nano-sized drug delivery constructs, which remain stable during processing and storage, and are safe and effective for use by patients. Candidate drugs include biopharmaceuticals, peptide/proteins, nucleic acids and poorly water-soluble compounds. Delivery systems of interest are; lipid-based vehicles and non-viral gene delivery systems employing modified cyclodextrins, nanoparticles and receptor-ligand mediated targeting.

Silvia Melgar is a Senior Research Co-ordinator and Faculty Investigator at APC Microbiome Ireland in UCC, Ireland. She received a BSc degree in Molecular Biology and Ph.D. in Immunology from Umeå University, Sweden. She joined AstraZeneca, Sweden as a post-doctoral fellow followed by a position as senior research scientist within the disease area of inflammatory bowel disease (IBD). In 2008, she joined GlaxoSmithKline (GSK) as principal scientist and *in vivo* research co-ordinator under the GSK-Alimentary Pharmabiotic Centre collaboration at UCC. She became an independent investigator at APC Microbiome Ireland in 2012. Dr Melgar' research aims to identify new molecular mechanisms associated with environmental factors such as diets, in bacteria-host interactions and their relevance in health and in intestinal disorders such as inflammatory bowel disease and colon cancer. Her group uses *in vitro*, primary *ex vivo* and *in vivo* systems.