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Mechanisms behind efficacy of tumor necrosis factor inhibitors in inflammatory bowel diseases

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ABSTRACT

Biological treatment with tumor necrosis factor (TNF) inhibitors is successful in the management of inflammatory bowel disease (IBD). All TNF inhibitors antagonize the pro-inflammatory cytokine TNF-α but with varying efficacies in IBD. The variations in efficacy probably are caused by structural differences between the agents that affect their mechanisms of action and pharmacokinetic properties. Several mechanisms have been proposed, such as modulation of the expression of pro-inflammatory mediators and a reduction in the number of activated immune cells. However, it seems that clinical efficacy is the result of a number of different mechanisms and that binding of transmembrane TNF by TNF inhibitors. Knowledge of the mechanisms of action has been obtained mainly through the use of *in vitro* assays that may differ significantly from the situation *in vivo*. This review discusses the available data on TNF inhibitors in order to identify mechanisms of importance for their efficacy in IBD. Thus, a better understanding of the mechanistic basis for clinical efficacy can lead to a more rational use of TNF inhibitors in the management of IBD.

Contents

1. Introduction

Inflammatory bowel disease (IBD) is an umbrella term for a range of diseases characterized by chronic inflammation of the gastrointestinal tract, of which ulcerative colitis (UC) and Crohn's disease (CD) are the two most prevalent entities (Hisamatsu et al., 2013). The incidence of these two immunologically distinct disorders is increasing worldwide (Molodecky et al., 2012), and active stages of IBD impair the quality of life of affected individuals (Hoivik et al., 2012; van der Have et al., 2014) and impose a great economic burden on the healthcare system (Barsig et al., 1995; Kawalec & Malinowski, 2015).

The introduction of tumor necrosis factor (TNF) inhibitors has revolutionized the treatment of IBD mainly as second-line therapy for patients not responding to conventional treatment (i.e., in a "step-up strategy")

Abbreviations: ADA, Adalimumab; ADCC, Antibody-dependent cellular cytotoxicity; CD, Crohn's disease; CDC, Complement-dependent cytotoxicity; CZP, Certolizumab pegol; ETA, Etanercept; FcγR, Fc-γ receptor; GLM, Golimumab; IBD, Inflammatory bowel disease; IFX, Infliximab; Ig, Immunoglobulin; IL, Interleukin; LPS, Lipopolysaccharide; LPTC, Lamina propria T cell; mAb, Monoclonal antibody; MMP, Matrix metalloproteinases; PBMC, Peripheral blood mononuclear cell; sTNF, Soluble tumor necrosis factor; TJ, Tight junction; tmTNF, Transmembrane tumor necrosis factor; TNF, Tumor necrosis factor; TNFR, TNF receptor; T_{reg}, Regulatory T cell; UC, Ulcerative colitis.

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Table 1
Characteristics of monoclonal anti-TNF antibodies approved for IBD.

	Infliximab (IFX)	Adalimumab (ADA)	Golimumab (GLM)	Certolizumab pegol (CZP)	Reference(s)
Indication(s)	CD and UC	CD and UC	UC	CD*	(Nielsen & Ainsworth, 2013; Biancheri et al., 2015)
Structure	Chimeric IgG1	Human IgG1	Human IgG1	Humanized pegylated Fab IgG4	(Tracey et al., 2008)
Route of administration	Intraveneous	Subcutaneous	Subcutaneous	Subcutaneous	(Nielsen & Ainsworth, 2013)
Dosage in IBD	5 mg/kg wks 0–2–6, and every 8 wks	160–80–40 mg/2 wks and 40 mg every other wk	200–100 mg/2 wks and 100 mg every 4 wks	400 mg 0–2–4 wks, then 400 mg every 4 wks	(Nielsen & Ainsworth, 2013)
$t_{(1/2)}$ (days)	7–12	10–20	7–20	~14	(Tracey et al., 2008; Armuzzi et al., 2014; Pasut, 2014)
C_{max} (mg/L)	118–192	4.7–7.7	5–6	43–49	(Armuzzi et al., 2014)

CD, Crohn's disease; C_{max}, peak concentration; IgG, immunoglobulin; UC, ulcerative colitis.
* Approved by FDA and few other countries, e.g. Switzerland, but not by EMA and in Canada for management of Crohn's disease.

(Nielsen & Ainsworth, 2013), although some clinicians have advocated for "top-down (i.e., first-line) therapy" in specific situations as well (D'Haens, 2010). At present (February 2016), four different biological TNF inhibitors are labeled for management of IBD (Table 1). These biologics were developed to antagonize TNF signaling and therefore are presumed to have similar mechanisms of action, clinical efficacy, and safety profiles in the treatment of IBD. However, this is not the case (Mei, Hu, Liu, Li, & Wang, 2015; Thorlund, Druyts, Toor, & Mills, 2015). In fact, etanercept (ETA), a TNF inhibitor that targets soluble TNF (sTNF) and has been used with success in rheumatoid arthritis, unfortunately, is inefficient in the treatment of IBD (Sandborn et al., 2001; Oikonomopoulos, van Deen, & Hommes, 2013).

Although TNF inhibitors have revolutionized the treatment of IBD, a large proportion (approximately 30%) of patients fails to respond to TNF inhibitors (i.e., "primary nonresponders"), and up to 50% of patients who initially benefited from treatment with TNF inhibitors lose the response over time (i.e., "secondary nonresponders") (Nielsen & Ainsworth, 2013; Steenholdt et al., 2014). Thus, a better understanding of the mechanisms of action of TNF inhibitors will help to increase the beneficial effect of anti-TNF treatment of IBD and may provide knowledge about other potential targets for the treatment.

Based on available knowledge, the aim of this review is to highlight the mechanisms of action of TNF inhibitors in IBD and to understand why individual TNF inhibitors have different clinical efficacies.

2. Search criteria

This review is based on articles retrieved from the PubMed and EMBASE databases up to December 2015 using the following search strategy: "adalimumab," "certolizumab pegol," "etanercept," "golimumab," "infliximab," "TNF antagonists," "TNF inhibitors" in combination with "Crohn's disease," "inflammatory bowel disease," "ulcerative colitis," "apoptosis," "cytokine suppression," "efficacy", "mechanisms," "reverse signaling," "signaling," "therapy," and "treatment."

The search was restricted to publications in English, and original papers and reviews were included. Publications concerning the mechanisms of action, and TNF-binding properties of the TNF inhibitors were scrutinized. Identified publications were selected by relevance based on title and abstract, and subsequently, the reference lists of relevant articles were hand searched to identify any additional studies.

3. Tumor necrosis factor and its relevance as a treatment target in inflammatory bowel disease

The pro-inflammatory cytokine TNF is a key mediator of the normal inflammatory response to microbes and tissue damage (Brown & Mayer, 2007). TNF is produced mainly by lymphocytes and activated monocytes/macrophages and to a lesser degree by other immune cells (e.g., dendritic cells, neutrophils, and mast cells) and nonimmune cells (e.g., keratinocytes and fibroblasts) (Peake et al., 2013). TNF production by monocytes and macrophages is induced upon activation of several different receptors (e.g., Toll-like receptors), and the initial signal might be microbial, dietary, or endogenous products, including cytokines, damage-associated molecular patterns, and complement factors (Steinert et al., 2007).

TNF exists in two homotrimeric forms: a transmembrane form (tmTNF) and sTNF that is converted from tmTNF by TNF-α-converting enzyme. Both forms mediate their biological function by binding as homotrimers to one of the two TNF receptors: TNFR1 or TNFR2. While most of the biological activities of sTNF are mediated via TNFR1, TNFR2 signaling is stimulated primarily by tmTNF (Tracey, Klareskog, Sasso, Salfeld, & Tak, 2008; Taylor, 2010; Chu, 2013). Induction of TNF signaling results in activation of several pathways involving mitogen-activated protein kinases and nuclear factor-κB promoting the expression of multiple pro-inflammatory and anti-apoptotic genes (Chu, 2013). Binding of tmTNF to TNFRs also induces activation of signaling cascades in tmTNF-expressing cells, resulting in "reverse signaling" (Tracey et al., 2008). Thus, TNF acts within a complex network of pro-inflammatory cytokines and mediators involving several positive-feedback loops that together amplify the inflammatory response and facilitate recruitment, activation, differentiation, and proliferation of various immune cells. In addition to mediating pro-inflammatory functions (Neurath, 2014a), TNF promotes production of some anti-inflammatory mediators [e.g., interleukin (IL)-10] (Tracey et al., 2008), enterocyte apoptosis (Schulzke et al., 2006; Gunther, Neumann, Neurath, & Becker, 2013), and a downregulated expression of tight junction molecules resulting in an impaired mucosal barrier function (Fries, Muja, Crisafulli, Cuzzocrea, & Mazzon, 2008; Coskun, 2014; Merga, Campbell, & Rhodes, 2014), which subsequently leads to flaring of IBD.

TNF plays a central role in the pathophysiologic mechanisms of a variety of immune-mediated inflammatory disorders, including IBD and rheumatoid arthritis (Tracey et al., 2008; Nielsen & Ainsworth, 2013). Because binding of TNF to its receptor results in increased expression of pro-inflammatory cytokines, chemokines, adhesion molecules, and other inflammatory mediators (Tracey et al., 2008), blocking TNF signaling hampers the inflammatory process (Nielsen & Ainsworth, 2013). The crucial role of TNF signaling in the pathophysiology of IBD is revealed by the fact that the concentration of TNF is elevated in the mucosa (MacDonald, Hutchings, Choy, Murch, & Cooke, 1990; Breese et al., 1994), serum (Murch, Lamkin, Savage, Walker-Smith, & MacDonald, 1991), and stool (Nielsen et al., 1999) of patients with active stages of IBD and by the fact that blocking of TNF signaling by TNF inhibitors is beneficial in the treatment of IBD (Nielsen & Ainsworth, 2013).