Cytokine Networks in the Pathophysiology of Inflammatory Bowel Disease

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SUMMARY

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract. Genetic and functional studies demonstrate a key role for cytokines in shaping the host's response to environmental triggers in homeostasis and inflammation. Cytokine-targeted therapies have transformed the treatment of IBD providing control of symptoms and longer relapse-free periods. However, many patients fail to respond highlighting the need for therapies tailored to the underlying cell and molecular disease drivers. Here we discuss the progression of IBD from the perspective of remodelling of cytokine networks. We place well-established and under-studied cytokine modules in the context of cellular interactions, their dynamic regulation in early and late stages of disease (i.e., fibrosis), and their current and potential use in the clinic. Examining how particular cytokine networks drive distinct features and phases of IBD will shed light on the aetiology of IBD and provide inroads into more effective treatments.

Introduction

Inflammatory bowel disease (IBD) represents a major healthcare burden of significant global morbidity, with highest prevalence in Europe and North America and rising incidence in Asia (Ng et al., 2018). Genetic, clinical and experimental studies show that IBD is a multi-factorial disease in which a genetically maladapted host response to environmental drivers leads to a breakdown of intestinal homeostasis (Maloy and Powrie, 2011). The diverse interplay between the host and environment results in IBD that presents as a spectrum of heterogeneous diseases falling under two main clinical entities: Crohn's disease (CD) and ulcerative colitis (UC) (Kaplan, 2015).

As an interface between the host and the environment, the intestine needs to perform key physiological functions such as nutrient and water resorption alongside maintaining active tolerance to commensal microbes and diet with efficient defense against pathogens and damage (Odenwald and Turner, 2017). Control of these diverse functions is conducted by a tissue-specialised cellular network including epithelial cell subsets in direct contact with luminal components, mesenchymal cell populations that provide the extracellular structure of the tissue, and a diverse population of tissue-adapted immune cells. Cytokines are key mediators of cellular interactions in the intestine in both physiology and pathophysiology. Over the last three decades, studies on human intestinal tissue and *in vivo* mouse models have established epithelial barrier function, host defense pathways, immune regulation and tissue repair as key pillars of intestinal homeostasis controlling the host-microbe dialogue. Breakdown of these pathways – and the cytokine networks they are regulated by – can lead to IBD (Maloy and Powrie, 2011). Many IBD risk loci are found in regions of genes encoding cytokines or their downstream signalling mediators (**Table 1**) (de Lange et al., 2017; Jostins et al., 2012; Liu et al., 2015). Furthermore, a number of Mendelian diseases that present with IBD (MD-IBD) are a consequence of deficiency or enhanced activation of cytokine pathways illustrating how deranged cytokine regulation can promote the breakdown of intestinal homeostasis (Uhlig and Powrie, 2018) (**Table 1**). These data from human studies are complemented by studies in mouse models that offer unique opportunities to dissect the dynamics of cytokine regulation and establish causal functional links to support the development of cytokine-targeted therapies in IBD (**Table 1,** for specifics of the discussed mouse models, please refer to (Kiesler et al., 2015)).

Understanding cytokine networks in the intestine has laid the foundations for development of a number of biological therapies that are transforming treatment of IBD. Anti-TNF-α targeting (anti-TNF) therapies are improving clinical score, mucosal healing and prolonging relapse-free periods in many patients. In CD, anti-Interleukin(IL)-12p40 (targeting the common

subunit of IL-12 and IL-23) is effective and promising early results targeting IL-23p19 or signalling mediators downstream of multiple cytokines offer great opportunity (Neurath, 2017). In spite of these successes, major challenges remain particularly for those who do not respond to first-line therapies and progress to chronic disease with long-term complications, such as fibrosis. Such therapy-refractory patients represent a major unmet clinical need that requires alternative therapeutic approaches.

Advances in single-cell analysis of samples from large IBD patient cohorts together with mouse models are revealing many cytokine and cellular pathways that are associated with intestinal inflammation, and are thus potential alternative therapeutic targets. However, it remains very difficult to target therapies to those patients most likely to respond. Currently our understanding of cytokine networks reflects a snapshot at a certain stage of disease. Cytokine functions are context dependent and can exert opposing effects depending on the stage of inflammation, with important implications for clinical targeting. To realise the potential of personalised medicine it will be crucial to understand the dynamics of cytokine networks using both *in vivo* models and longitudinal IBD cohort studies. In this review, we discuss how cytokine networks maintain intestinal homeostasis, and how they become deranged to drive pathology and disease progression (**Figure 1**). In addition to reviewing established cytokine networks in IBD, we highlight emerging candidate pathways that could serve as novel therapeutic targets, in particular for therapy-resistant IBD and IBD-associated fibrosis (**Figure 2**).

Cytokine-mediated control of intestinal homeostasis

An organised cellular network maintains intestinal homeostasis by physically excluding commensal microbes from penetrating host tissue and actively promoting host defense and immune regulation. Below, we discuss how cytokines guide these multi-cellular mechanisms in the healthy gut (**Figure 1**, left). Microbial sensing plays a key role in cytokine production and cytokine responsiveness by immune and intestinal cells and is reviewed in detail elsewhere (Pickard et al., 2017).

The single columnar layer of intestinal epithelial cells (IEC) in the gut represents not only the physical barrier separating the microbiota from the mucosa, but also integrates incoming signals from commensals, pathogens and dietary components. Its integrity depends on the balance between differentiation and renewal of IEC, permeability of the barrier and the production of anti-microbial peptides (Odenwald and Turner, 2017). These processes are tightly regulated by cytokines and growth factors produced by gut-resident cells. In particular lymphoid cells, such as natural killer T cells (NKT), γδ T cells, intraepithelial lymphocytes

(IEL), $CD8^+$ mucosal-associated invariant T cells (MAIT), as well as innate lymphoid cells (ILC), produce cytokines that induce transcription factor signal transducer and activator of transcription (STAT) 3 signalling in IEC to promote proliferation and survival. Consequently, IEC-specific STAT3 deletion augments dextran-sodium sulfate (DSS)-induced epithelial erosions and impaired proliferation (Pickert et al., 2009). Produced by T helper (Th) 17 cells, group 3 innate lymphoid cells (ILC3) and γδ T cells, the IL-10 family member IL-22 primarily acts on IEC, activating STAT3 to promote antimicrobial defense, barrier integrity and repair (Zhou and Sonnenberg, 2018). IL-22 production is downstream of environmental sensing. For example, signals from the commensal microbiota induce IL-1β, IL-6 and IL-23 production by mononuclear phagocytes (MNP) leading to IL-22 production by ILC3 (Fung et al., 2016). Similarly, microbiota-dependent IL-6 production in IEL also promotes barrier function and mucus secretion through STAT3 signalling in IEC (Kuhn et al., 2018). In addition, dietary metabolites, such as the Vitamin A metabolite retinoic acid (RA) or aryl hydrocarbon receptor (AHR) ligands, enhance IL-22 production by ILC3 (Grizotte-Lake et al., 2018; Schiering et al., 2017). Besides ILC3, Th17 cells produce barrier-protective IL-22, as well as IL-17, in an IL-23- and serum amyloid A (SAA)-dependent manner downstream of signals from the commensal microbiota, in particular segmented filamentous bacteria (SFB) (Ivanov et al., 2009; Shih et al., 2014). IL-17 family members IL-17A and IL-17F have also been shown to enhance antimicrobial peptide secretion, IEC tight junction formation and proliferation (Lee et al., 2015; Maxwell et al., 2015).

In contrast to STAT3 inducing cytokines, type I interferon (IFN) signalling enhances barrier integrity via STAT1 and STAT2 pathways. These cytokines regulate IEC turnover by preventing apoptosis and promoting differentiation and barrier integrity (Kotredes et al., 2017). Type I IFN produced by MNP promote anti-inflammatory cytokine production and $CD4^+$ regulatory T cell (Treg) responses (Kole et al., 2013). Polymorphisms in the type I IFN receptor gene *IFNAR1* have been linked to susceptibility to IBD (Jostins et al., 2012) (**Table 1**). Whether this reflects effects on IEC or its contribution to anti-inflammatory signalling in MNPs remains to be determined.

Alongside barrier enhancing functions, cytokines also mediate key immune regulatory properties that control immune system-microbiota interactions. In particular MNPs play a key role in integrating microbial cues to promote a regulatory T cell response. Foremost amongst the cytokines regulating this response is IL-10 which plays a non-redundant role in intestinal homeostasis. Mutations in *IL10, IL10RA*, and *IL10RB* genes result in MD-IBD characterised by severe intestinal inflammation with early onset (Glocker et al., 2009). Similarly, both IL-10 and IL-10R-deficient mice develop spontaneous colitis (Kuhn et al., 1993; Spencer et al., 1998). Whereas many cell types such as MNP and B cells can produce IL-10 in the intestine

(Saraiva and O'Garra, 2010), $CD4^+$ T cells appear to be a key functional source (Roers et al., 2004; Rubtsov et al., 2008). Recently the transcription factor c-Maf has been shown to drive IL-10 production in $CD4^+$ T cells, including $Foxp3^+$ Treg cells and Tr1 cells (Gabrysova et al., 2018; Xu et al., 2018). Two distinct Treg populations, $Foxp3^-$ T regulatory type 1 cells (Tr1) and $Foxp3^+$ Treg cells, suppress colitogenic T cell responses through the production of IL-10 (Maloy and Powrie, 2011). Although MNP-derived IL-10 is dispensable for intestinal homeostasis, IL-10 signalling into MNP is required to prevent colitis (Shouval et al., 2014; Takeda et al., 1999; Zigmond et al., 2014). This is consistent with the well-described ability of IL-10 to induce an anti-inflammatory macrophage phenotype (Moore et al., 2001), an activity that has recently been shown to involve metabolic reprogramming (Ip et al., 2017). Underlying the IEC barrier, a dense network of MNP directly sense and phagocytose bacteria, and respond to cues from the epithelium by producing anti-inflammatory cytokines which promote intestinal tolerance. Examples of this are *Helicobacter hepaticus* and *Bacteroides fragilis* polysaccharides that can induce IL-10 production from gut-resident MNPs and T cells (Danne et al., 2017; Mazmanian et al., 2008).

IL-2 and TGF-β are also key components of intestinal homeostasis in part through their role in shaping the $Foxp3^+$ Treg cell pool (Chinen et al., 2016; Li and Flavell, 2008). Early studies have shown that TGF-β1 or IL-2 deficiency results in colitis in mice (Kulkarni et al., 1993; Sadlack et al., 1993) and loss of function mutations in *IL2RA* and *TGFB1* have been detected in MD-IBD (Caudy et al., 2007; Kotlarz et al., 2018). Although many cell types produce and respond to TGF-β1, there is evidence that $CD4^+$ T cells are required as both producers and responders for intact intestinal immune regulation which may reflect the ability of TGF-β1 to induce the peripheral development of $Foxp3^+$ Treg cells (Li and Flavell, 2008; Li et al., 2006). Bioactive TGF-β1 requires proteolytic liberation of mature TGF-β1 from latency-associated peptide by αvβ8 integrins on DC (Travis et al., 2007), highlighting the importance of T cell-MNP interactions in homeostasis. $Foxp3^+$ Treg cells express high amounts of the IL-2 receptor alpha (CD25) and its activation drives their differentiation in the thymus and maintenance in the periphery (Chinen et al., 2016). In addition to production by T cells, there is also evidence that MNP-derived IL-2 contributes to $Foxp3^+$ Treg cell-mediated control of colitis (Mencarelli et al., 2018).

Finally, the gut is enriched in activated B cells and plasma cells, which are mainly localised in Peyer's patches (PP) of the small intestine and solitary intestinal lymphoid tissues of the large intestine (Buettner and Lochner, 2016). Secretory IgA facilitates effective defense by coating pathogenic bacteria to prevent their direct interaction with the epithelium (Macpherson et al., 2018). Class switching of IgM and IgG to IgA is essential for gut homeostasis and is controlled by cytokines such as TGF-β1 and IL-21 in a T cell dependant

manner. DC present in the PP also favour IgA class switching by producing B cell stimulating factors BAFF, APRIL and the cytokines IL-10, IL-6 and TGF-β1 in response to microbial sensing (Cerutti, 2008).

In summary, intestinal homeostasis is maintained by complex, cytokine-guided interactions between epithelial and immune cells (**Figure 1**, left). STAT3-inducing cytokines, in particular IL-22 and IL-6, together with IL-17 cytokines, promote survival of IEC and antimicrobial defense. In addition, microbial and metabolite-induced IL-10 and TGF-β1 play a key role in promoting tolerance through MNP-Treg cell interactions. IL-10 drives anti-inflammatory and tolerising programs in MNP, which feeds back to $Foxp3^+$ Treg cells. By this, the cross talk between MNP, $Foxp3^+$ Treg and B cells represents a key adaptation of the host to microbial stimuli, which if defective, can induce IBD.

Innate-derived cytokines initiate intestinal inflammation

Breakdown of epithelial barrier function and microbial dysbiosis are key events in the initiation of IBD. Both IEC and MNP are capable of sensing bacteria or bacterial components and eliciting appropriate defense mechanisms via pattern-recognition receptors, such as Toll-like receptors (Xavier and Podolsky, 2007). Autophagy controls the breakdown of intracellular components in response to stress or infection, and confers protection against bacterial infections. The conserved intracellular mechanisms of endoplasmatic reticulum stress and unfolded protein response ensure the correct functioning of protein trafficking, required for the proper functioning of highly secretory IEC types, such as goblet cells and Paneth cells, and highly phagocytic cells, such as macrophages (Kaser et al., 2010). Downstream of these responses, the correct assembly of the inflammasome complex is essential for the production of IL-1 family cytokines. Genetic defects (often gain of function) in such pathways can lead to spontaneous colitis, highlighting their role in the initiation of IBD (Kaser et al., 2010; Uhlig and Powrie, 2018). Below we discuss the cytokine pathways initiating inflammation in the gut (**Figure 1**).

The IL-1 family cytokines IL-1β and IL-18 are produced by MNPs and IEC and associated with pro-inflammatory effector functions in the context of intestinal inflammation. Deletion of the inflammasome component caspase-1 prevents the release of IL-1β and IL-18 and ameliorates Dextran-sodium-sulfate (DSS)-induced colitis in mice (Siegmund et al., 2001b). In general, genetic deficiency in, or the blockade of, IL1-β and IL-18 signalling ameliorates experimental colitis (Dinarello et al., 2013; Lopetuso et al., 2013). IL-1β can promote pathogenic T cell responses, such as Th17 cell differentiation and IFN-γ production (Coccia et al., 2012; Zielinski et al., 2012). Notably, MNPs from mice and patients with defective IL-

10R signalling produce colitogenic amounts of IL-1β, highlighting the importance of intact IL-10 signalling in MNPs to suppress inflammation (Shouval et al., 2016). In contrast to IL-1β, IL-18 exerts major colitogenic effects through its action on IEC, disrupting goblet cell maturation and function (Nowarski et al., 2015).

An additional member of the IL-1 family, IL-33, has also been linked to intestinal inflammation. Administration of IL-33 aggravates, whereas the blockade of IL-33 or its receptor ST2, suppresses early acute colitis in DSS- and 2,4,6-trinitrobenzenesulfonic acid solution (TNBS)-induced models (Oboki et al., 2010; Sedhom et al., 2013). However, lack of IL-33 later on delays neutrophil-dependent resolution of inflammation in the DSS model, resulting in delayed lesion repair and body weight recovery (Oboki et al., 2010). IL-33, primarily derived from IEC and mesenchymal cells in the gut (Sedhom et al., 2013), also acts directly on Foxp3$^+$ Treg cells to promote their accumulation and to restrict IL-23-mediated signalling in a bacteria-driven colitis model (Schiering et al., 2014). Taken together, IL-33 seems to be pro-inflammatory in acute colitis settings, but confers protection by promoting repair and Foxp3$^+$ Treg cell responses in more chronic phases of inflammation.

Consistent with results of therapeutic targeting, TNF-α is a MNP-derived high level driver of intestinal inflammation with pleiotropic effects on various cells of the intestine. Initial findings in T cell transfer colitis showed increased amounts of intestinal TNF-α and attenuation of disease following TNF-α neutralisation (Powrie et al., 1994a). Excessive TNF-α alters epithelial integrity and induces apoptosis in IEC, thus weakening barrier function (Garrett et al., 2007; Nenci et al., 2007; Pott et al., 2018). Impaired regulation of TNF-α is sufficient to induce colitis, since *TNF*$^{\Delta ARE}$ (*TNFdARE*) mice, which lack post-transcriptional regulation of TNF-α resulting in its over-production by MNP's, develop spontaneous Crohn's-like ileitis (Kontoyiannis et al., 1999). Full blown ileitis in that model requires CD4$^+$ and CD8$^+$ T cell effector function downstream of TNF-α, but TNF-α signalling into mesenchymal cells is sufficient to drive disease. Analysis of IBD patient-derived cells showed that the membrane-bound TNF-α (mTNF) on MNPs prevents apoptosis of CD4$^+$ T cells via TNFR2 signalling (Atreya et al., 2011), and thus can promote survival of pro-inflammatory T cells in colitis.

Intestinal MNPs, epithelial cells and mesenchymal cells produce elevated amounts of IL-6 upon challenge with inflammatory cytokines. Most cell types are able to respond to IL-6 through shedding of the soluble IL-6R, and thus trans-signalling (Hunter and Jones, 2015). As a consequence, its effects on the immune system are pleotropic, and highly dependent on the phase of inflammation and on the target cell. During the initiation of inflammation, IL-6 acts on mesenchymal and epithelial cells to induce the recruitment of polymorphonuclear leukocytes (PMN) and macrophages essential for wound healing early defense (Hunter and

Jones, 2015). IL-6 however also promotes survival and cytokine secretion by Th1, Th2 or Th17 $CD4^+$ T cells (Hunter and Jones, 2015), which may in part reflect the general ability of IL-6 signalling in T cells to prevent apoptosis (Atreya et al., 2000). The blockade of IL-6 signalling prevents T cell expansion and attenuates Th1 cell-driven intestinal inflammation (Atreya et al., 2000; Yamamoto et al., 2000).

In summary, the production of IL-1β, IL-18 and TNF-α by MNPs and IECs represent key pro-inflammatory events in the initiation of colitis. IL-33 and IL-6 can exert contrasting effects, depending on the context and stage of disease, suggesting a Janus-like behaviour of these cytokines. IL-33 induces an early acute inflammatory response yet drives repair later on in the resolution phase. Similarly, the pro-inflammatory effects of IL-6 in colitis arise from its ability to prevent T cell apoptosis, but it also exerts major pro-resolution and repair functions through effects on the epithelial barrier and MNPs.

Progression towards chronic colitis – innate immunity shapes pathogenic T-effector responses

Sustained activation of innate responses, for example as a consequence of impaired regulation or deficient anti-microbial immunity, can drive pathogenic T cell responses. Key orchestrators include recruited inflammatory MNPs and PMN which produce a range of pro-inflammatory cytokines that promote pathologic T cell responses at the expense of regulatory T cells (Maloy and Powrie, 2011; Uhlig and Powrie, 2018). Below we focus on the cytokine-mediated interactions between MNPs and T cell subsets that promote chronic intestinal inflammation (**Figure 1**).

Mononuclear phagocytes are capable of shaping the adaptive immune response by creating a polarising cytokine milieu containing IL-1, IL-4, IL-6, IL-12 and TNF family members that drive distinct effector T cell responses. Early studies using a T cell transfer model highlight the colitogenic potential of naïve T cells when transferred into immunodeficient hosts in the absence of a regulatory T cell compartment (Powrie et al., 1993). In several models of colitis, pathogenic T cell responses are driven by IL-12 and IL-23 production by MNP in part due to deficiencies in IL-10 and TGF-β pathways (Arnold et al., 2016; Siddiqui et al., 2010). The identification of IL-23, which shares the IL-12p40 subunit with IL-12 (Oppmann et al., 2000), represented a step change in the field. It led to observations that IL-23, as opposed to IL-12, is a major driver of chronic colitis (Hue et al., 2006; Uhlig et al., 2006; Yen et al., 2006). While IL-12 induces differentiation of IFN-γ producing Th1 cells, IL-23 reinforces and shapes the Th17 cell response (Teng et al., 2015). In both human and mouse, sustained production of IL-23 can subvert barrier promoting Th17 cell responses (Stockinger and Omenetti, 2017)

into a pathogenic mode through induction of multiple cytokines, including IFN-γ, IL-17A and GM-CSF (Ahern et al., 2010; Griseri et al., 2015; Kleinschek et al., 2009). IL-1β acts as a co-factor with IL-23 in promoting pathogenic responses through inducing IL-17 production in T cells and ILCs (Coccia et al., 2012; Zielinski et al., 2012). In addition, IL-23 also antagonises anti-inflammatory Foxp3$^+$ Treg cell responses to promote intestinal inflammation (Izcue et al., 2008; Schiering et al., 2014).

In the last decade, ILC have emerged as important mediators of the IL-23 response in the intestine (Geremia and Arancibia-Carcamo, 2017). RORγt- ILC1s drive colitis through production of IFN-γ (Powell et al., 2012; Vonarbourg et al., 2010). By contrast, IL-23-dependent RORγt$^+$ ILC3s produce IL-17A, IL-22 and IFN-γ, which drives pathology in T cell-independent colitis (Buonocore et al., 2010). IL-23-responsiveness of ILC3s is critical for their mobilisation and production of GM-CSF, in turn leading to the recruitment of inflammatory monocytes to the intestine (Pearson et al., 2016; Song et al., 2015). GM-CSF-dependent mobilisation and activation of pro-inflammatory granulocyte-monocyte precursors, as well as eosinophils, from the bone marrow to the intestine is suggested as a key component of the IL-23 driven inflammatory response (Griseri et al., 2015; Griseri et al., 2012). However, there are opposing effects of GM-CSF in the intestine, including DC-mediated stimulation of Foxp3$^+$ Treg cell responses (Mortha et al., 2014), suggesting context dependent functions. Neutralising anti-GM-CSF autoantibodies are associated with increased severity in CD (Han et al., 2009; Kugathasan et al., 2017). In addition, IBD susceptibility is associated with frameshift mutations in GM-CSF receptors, resulting in reduced responsiveness of monocytes to GM-CSF (Chuang et al., 2016).

The role of Th17 cell effector cytokines IL-17A and IL-17F in colitis remains controversial. Protective (O'Connor et al., 2009; Ogawa et al., 2004; Yang et al., 2008) and pathogenic (Buonocore et al., 2010; Chaudhry et al., 2009) functions of IL-17A and IL-17F individually have been reported, with evidence that blockade of both IL-17A and IL-17F is required to ameliorate T cell transfer colitis (Leppkes et al., 2009). Overall, the activities of IL-17A and IL17F in the gut appear to be highly context dependent and in some circumstances show redundancy. Importantly, IL-17A and IL-17F functions are determined by the target organ: IL-17A has pivotal barrier-protective function in the gut but not skin (Lee et al., 2015; Maxwell et al., 2015), possibly explaining why anti-IL-17A therapy is effective in psoriasis, but not CD (Hueber et al., 2012). IL-22, produced in high amounts by Th17 cells and ILC3 following IL-23 stimulation promotes epithelial repair and antimicrobial defense (Zhou and Sonnenberg, 2018). In colitis, IL-22 deficiency and IL-22 neutralisation leads to impaired wound healing in T cell transfer and DSS colitis models (Pickert et al., 2009). Consequently, innate and adaptive-derived IL-22 has been shown to protect from intestinal inflammation

(Zenewicz et al., 2008). Therapeutic potential is suggested by findings that the delivery of IL-22 alleviates colitis (Bootz et al., 2016; Sugimoto et al., 2008). Based on those results, therapeutic delivery of recombinant human IL-22-Fc is currently being tested in clinical trials for moderate-to-severe UC and CD (NCT03650413). However, reparative effects on IEC can render IL-22 a pathogenic player in intestinal tumorigenesis if uncontrolled (Huber et al., 2012; Kirchberger et al., 2013), which may eventually limit its clinical utility.

Another anti-inflammatory cytokine is IL-35, a heterodimer composed of IL-12p35 and EBI3 (IL-27β) subunits (Su et al., 2018). EBI3 is a direct target of the transcription factor Foxp3, and IL-35 is highly expressed in Foxp3$^+$ Treg cells but not effector CD4$^+$ T cells (Collison et al., 2007). Early studies suggested a functional anti-colitic role as Foxp3$^+$ Treg cells deficient in IL-35 production fail to suppress colitis in a T cell transfer model (Collison et al., 2007). Further studies demonstrate that lack of EBI3, the subunit shared by both IL-35 and IL-27, exacerbates T cell transfer colitis (Wirtz et al., 2011). This effect is not observed in mice lacking the IL-27-specific subunit IL-27p28, suggesting IL-35 rather than IL-27 exerts protective effects in colitis. The same study also demonstrated the feasibility of delivering recombinant IL-35 to ameliorate DSS-induced colitis.

Although less investigated, there is evidence that IL-4 dependent Th2 cell responses can also drive colitis in some acute and chronic models of colitis (Boirivant et al., 1998; Mizoguchi et al., 1999). This extends not only to Th2 cells but also CD1d-dependent NKTs which mediate oxazolone-induced colitis through production of IL-13 (Heller et al., 2002). Overall the data suggest that IL-4 and IL-13 drive colitis associated with type 2 responses, particularly at later stages of disease involving tissue repair and fibrosis (as discussed in more detail below and shown in **Figure 1**).

In summary, studies on MNP-T cell interactions in IBD have highlighted IL-23-driven CD4$^+$ T cell responses as a key pathologic feature in experimental colitis and human IBD. Pathogenic T cell populations shaped by IL-23 drive intestinal inflammation through the production of effector cytokines IFN-γ, IL-17 and GM-CSF which further stimulate the myeloid cell response both in the bone marrow and locally in the intestine. ILCs, some of which are found in increased abundance in the intestine of IBD patients (Fuchs et al., 2013; Geremia et al., 2011), can contribute to the production of colitogenic effector cytokines although their functional role in IBD remains to established. The clinical relevance of this pathway is highlighted by the success of anti-IL-12p40 and anti-IL-23p19 biologics in IBD (as discussed below). IL-22 derived from CD4$^+$ T cells and ILCs represents a major barrier-protective signal that should be preserved when targeting the IL-23 response. IL-35 derived

from Foxp3$^+$ Treg cells inhibits CD4$^+$ T-effector responses in colitis, and its therapeutic application could potentially ameliorate intestinal inflammation.

Cytokine targeting therapies in the clinic

The discovery and characterisation of intestinal cytokine networks that either promote or suppress intestinal inflammation has led to a number of efficacious therapeutics for IBD either in use or being tested in the clinic (Abraham et al., 2017) (**Table 1**). In general these therapies can be grouped into two categories: blockade of pro-inflammatory or enhancement of anti-inflammatory cytokine pathways (**Figure 2**).

TNF-α targeting drugs are currently the most effective biologic treatment for IBD. From its first trial in CD patients (Derkx et al., 1993), various formulations of anti-TNF agents have shown efficacy by inducing clinical response (e.g., reduction in Crohn's disease activity index), biochemical response (e.g., reduction in blood C-reactive protein) and histological mucosal healing (Neurath, 2017). Two mechanisms of action have been proposed: the induction of T cell apoptosis and the Fc-receptor-dependent promotion of reparative wound healing macrophages (Levin et al., 2016). The combined action of these pathways may explain the ability of anti-TNF therapies to both inhibit inflammation and promote mucosal healing.

In addition to TNF-α, other MNP-derived pro-inflammatory cytokines have been targeted in IBD. Although showing no efficacy in rigorous clinical trials, the administration of IL1-R antagonist (IL-1Ra) or IL-18 binding protein (IL-18BP) ameliorates colitis in MD-IBD patients with genetic defects in IL-10 and mevalonate kinase pathways (Canna et al., 2017; Levy et al., 2013). This highlights blockade of IL-1β and IL-18 as promising approaches in certain subgroups of patients where similar pathway defects are observed. In phase I/II trials neutralisation of IL-6R with the monoclonal antibody tocilizumab induces a clinical response in CD patients, but remission has been observed in only a minority of patients (Ito et al., 2004). Results from a very recent clinical trial using blockade of IL-6 itself demonstrates significant clinical response and induction of remission in moderate-to-severe CD patients with previous non-response to anti-TNF (Danese et al., 2019). However, gastrointestinal abscesses and perforation are observed as common side-effects in that study, probably arising from the critical role of IL-6R signalling in IEC repair.

Cytokine pathways associated with polarised effector T cell responses have also yielded successful treatments for IBD. So far, targeting the IL-13-Th2 cell axis in IBD has had no therapeutic success: anti-IL-13 has not improved clinical response in UC (Danese et al.,

2015; Reinisch et al., 2015), however it remains to be determined whether it would be effective specifically in fibrotic and fistulising CD. In contrast, targeting the IL-23 axis is already applied in the clinic: ustekinumab, neutralising the IL-12p40 subunit shared by IL-12 and IL-23, is approved for therapy in CD patients (Feagan et al., 2016). Within the same pathway, IL-23p19 neutralisation has given promising results in moderate-to-severe CD (Feagan et al., 2017; Sands et al., 2017). By contrast, blocking Th1 or Th17 effector cytokines has had more limited success. Despite a clear pro-inflammatory role in experimental models, antibody-mediated neutralisation of IFN-γ by fontolizumab has not shown a strong clinical response in moderate-to-severe CD (Hommes et al., 2006; Reinisch et al., 2006). The monoclonal anti-IL-17A antibody Secukinumab also shows no beneficial effect in CD, and some patients developed severe adverse events under therapy (Hueber et al., 2012). Similarly, therapeutic blockade of IL-17RA (Brodalumab), the common receptor subunit for all IL-17 family cytokines, has been terminated due to worse disease in treatment groups (Targan et al., 2016). As discussed above, targeting IL-17 in the intestine also blocks its barrier-promoting effects, providing a possible explanation for the lack of efficacy. It is notable that IL-17A dependent intestinal barrier function is IL-23 independent, indicating this important host defense function will be maintained in IL-23 targeting {Maxwell, 2015 #361;Lee, 2015 #360}. Despite important host protective functions of Th17 effector cytokines, Vidofludimus, which inhibits dihydroorotate dehydrogenase upstream of IL-17A, IL-17F and IFN-γ production in T cells, shows efficacy in CD patients (Herrlinger et al., 2013). Along similar lines, Phosphodiesterase 4 (PDE4) inhibitors (e.g., apremilast) are approved for use in psoriasis and psoriatic arthritis, and could represent a valuable therapy in IBD due to their ability to block the release of pro-inflammatory cytokines in the intestinal mucosa (Spadaccini et al., 2017). Tofacitinib, an inhibitor of the Janus-kinases (JAK) upstream of STAT signalling used by many cytokines, is approved for use in UC patients (Sandborn et al., 2012). Tofacitinib treatment has not shown efficacy in CD patients so far (Sandborn et al., 2014), which may reflect differing cytokine profiles between UC and CD (Abraham et al., 2017). In fact, more selective JAK inhibitors, such as Filgotinib which impairs signalling downstream of IL-6, IL-10 and IFN family cytokines by inhibiting JAK1, show a clinical response in CD patients (Vermeire et al., 2017). Those examples suggest that treatments targeting multiple cytokine pathways may be more effective.

In addition to blocking pro-inflammatory cytokine signalling, boosting anti-inflammatory pathways to re-establish intestinal homeostasis is an increasing area of focus. Although the systemic administration of IL-10 has not been beneficial in IBD (Colombel et al., 2001; Schreiber et al., 2000), the local production of IL-10 in the gut by *Lactococcus lactis* appears safe (Braat et al., 2006) and ameliorates DSS-induced and IL-10 deficiency colitis (Steidler

et al., 2000). That strategy has not shown efficacy in the clinic, however targeting of IL-10 to the gut remains an attractive approach. An alternative is to harness the anti-inflammatory properties of TGF-β1 through targeting the negative regulator of TGF-β1 signalling mothers against decapentaplegic homolog 7 (Smad7). Early studies showed that T cells from the inflamed IBD mucosa express high amounts of Smad7 and are unresponsive to TGF-β1. Responsiveness can be restored by treatment with antisense oligonucleotides targeting Smad7 (Monteleone et al., 2001). Despite promising early studies using an antisense oligonucleotide targeting Smad7 (Mongersen) in CD (Feagan et al., 2018; Monteleone et al., 2015), this approach was terminated due to lack of clinical efficacy (https://www.businesswire.com/news/home/20171019006519/en/). Overall these results suggest that the strategy of restoring sensitivity to TGF-β1 in IBD is promising, but might require approaches other than antisense nucleotide targeting. The recent development of IL-2 agents successfully delivered the proof-of-concept that anti-inflammatory mechanisms can be boosted through targeting regulatory T cell responses. Studies have demonstrated the *in vitro* expansion of functional and stable autologous $CD25^{+}CD45RA^{+}$ Treg cells (Canavan et al., 2016), opening avenues for their therapeutic application. Similarly, IL-2-antibody complexes have been shown to promote $CD25^{hi}$ Treg cell responses over T effector responses in a therapeutic setting (Spangler et al., 2015), and hyper-stable IL-2 mimetics for therapeutic use have been developed (Silva et al., 2019), but await testing in clinical trials. Currently, the subcutaneous administration of low-dose IL-2 is undergoing phase I trial in moderate-to-severe UC (NCT02200445).

In summary, therapeutic targeting of TNF-α and IL-12p40 represented a major breakthrough in reducing disease burden in IBD. Additional cytokine-targeted therapies are on the horizon, including anti-IL-23p19, and may offer an alternative, particularly for patients that do not respond to anti-TNF therapy. Promoting anti-inflammatory cytokine responses through application of IL-2, IL-10 or TGF-β1 has proven feasible in pre-clinical and clinical studies, but has not undergone rigorous clinical trials. The case of Vidofludimus and JAK inhibitors demonstrates that targeting multiple cytokines by one agent or combination therapies might represent a valuable approach. Furthermore, the prospect of specifically targeting cytokine networks underpinning distinct pathophysiologies in IBD creates opportunities for precision medicine.

Therapy-resistance in IBD

Despite the success of anti-TNF treatment in IBD, up to 40% of IBD patients show primary or secondary non-response (Ben-Horin and Chowers, 2014; Guerra and Bermejo, 2014). Non-

response to anti-TNF and other first-line therapies (e.g., Azathioprine) still represents a major unmet need in IBD, and has recently been linked to the activation of alternative cytokine pathways, in particular IL-23 and the IL-6 family member Oncostatin M (OSM).

Recent studies suggest that IL-23 blockade is effective in CD patients that do not respond to anti-TNF therapy (Feagan et al., 2017; Sands et al., 2017). Although the mechanisms are not understood it may relate to the distinct pathways of inflammation driven by TNF or IL-23, the latter involved in promoting pathogenic T cell responses while restraining the $Foxp3^+$ Treg cell axis (Ahern et al., 2010; Izcue et al., 2008). The emergence of $TNFR2^+IL\text{-}23R^+$ expression on T cells has recently been linked to non-responsiveness to anti-TNF therapy through IL-23-induced resistance to apoptosis (Schmitt et al., 2018), suggesting that IL-23 can elicit a TNF-α-independent signal to prevent apoptosis in addition to promoting a pathogenic T cell phenotype.

Recently, we found a strong association of elevated intestinal expression of OSM and OSMR with non-response to anti-TNF therapy (West et al., 2017). Experimental colitis in an anti-TNF-refractory model was ameliorated by therapeutic treatment with a soluble OSMR-gp130-Fc fusion protein, identifying OSM in the pathogenesis of disease. OSM primarily signals into cells of mesenchymal origin (i.e., fibroblasts and endothelial cells) through its specific receptor subunit OSMR, eliciting production of chemoattractants for inflammatory MNP, PMN and T cells (West et al., 2017) (**Figure 1**). Given the identification of mesenchymal cells as targets of both TNF (Armaka et al., 2008) and OSM (West et al., 2017) signalling in experimental colitis, they may represent an interesting cellular target in IBD. This is supported by single-cell transcriptomics, where $CCL19^+$ and $IL\text{-}13RA2^+IL\text{-}11^+$ mesenchymal cell subsets are associated with colitis and therapy-resistance in UC (Kinchen et al., 2018)(Smillie et al., published on bioRxv October 2018, doi: https://doi.org/10.1101/455451). It is tempting to speculate that TNF and OSM elicit distinct downstream responses in mesenchymal cells, and that in patients with established disease and lack of response to anti-TNF therapy, OSM becomes a dominant driver of chronic inflammation (West et al., 2017). Further studies are required to assess the role of IL-11, IL-13 and CCL19 in such responses.

Taken together, recent advances demonstrate IL-23 and OSM as two alternative pathogenic drivers in anti-TNF therapy-resistant IBD, highlighting their potential as therapeutic targets. Measurement of IL-23- or OSM-driven signatures in tissues may also help identify patients more likely to fail to anti-TNF therapy, and therefore facilitate personalised medicine approaches. High but distinct responsiveness of mesenchymal cells to both TNF and OSM puts mesenchymal cells in the spotlight as potential contributors to therapy-resistance.

Indeed, mesenchymal cells may represent an important link between therapy-resistance and tissue fibrosis, a major complication and unmet clinical need particularly in late-stage disease.

Evolution of cytokine networks over disease course

The delicate balance between beneficial or destructive inflammation in the intestine makes it necessary that the cytokines guiding these processes are tightly controlled in a spatial, temporal and quantitative manner. Under normal conditions, a pro-inflammatory initial phase elicited by infection or damage is followed by pathogen clearance and tissue repair which ultimately restores homeostasis. Tissue repair requires pro- and anti-inflammatory cytokines, as well as growth factors, that promote remodelling of the extracellular matrix (ECM), support epithelial regeneration and induce angiogenesis. At the mucosal barrier, IEC, resident macrophages, T cells and mesenchymal cells are the main cellular drivers of repair through a complex cross-talk involving cytokines, growth factors, neuropeptides and metabolites (Vannella and Wynn, 2017). During the repair phase, resident MNP producing IL-10 and TGF-β1 can resolve inflammation by counteracting pro-inflammatory pathways, whereas IL-4 and IL-13 promote wound healing by inducing the expression of scavenger receptors, collagens, matrix metalloproteinases (MMP) and growth factors (Vannella and Wynn, 2017). Failure to resolve inflammation, however, results in chronic inflammation and uncontrolled tissue remodelling, such as fibrosis (Karin and Clevers, 2016).

Roughly a third of newly diagnosed CD patients eventually present with fibrotic complications such as strictures, and this proportion increases up to two-thirds 10 years after diagnosis (Rieder et al., 2017). Seemingly contradicting the concept of inflammation as a driver of fibrosis, clinical studies show that effective anti-inflammatories such as anti-TNF at best delay, but do not ameliorate fibrosis. This could be explained by a model whereby inflammation initiates tissue fibrosis, but at later stages excessive repair in the tissue occurs independently of classic pro-inflammatory mediators. Therefore, it is essential to look at alternative cytokine responses that arise later in the disease course to effectively target established fibrosis (**Figure 1A**).

To date, TGF-β1 isoforms represent the best characterised pro-fibrotic cytokines and have been linked to CD stricture formation (Rieder et al., 2017). TGF-β1 has been long known to modulate ECM matrix deposition and degradation, and to promote the expansion of mesenchymal cells. Direct evidence for the pathologic role of TGF-β1 comes from mouse models, where the overexpression of TGF-β1 leads to severe fibrosis in the proximal colon associated with hyperplasia of smooth muscle cells (Vallance et al., 2005). Despite clear

pro-fibrotic effects, targeting TGF-β1 is a difficult prospect given its marked anti-inflammatory properties. Understanding of pathways downstream of TGF-β1 in mesenchymal cells that specifically convey a pro-fibrotic phenotype could yield more feasible approaches for targeting.

The gold-standard for testing additional therapies for treating IBD-associated fibrosis are pre-clinical mouse models. However, a major drawback of most currently available models is their inability to mimic chronicity and late stage severe disease. Most experimental colitis models either resolve spontaneously upon withdrawal of the challenge or result in intolerable toxicities with sustained challenge. Repeated administration of lower amounts of chemicals agents have achieved more chronic disease associated with a shift of the immune response from type 1 during the early phase of inflammation to a type 2 and type 17 cytokine profile later on (Dohi et al., 2000; Fichtner-Feigl et al., 2008). Together these data suggest that in epithelial damage models of colitis, Th1 cell associated cytokines drive initiation of disease, while Th2 and Th17 cell cytokines might be critical to promote the repair phase. If uncontrolled, type 2 and type 17 cell responses could drive tissue fibrosis through the excessive deposition of ECM. In support of this, spontaneous ileitis in the SAMP1/YitFcsJ mouse model manifests as a type 2 dominant response (IL-4, IL-5, IL-13) at a late stage, associated with the presence of fibrosis (Bamias et al., 2005). Similarly, in chronic TNBS-induced colitis, IL-4 and IL-13 increase over time and in parallel with ECM deposition (Fichtner-Feigl et al., 2008). IL-13 normally signals via a heterodimeric receptor composed of IL-13Rα1 and IL-4Rα subunits. Fibrosis in the TNBS model is dependent on IL-13 signalling via the IL-13Rα2 subunit as blocking of IL-13Rα2 leads to a reduction of TGF-β1 expression and amelioration of fibrosis (Fichtner-Feigl et al., 2006). As discussed above, mesenchymal cell populations with high expression of IL-13Rα2 have been linked to therapy-resistance in IBD and inflammation (Smillie et al., published on bioRxv October 2018, doi: https://doi.org/10.1101/455451). As IL-13Rα2 is an inducible receptor expressed in parallel to IL-13 at later stages of disease, it represents an interesting therapeutic target as opposed to IL-13 blockade which would also eradicate the beneficial effects of IL-13Rα1 signalling.

Recent studies suggest that the blockade of Th17-related cytokines, in particular IL-22, ameliorates fibrosis and acts downstream of IL-36. Defective autophagy in MNPs promotes fibrosis in TNBS colitis via MNP-derived IL-23 driving the T cell-independent production of IL-22 (Mathur et al., 2019). IL-36 stimulates IL-23 production in MNPs, which drives downstream IL-22 release (Ngo et al., 2018). Of note, earlier studies described neutrophils as an important source of IL-22 in inflammation (Zindl et al., 2013), and neutrophil recruitment is dependent on IL-36R signalling (Scheibe et al., 2017). Consequently, the blockade of IL-36R signalling ameliorates TNBS- and DSS-induced fibrosis, with IL-36 also

directly eliciting a pro-fibrotic transcriptional program in mesenchymal cells (Scheibe et al., 2018). Interestingly, the latter study found a concerted increase of IL-36 producing MNPs and activated mesenchymal cells in the gut of IBD patients, further reinforcing the concept of myeloid-mesenchymal cross-talk to be crucial in fibrosis.

Although direct mechanistic evidence in the intestine is lacking, the IL-6 family member IL-11 is produced in high amounts by intestinal mesenchymal cells (Disson et al., 2018) and has recently been demonstrated to promote fibrosis in various tissues. In the heart, TGF-β1 induces IL-11 production which acts in an autocrine manner on mesenchymal cells; injection of IL-11 induces collagen deposition, whereas *Il11ra*$^{-/-}$ mice exhibit reduced cardiac and renal fibrosis (Schafer et al., 2017). Of note, high IL-11 and IL-13Rα2 gene expression in the tissue of anti-TNF refractory IBD patients is associated with high expression of *OSMR* suggesting a link between therapy-refractory IBD and fibrosis (Smillie et al., published on bioRxv October 2018, doi: https://doi.org/10.1101/455451).

Together the data suggest that development of intestinal fibrosis represents an evolution of the inflammatory response towards deranged repair most likely controlled by both host and environmental factors (Vannella and Wynn, 2017). Although well appreciated that fibrogenic cytokines are distinct from those that drive acute inflammation, it has proved challenging to tackle IBD-associated fibrosis in the clinic. Alternative targets are emerging and in particular targeting the IL-36-IL-22 axis is promising in pre-clinical models. Similarly, IL-11, OSM and IL-13Rα2 are interesting since they have been linked with mesenchymal cell populations in the inflamed colons of anti-TNF therapy resistant IBD patients. On a cellular level, disrupting the cross-talk between resident MNPs, T cells and the mesenchymal compartment represents an appealing avenue to treat fibrosis.

Conclusion and future perspective

Mechanistic studies of cytokine biology in intestinal inflammation over the last three decades have revealed pathogenic drivers of disease and their successful translation into the clinic as drug targets. This led to an era where symptoms in IBD can be controlled and long periods of disease remission established. The lack of response to currently approved cytokine-targeted therapies could soon be partly overcome by blocking alternative cytokine pathways which has already proven successful in clinical trials. Harnessing anti-inflammatory and pro-resolving cytokine networks either directly or through modulation of the microbiome has become feasible, and represents a promising approach to to halt inflammation and promote tissue healing. A key future challenge will be finding ways of how to select those patients most likely to respond to a specific therapy, in order to facilitate personalised medicine

approaches in IBD. Causally linking cytokine signatures to certain IBD patient subgroups and disease phenotypes could guide such process-targeted therapies. Despite all this progress, IBD-associated fibrosis continues to be a challenging unmet need not treated by current anti-inflammatories. One reason for that could be the described Janus-like activity of many cytokines, resulting in highly context dependent outcomes of their inhibition at late stage fibrotic disease as opposed to early stage acute inflammation. In order to address this, future studies should move away from static analysis of cytokine activity towards assessing dynamic cytokine regulation to understand drivers of fibrosis at later stages of IBD. In an era where single-cell, high-throughput methods yield informative associations of a given cell type with a disease state, animal models of colitis remain key for delivering added mechanism and dynamics to these associations to validate the potential for clinical translation.

Tables and Figures

candidate cytokine gene(s) per unique locus (de Lange et al., 2017; Huang et al., 2017; Jostins et al., 2012)	**MD-IBD**	**spontaneous colitis in mouse**	**targeting in pre-clinical models**	**used in clinics or tested in clinical trials**
LTA, LTB*, TNF**	-	*TNF*$^{\Delta ARE}$ (Kontoyiannis et al., 1999)	anti-TNF ameliorates T cell transfer colitis (Powrie et al., 1994b)	anti-TNF (approved for UC and CD) (Hanauer et al., 2002; Rutgeerts et al., 2005; Targan et al., 1997)
TNFSF15, ***TNFSF8***				
LTBR, TNFRSF1A				
IL1RL1*, IL1RL2,* ***IL18R1****,* ***IL18RAP****, IL1R1, IL1R2*	-	-	anti-IL1Ra ameliorates DSS colitis (Siegmund et al., 2001b) anti-IL-18 ameliorates DSS colitis (Siegmund et al., 2001a)	IL1-RA (case study, MD-IBD) (Levy et al., 2013; Shouval et al., 2016) rhIL18BP (case study, MD-IBD) (Canna et al., 2017)
IL12B	strong protection conferred by rs11209026 variant in *IL23R* (Duerr et al., 2006) (not MD-IBD)	-	anti-IL-23p19 and anti-IL-12p40 ameliorate anti-CD40- and *Helicobacter hepaticus*-induced innate colitis, and *Il10* -/- colitis (Kullberg et al., 2006; Uhlig et al., 2006; Yen et al., 2006)	anti-IL-12p40 (approved for moderate-to-severe CD) (Feagan et al., 2016) anti-IL-23p19 (clinical and histologic improvement in CD) (Feagan et al., 2017; Sands et al., 2017)
IL12RB2, ***IL23R***				
IL6ST, IL31RA	-	-	anti-IL6R ameliorates TNBS, *Il10* -/- and T cell transfer colitis	anti-IL6R (clinical improvement) (Ito et al., 2004) anti-IL6 (clinical improvement, but
IL27				

OSMR *LIF, OSM*			(Atreya et al., 2000; Yamamoto et al., 2000) OSMR-gp130-Fc ameliorates *Helicobacter hepaticus*/ anti-IL-10R colitis (West et al., 2017)	safety concerns) (Danese et al., 2019)
IL17REL	-	-	anti-IL-17A aggravates DSS colitis (Ogawa et al., 2004) anti-IL-17A ameliorates *Il17f -/-* T cell transfer colitis (Leppkes et al., 2009)	anti-IL-17A (no beneficial effect) (Hueber et al., 2012) anti-IL-17RA (no beneficial effect) (Targan et al., 2016)
IFNG, *IL22, IL26* *IFNGR2, IFNAR1, IL10RB* ***IL10, IL19, IL20, IL24***	LOF in *IL10RA, IL10RB, IL10* (Glocker et al., 2009)	*Il10rb -/-* (Spencer et al., 1998) *Il10 -/-* (Kuhn et al., 1993)	IL-22 application ameliorates *TCRa -/-* and DSS colitis (Bootz et al., 2016; Sugimoto et al., 2008) IL-10-producing *L. lactis* ameliorates *Il10 -/-* and DSS colitis (Steidler et al., 2000)	Anti IFN-γ (no beneficial effect) (Hommes et al., 2006; Reinisch et al., 2010; Reinisch et al., 2006) recombinant IL-10 (no beneficial effect) (Colombel et al., 2001; Schreiber et al., 2000) IL-10-producing *L. lactis* (safe) (Braat et al., 2006)
IL2, *IL21* ***IL2RA***, *IL15RA*	LOF in *IL21* (Salzer et al., 2014) LOF in *IL2RA* (Caudy et al., 2007) partial LOF in *IL2RG* (DiSanto et al., 1994)	*IL2 -/-* (Sadlack et al., 1993) *Il2rb -/-* (Spencer et al., 1998)	-	-
-	LOF in *TGFB1* (Kotlarz et al., 2018)	*Tgfb1 -/-* (Kulkarni et al., 1993)	-	SMAD7 antisense oligonucleotide (terminated) (Feagan et al., 2018; Monteleone et al., 2015)
JAK inhibition targeting multiple cytokines			-	Tofacitinib (pan-JAK inhibitor) (approved for moderate-to-severe UC) (Sandborn et al., 2012) Filgotinib (JAK1) (clinical improvement) (Vermeire et al., 2017)

Table 1 – genetic deficiencies in cytokine networks associated with IBD and their targeting in pre-clinical and clinical settings. Candidate cytokine pathway genes are shown per unique IBD susceptibility locus (column 1), based on most recent GWAS and fine-mapping studies. In **bold** are candidate genes that convey IBD susceptibility with high confidence, as defined by being replicated in more than one recent GWAS study and/or fine-mapping. ***** indicates candidate genes within a susceptibility locus, but where other (non-cytokine) candidate genes are more likely to convey susceptibility to IBD. Loss-of-function (LOF) mutations in cytokine pathway genes that associate with Mendelian diseases presenting with IBD or spontaneous colitis in mice are listed in columns 2 and 3, respectively. Examples for pre-clinical targeting of a given cytokine pathway in mouse models of colitis are shown (column 4), as well as clinical trials and approved use in clinics (column 5). Abbreviations: IFN, Interferon; IL, interleukin; IL12RB2, Interleukin 12 receptor beta 2 subunit; *L. lactis*, *Lactococcus lactis*; LIF, leukemia inhibitory factor; LT, lymphotoxin; OSM, Oncostatin M; R, receptor; RAP, receptor accessory protein; REL, receptor E-like; RL, receptor-like; ST, signal transducer; TNFRSF, tumor necrosis factor receptor superfamily; JAK: janus kinase; LOF, loss-of-function; IL2RG. IL-2-receptor gamma.

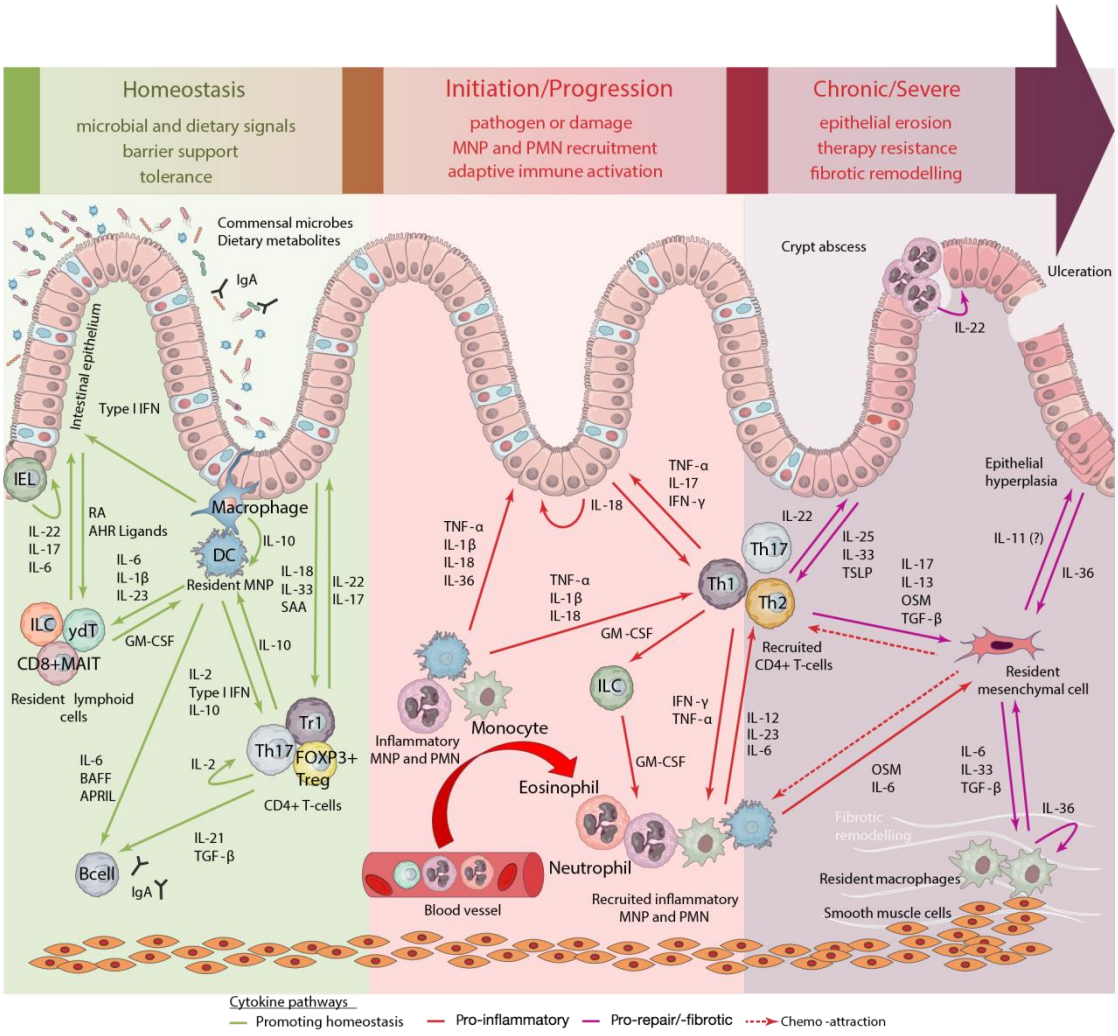

Figure 1 – Dynamic remodelling of cytokine networks in the intestine in IBD. Cytokine networks that moderate the cross-talk of epithelial cells with innate and adaptive immune cells maintain the epithelial barrier and tolerance to the microbiota in homeostasis (green arrows, Figure 1A). Disruption of this cytokine-guided cross-talk leads to the initiation of inflammation, mostly by innate-derived pro-inflammatory cytokines in the early phase of IBD (red arrows, Initiation & Progression phase). If this initial inflammation is not resolved, pro-inflammatory MNP and PMN are recruited to the tissue (dashed arrows), creating a cytokine environment that shapes pathogenic Th1 and Th17 responses (red arrows, Initiation & Progression phase). Establishment of chronic inflammation is characterised by a substantial pro-inflammatory response driven by adaptive immune mechanisms, which can evolve over time towards a pro-repair type 2 response (purple arrows, Chronic & Severe phase). Persistent chronic inflammation for instance due to lack of response to therapy may drive repair responses that overshoot and lead to fibrotic remodelling in late stage IBD. Abbreviations: AHR, Aryl hydrocarbon receptor; APRIL, A proliferation-inducing ligand; BAFF, B-cell activating factor; FOXP3, DC, dendritic cell; forkhead box P3; GMCSF, Granulocyte-macrophage colony-stimulating factor; IEL, intraepithelial lymphocyte; IFN, interferon; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; MAIT, mucosal associated invariant; MNP, mononuclear phagocytes; OSM, Oncostatin M; PMN: polymorphonuclear leukocyte; RA, retinoic acid T cell; SAA, Serum amyloid A; TGF, transforming growth factor; Th, T-helper; TNF, tumor necrosis factor; Tr1, regulatory type 1 cells; TSLP, thymic stromal lymphopoietin.

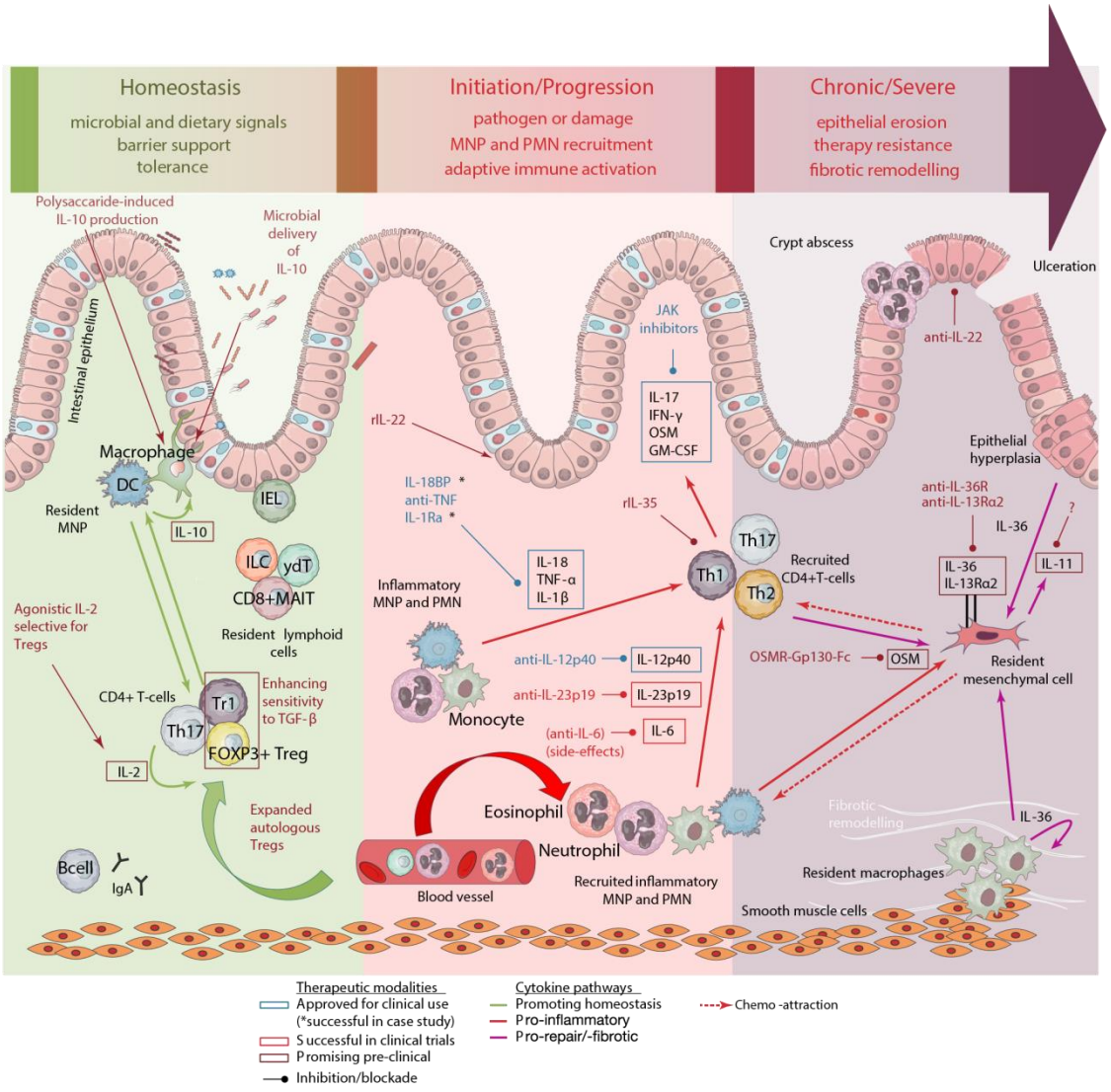

Figure 2 – Cytokine targeting therapies used in clinics or tested in clinical trials. Several biologics target the initiation and progression phase of disease, with anti-TNF and anti-IL12p40 therapy already used in the clinic (blue). Alternative therapies have proven successful in clinical trials, in particular anti-IL23p19 and anti-IL-1β/18 (pink). Currently, no treatment is available for halting or reversing fibrotic remodelling in the late stage of disease. Based on findings in pre-clinical models, therapies targeting OSM and IL-36 represent promising candidates to inhibit fibrotic processes by targeting immune-stromal interactions (brown, Figure 1B). Abbreviations: BP, binding protein; FOXP3, DC, dendritic cell; forkhead box P3; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IEL, intraepithelial lymphocyte; IFN, interferon; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; MAIT, mucosal associated invariant; MNP, mononuclear phagocytes; OSM, Oncostatin M; PMN: polymorphonuclear leukocyte; r, recombinant; RA, receptor alpha subunit; TGF, transforming growth factor; Th, T-helper; TNF, tumor necrosis factor; Tr1, regulatory type 1 cells.

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