Multi-site therapeutic modalities for inflammatory bowel diseases – mechanisms of action

GERHARD ROGLER

Introduction

Genetic susceptibilities such as the recently identified polymorphisms in the NOD2 gene, as well as environmental factors such as certain bacteria, play a role in the etiology of inflammatory bowel diseases (IBD). Over the years many factors have been identified that contribute to the pathogenesis and the process of inflammation in Crohn’s disease (CD) and ulcerative colitis (UC), leading to new therapeutic concepts. Among these contributing factors are cytokines and chemokines, as well as adhesion molecules, which are relevant for the emigration of immune cells into the intestinal mucosa. Mucosal and systemic concentrations of many pro-inflammatory cytokines are elevated in IBD. An inadequate, and/or prolonged activation of the intestinal immune system plays an important role in the pathophysiology of chronic mucosal inflammation. An ‘imbalance’ between proinflammatory and anti-inflammatory cytokines has been described in the inflamed mucosa of patients with CD and UC.

Many, if not all, of the involved cytokine-mediated pathways have back-up systems. Therefore a therapeutic intervention at a particular, singular, very specific point in the complex network of cytokine and chemokine interactions with each other or their receptors is frequently less likely to be successful than a multi-site targeted anti-inflammatory strategy.

Even when the etiology of IBD is completely elucidated a causative therapy might not be possible, and the multi-site anti-inflammatory strategy could still be favorable. Therefore the improvement of ‘classic’ multi-site targeted anti-inflammatory therapies, as well as the development of new concepts for this approach, is of great importance for the future management of patients with IBD. The improvement of ‘classic’ concepts and therapies is necessary, as so far no therapeutic strategy has proved successful in all patients. Clinically we observe a ‘resistance’ of a certain percentage of patients to any particular therapy. An important goal for the future must be a better understanding of mechanisms leading to a relative resistance to classic multi-site anti-inflammatory strategies. This would allow the early identification of patients who are not likely to respond to a treatment modality, would avoid frustrating treatments for the patient and the physician, and could allow more specific concepts for the individual patient. To understand the mechanisms of resistance to a particular multi-site targeted anti-inflammatory therapy we first have to understand the molecular and cellular mechanisms involved in an effective therapy. Important insights into a number of those mechanisms of drug action have been made in the last two decades.

A classic example for a multi-site targeting anti-inflammatory treatment is therapy with glucocorticoids. Therefore the principles of glucocorticoid therapy, the structure of the effect-mediating receptor, the molecular mechanisms of action and the effects on the cellular levels will be highlighted first in this chapter. The glucocorticoid receptor (GR) is a member of a family of receptors, the so-called nuclear receptor superfamily, which shares structural and functional similarities. Other members of this family are the peroxisome proliferation-activated receptors (PPAR). Ligands to PPARγ have recently been shown to be effective in animal models of IBD whereas potential ligands of PPAR-α were beneficial in a clinical study in active IBD. The inhibition of the proinflammatory transcription factor nuclear factor kappa B (NF-κB) is likely to be the most important target of glucocorticoid therapy as well as PPAR-mediated effects. Therefore, finally the mechanisms and pathways of NF-κB activation, as well as the consequences of NF-κB inhibition, will be explained.
Glucocorticoids

Glucocorticoids are used for the suppression or reduction of inflammation in a wide variety of diseases such as rheumatoid diseases, allergic diseases, IBD and in general autoimmune diseases [2–8]. In many of these cases they are still the standard or first-line therapy due to their high efficiency; however, their use is limited by systemic side-effects. The understanding of the mechanisms by which glucocorticoids suppress or reduce inflammation has increased dramatically during recent years [9–14].

Glucocorticoids have been proven to be the first choice in the treatment of acute flares of IBD in several major studies [15–23]. The systemic administration of glucocorticoids (orally or intravenously) during the acute exacerbation of CD or UC is followed by a multitude of different effects in different body cells. One of the intended effects is the down-regulation of proinflammatory cytokines [24]. This mechanism is part of the feedback system between inflammation-derived cytokines and the central nervous system–adrenal axis regulating corticosteroid synthesis with the physiological relevance to balance host defense and anti-inflammatory systems of the body [25, 26]. Among the molecules down-regulated by GR action are multiple cytokines and their receptors, chemokines and their receptors, kinins and their receptors, adhesion molecules and inflammation-associated enzymes such as inducible nitric oxide synthase (iNOS) and the inducible cyclooxygenase (COX-2) [3, 27].

Principal mechanisms of glucocorticoid action

Most, if not all, effects on cells of naturally occurring glucocorticoids such as cortisol or synthetic corticosteroids such as prednisolone and its methylated or acetylated derivates (triamcinolone, dexamethasone or beclomethasone) are mediated by binding to cytosolic GR. GR are present in almost all body cells in concentrations between 2000 and 30 000 binding sites/cell [28].

The GR is a member of the nuclear receptor superfamily, which also includes PPARα, PPARγ and PPARδ (see below). GR consists of 777 amino acids (AA) and was cloned in 1985 [29–31]. There is only a single GR binding glucocorticoids, with no evidence for subtypes of differing affinity in different tissues [3]. A splice variant of GRα, termed GRβ, has been identified that is not able to bind glucocorticoids (see below).

Normally the interaction of glucocorticoids with GRα is followed by an activation and dissociation of GR from its inhibitory protein complex and by a translocation of the receptor into the nucleus, where the complex of steroid and receptor interacts with promoter regions of different genes, finally leading to an increase or decrease of gene transcription (Fig. 1). This process is very similar within the family of nuclear receptors, which show a high degree of genetic similarity with 40–90% of identical AA sequences [32–34].

An important problem for the therapy of patients with IBD and in general chronic inflammatory diseases is the occurrence of glucocorticoid responders and non-responders. Non-response to glucocorticoids may be mediated by mutations of the receptor, a reduced number of GR or a down-regulation of the receptor [35]. Studies demonstrated that primary (hereditary) abnormalities in the GR gene make only 2.3% of patients with asthma relatively ‘resistant’.

‘Resistance’ to the beneficial clinical effects of glucocorticoid therapy in patients with IBD, therefore, is probably rarely related to generalized primary (hereditary) glucocorticoid resistance. In the majority of patients with rheumatoid arthritis or asthma the glucocorticoid resistance seems to be acquired and localized to the sites of inflammation, where it reflects high local cytokine production, which interferes with glucocorticoid action [36]. One of the basic mechanisms that could be responsible for glucocorticoid resistance, the competition for co-factors, will be explained in detail later.

Glucocorticoid levels ($B_{max}$) and binding affinities ($K_d$) vary among patients and have been correlated to patient response. A certain threshold level of GR is necessary for glucocorticoid responsiveness [37]. In patients with rheumatoid arthritis a decrease of systemic GR in leukocytes has been found [38]. However, the GR density did not correlate with inflammatory disease activity.

The molecular structure of glucocorticoid receptor

The mechanisms mediating the glucocorticoid response via GR are complex. Regulation of gene expression and GR actions occurs at several levels in the body and the single cell. However, the glucocorticoid-mediated anti-inflammatory mechanisms are a classic example for the transmission of basic research to the bedside. It is important to first understand the structure of GR and then the molecular