

Review

Hypoxia

Regulation of NFκB signalling during inflammation: the role of hydroxylases

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Published: 23 February 2009

This article is online at <http://arthritis-research.com/content/11/1/215>

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Arthritis Research & Therapy 2009, **11**:215 (doi:10.1186/ar2575)**Abstract**

NFκB is a master regulator of innate immunity and inflammatory signalling. Microenvironmental hypoxia has long been identified as being coincident with chronic inflammation. The contribution of microenvironmental hypoxia to NFκB-induced inflammation has more recently been appreciated. Identification of the co-regulation of NFκB and hypoxia inducible factor (HIF) pathways by 2-oxoglutarate-dependent hydroxylase family members has highlighted an intimate relationship between NFκB inflammatory signalling and HIF-mediated hypoxic signalling pathways. Adding another layer of complexity to our understanding of the role of NFκB inflammatory signalling by hypoxia is the recent recognition of the contribution of basal NFκB activity to HIF-1α transcription. This observation implicates an important and previously unappreciated role for NFκB in inflammatory disease where HIF-1α is activated. The present review will discuss recent literature pertaining to the regulation of NFκB inflammatory signalling by hypoxia and some of the inflammatory diseases where this may play an important role. Furthermore, we will discuss the potential for prolyl-hydroxylase inhibitors in inflammatory disease.

NFκB

The transcription factor NFκB has been investigated for its diverse range of functions in innate immunity, stress responses, cell survival and development. It is also the master regulator of the inflammatory response [1]. An in-depth review of the NFκB pathway is beyond the scope of the present article, and there are several excellent reviews dedicated specifically to this topic [2,3].

Briefly, the NFκB family comprises five members: p65, Rel B, c-Rel, p50 and p52. These proteins share a highly conserved Rel homology domain. In order to bind DNA and modulate gene expression, family members form homodimers or heterodimers – with the exception of Rel B, which will only form heterodimers

with p50 or p52 [4]. The most commonly encountered dimer complex is the p50–p65 dimer [5]. There are two primary activation pathways for NFκB: the canonical pathway, which is predominantly dependent on inhibitor of κB kinase (IKK) beta, and the IKKα-dependent noncanonical pathway [6].

Under resting conditions, NFκB is bound to its co-repressor molecule IκB in the cytosol, with which it interacts through multiple ankyrin repeats. A nuclear localisation sequence of the p65 protein is masked and it remains predominantly sequestered in the cytosolic compartment. Upon stimulation IκBα is phosphorylated at serine 32 and serine 36, targeted for ubiquitination and thereafter degraded proteolytically by the 26S proteasome [7]. A nuclear localisation sequence of NFκB is then revealed, and this is free to translocate and accumulate in the nucleus where it can become transcriptionally active by binding to specific κB sites within the promoter regions of its target genes [8]. The stimulus for IκBα to release the inhibition of NFκB has been identified as phosphorylation by the 700 kDa IKKα/β/γ protein complex.

Genes induced by NFκB include those responsible for encoding inflammatory genes such as TNFα, IL-1, IL-6, IL-8, macrophage inflammatory protein 1 alpha and methyl-accepting chemotaxis protein 1, cell surface adhesion molecules such as E-selectin, vascular adhesion molecule 1 and intracellular cell adhesion molecule 1, inducible enzymes including cyclooxygenase 2 and inducible nitric oxide synthase, and survival molecules such as cellular inhibitor of apoptosis molecule 1, cellular inhibitor of apoptosis molecule 2 and BCL-X_L [9]. A number of stimuli have been shown to activate NFκB through the canonical pathway, including proinflammatory cytokines, bacterial products, growth factors

ARD = ankyrin-repeat domain; DMOG = dimethylallylglycine; FIH = factor-inhibiting hypoxia inducible factor; HIF = hypoxia inducible factor; IBD = inflammatory bowel disease; IKK = inhibitor of κB kinase; IL = interleukin; NF = nuclear factor; PHD = prolyl hydroxylase; PHDI = prolyl-hydroxylase inhibitor; RA = rheumatoid arthritis; TNBS = trinitrobenzene sulphonic acid; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor.

[10] and hypoxia [11-13]. The convergence point for these diverse stimuli is at the level of the IKK complex. NFκB is also activated by ultraviolet light [14,15], by oxidative stress [16], by shear stress [17] and by other mechanisms.

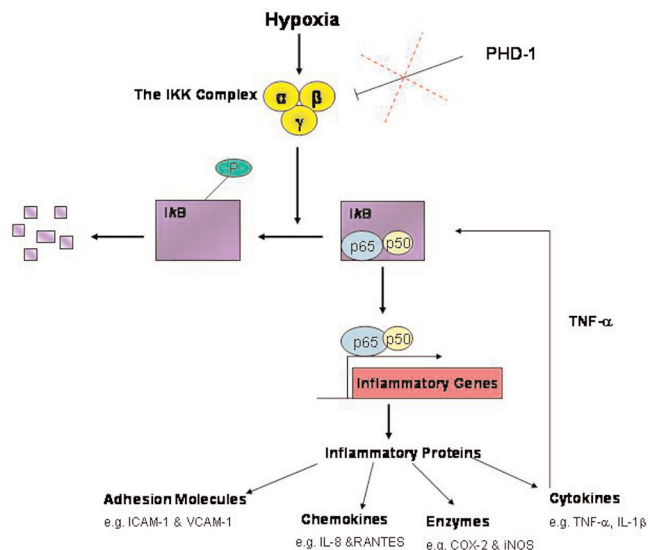
NFκB, hypoxia and hydroxylases

NFκB has been shown to be activated by hypoxia in a number of studies [12,18,19]. Cyclooxygenase 2 [20], TNFα [21], IL-6 [22] and macrophage inflammatory protein 2 [23] are among the target genes identified for hypoxia-induced NFκB, and these underline the factor's importance in inflammatory signalling. While several groups have previously identified hypoxia as playing a role in NFκB signalling, the mechanism whereby a decrease in available oxygen could elicit the activation of a transcription factor that is predominantly activated by more traditional receptor–ligand activation signalling pathways was unclear. While canonical NFκB signalling is sensitive to a diverse range of ligands and employs a plethora of signalling molecules, these signal transduction pathways converge on the IKK complex.

We recently demonstrated a mechanism by which hypoxia activates NFκB through IKKβ activation, leading to phosphorylation-dependent degradation of IκBα and activation of NFκB. Pharmacological hydroxylase inhibition with dimethyl-oxallylglycine (DMOG) activated NFκB signalling and defined a repressive role for prolyl hydroxylase (PHD)-1 controlling activity of NFκB. IKKβ expression and activity were found to be increased by hypoxia [11]. Interestingly, IKKβ (and IKKα) contains an evolutionarily conserved LXXLAP motif that resembles the prolyl hydroxylation sites in hypoxia inducible factor (HIF) alpha. In this pathway, therefore, hypoxia appears to activate NFκB through decreased PHD-dependent hydroxylation of IKKβ, although hydroxylation of IKKβ at proline 191 has yet to be demonstrated. Further work on IKKβ and the inflammatory response supports the theory that hypoxia has the potential to modulate the NFκB response to inflammatory stimuli through catalytic upregulation of IKKβ [13]. See Figure 1 for a schematic of hypoxia-induced NFκB activation.

While it has yet to be proven that IKKβ is hydroxylated by the PHDs, they do have an important role in regulating the stability of HIF, especially the PHD-2 isoform [24]. Hydroxylation of specific prolyl residues (proline 402 and proline 564 for human HIF-1α) regulates oxygen-dependent degradation of HIF-1α. Under conditions of hypoxia or by direct inhibition of the PHD enzymes, HIF-1α escapes hydroxylation and becomes stabilised [25,26]. Furthermore, the asparaginyl hydroxylase factor-inhibiting hypoxia inducible factor (FIH)-1 is a Fe(II)-dependent and 2-oxoglutarate-dependent dioxygenase, like the PHD family members and plays a role in regulating HIF transcriptional activity. FIH-1 was identified as being the oxygenase catalysing hydroxylation of asparagine 803 in HIF-1α, thus preventing interaction with the p300 CH1 domain and preventing HIF transactivation [27,28].

Figure 1



Hypoxia activates NFκB signalling via inhibitor of κB kinase. Under conditions of hypoxia, the hydroxylase-mediated repression of inhibitor of κB kinase (IKK) beta is suppressed – leading to enhanced IKKβ activity, enhanced IκBα phosphorylation and degradation as well as increased p65 NFκB activity. Factor-inhibiting hypoxia inducible factor inhibition by hypoxia or pharmacological inhibition reduces IκBα asparaginyl hydroxylation but does not appear to affect IκBα degradation. COX-2, cyclooxygenase 2; ICAM-1, intracellular adhesion molecule 1; iNOS, inducible nitric oxide synthase; RANTES, regulated upon activation normal T-cell expressed and secreted; PHD-1, prolyl hydroxylase 1; VCAM-1, vascular cell adhesion molecule 1.

Other FIH substrates have been identified recently, and include members of the NFκB [29] and Notch [30,31] signalling pathways. Cockman and colleagues discovered that both p105 (the precursor of the p50 component of NFκB) and IκBα are hydroxylated by FIH-1 at specific residues in their ankyrin-repeat domains (ARDs) [29]. Treatment of the cells with hypoxia or DMOG resulted in the repression of hydroxylation. The inhibitory action of IκB on NFκB DNA binding was unaffected by ARD hydroxylation, however, and the function of ARD hydroxylation is unknown to date. Given that some ARDs bind FIH-1 with higher affinity than the ARD of HIF-1α, ARDs may compete with HIF-1α for FIH-1, thus restricting the action of FIH-1 on HIF [30,31]. The consequences of such competition would probably be extremely complex given the high number of ARDs in the proteome and the probable identification of new hydroxylase substrates.

NFκB and hypoxia inducible factor cross-talk

The hypoxic response is predominantly regulated by HIF-1, the α subunit of which is stabilised under low oxygen conditions leading to the induction of genes to restore blood supply and nutrients to the cell as well as allowing resumption of energy production. Upregulation of HIF by bacterial and viral compounds in cells of the immune system prepares the

cells for migration to the hypoxic environment of inflamed and injured tissues. Furthermore, HIF-1 α is essential for myeloid cell-mediated inflammation. Myeloid cells lacking HIF-1 α had a lower glycolytic capacity, resulting in impairments in myeloid cell aggregation, motility, invasiveness and bacterial killing [32]. Elevated levels of HIF-1 α have been found in the inflamed joints of patients suffering from rheumatoid arthritis (RA) [33]. HIF therefore appears to have an important role in the coordination of cellular responses under conditions of inflammation.

A molecular link between NF κ B and HIF-1 α was proposed initially in a study examining erythropoietin expression [34]. This article was followed by a number of studies from Jung and colleagues examining the cross-talk between NF κ B and HIF-1 α [35-37]. Their work reported that the inflammatory cytokine IL-1 β upregulated HIF-1 α protein via an inflammatory signalling pathway involving NF κ B and cyclooxygenase 2. This upregulation occurred under normoxic conditions but provided the basis for future observations regarding links between NF κ B and HIF [13,38-44].

On the other hand, a positive role for HIF and NF κ B interaction in inflammatory signalling under conditions of hypoxia was described by Walmsley and colleagues, who investigated hypoxia-induced neutrophil survival [45]. Neutrophils are the key effectors of the innate immune system, and hypoxia has been shown to inhibit neutrophil apoptosis. Investigation of this phenomenon led to the discovery that HIF-1 α -dependent upregulation of NF κ B p65 and IKK α occurred in neutrophils, and this led to the conclusion that HIF-1 α -dependent NF κ B signalling is of critical importance in the hypoxic response in neutrophils [45].

The presence of an NF κ B site within the HIF-1 α promoter -197/-188 base pairs upstream of the transcriptional start site provides further evidence of the link between these two crucially important transcription factors [39]. When this site was mutated, induction of HIF-1 α by hypoxia was lost. Binding of NF κ B p50 and p65 to the HIF-1 α promoter in response to hypoxia gave evidence that NF κ B regulates HIF-1 α via a transcriptional mechanism [38].

Compelling *in vivo* evidence for cross-talk between NF κ B and HIF-1 α comes from a recent paper by Rius and colleagues [13]. This work directly linked NF κ B, innate immunity and the hypoxic response through studies involving the depletion of a component of the NF κ B signalling pathway. Using mice lacking IKK β (the key catalytic subunit in inflammatory signalling) in a variety of cell types, NF κ B was shown to be a critical transcriptional activator of HIF-1 α [13]. This evidence provides support for the concept of NF κ B and HIF-1 α engaging in a positive enhancement loop under conditions of hypoxia and inflammation. Significantly, basal NF κ B activity is required for the accumulation of HIF-1 α in cultured cells under conditions of hypoxia as well as in the liver and brain of hypoxic animals. IKK β links the hypoxic

response and innate immunity since a deficiency in IKK β leads to ineffective induction of HIF-1 α target genes, meaning that resolution of inflammation in the injured cell is likely to be impaired. Furthermore, defects in HIF-1 α expression are observed in mice exposed to hypoxia and to macrophages experiencing a bacterial infection in the absence of IKK β [13]. A single component part of the NF κ B signalling cascade has therefore been shown to play a crucial role in the cross-talk between the two pathways.

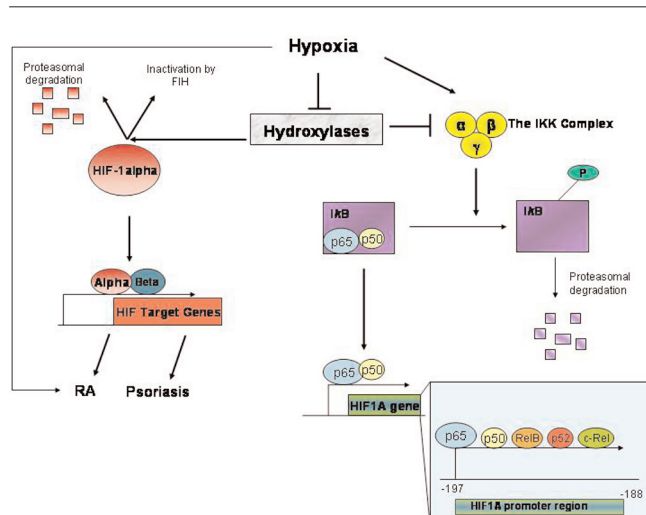
In another recent study, van Uden and colleagues suggest that both catalytic subunits of the IKK complex, IKK α and IKK β , must be depleted for hypoxia-induced HIF-1 α stabilisation to be impaired in mouse embryonic fibroblasts [44]. The different cell types used by the groups of van Uden and of Rius may account for the contrasting results observed. Rius and colleagues used bone-marrow-derived macrophages from IKK β ^{-/-} mice while van Uden and colleagues used mouse embryonic fibroblasts to inform their conclusions [13]. Interestingly, van Uden and colleagues showed that the individual NF κ B members have differential effects on HIF-1 α mRNA levels [44], illustrating another level of complexity in this relationship. Several NF κ B subunits (RelA, RelB, c-Rel, p50, p52) were found at the HIF-1 α promoter using chromatin immunoprecipitation, indicating that the basal level of HIF-1 α mRNA is directly modulated by NF κ B [44].

The signalling subtleties with respect to the individual NF κ B family proteins bound to the HIF-1 α promoter have yet to be fully elucidated. Specific reviews on the cross-talk between HIF and NF κ B at inflammatory hypoxic loci have recently been published [46,47] and provide interesting interpretations of the recent published data. While the evidence to date does not lead to an unequivocal thesis, what is clear is that there is significant cross-talk between HIF-1 α and NF κ B transcriptional repertoires – with each being able to influence expression of the other's members in some cells. This is an important consideration with respect to designing intervention strategies in inflammatory disease. See Figure 2 for a schematic of NF κ B and HIF-1 α cross-talk.

Hypoxia and inflammation

Hypoxia is a feature of sites of chronic inflammation, for example in the RA synovium, in atherosclerotic plaques, in sites of bacterial infection and at growing tumours [48]. This occurs when the cellular demand for oxygen, in order to meet the metabolic needs of the tissue to produce ATP, exceeds the vascular supply. While angiogenesis is a feature of hypoxic inflammation as well as being an adaptive response to decreased oxygen availability, the microvascular architecture is dysregulated in chronic inflammatory disease. Therefore, while there are more capillaries to deliver oxygen to a site of inflammation, the efficiency is poor. Furthermore, what limited oxygen is delivered to an inflammatory locus can be depleted further by oxygen consumption by highly metabolically active resident and infiltrating cells [49].

Figure 2



NFκB and hypoxia inducible factor 1 alpha cross-talk. Hypoxia acts as a stimulus for the activation of the inhibitor of κB kinase (IKK) complex as shown in Figure 1. Basal IKKβ-dependent NFκB activity is required for transcriptionally active dimer complexes to translocate to the nucleus and bind to a region -197/188 base pairs upstream of the hypoxia inducible factor (HIF)-1α promoter. This results in an increase in HIF-1α mRNA and protein levels. Several NFκB proteins have been detected at the HIF-1α promoter region by chromatin immunoprecipitation. Increased levels of HIF-1α are observed in chronically inflamed tissue such as the rheumatoid arthritis (RA) synovium and in the dermal glands of psoriatic skin. FIH, factor-inhibiting hypoxia inducible factor.

Rheumatoid arthritis

RA is a systemic autoimmune disorder that is characterised by persistent inflammation of a hyperplastic synovium, which consists of various cell types including synovial fibroblasts, B cells, T cells and macrophages. Cartilage and bone are invaded by the hyperplastic synovium, resulting in the progressive destruction of these joints [50]. An hypoxic environment has been shown to exist in RA synovium [51,52] as well as an increase in the level of hypoxic metabolites compared with normal synovium [53].

A number of growth factors and cytokines capable of activating HIF-1α are known to be upregulated in RA; for example, the NFκB target genes TNFα and IL-1β. In addition, incubation of cultured synovial fibroblasts with IL-1β results in stabilisation of HIF-1 [54]. Studies have shown increased levels of HIF-1α protein in rheumatoid synovial tissues [33,55], which has led to the hypothesis that tissue hypoxia together with HIF-1α-mediated expression of vascular endothelial growth factor (VEGF) is essential for the progression of RA through promotion of angiogenesis [56]. Angiogenesis provides the necessary vasculature so that migration of cells into the joints can occur [48]. HIF also promotes arthritis through the induction of the transcription factor Ets-1 [57]. Ets-1 is responsible for the induction of matrix metalloproteins, which are involved in cartilage and bone destruction [58].

To date, no strong links have been demonstrated between hypoxia-induced NFκB and RA. Hitchon and El-Gabalawy, however, suggest that cycles of hypoxia and reoxygenation in the arthritic joint lead to reactive oxygen species production, which would serve as a stimulus for NFκB activation [59].

Psoriasis

Angiogenesis induced by VEGF also appears to play a crucial role in the formation of psoriatic plaques. VEGF mRNA and mRNA for its receptor Flt-1 are increased in psoriatic skin compared with normal human skin [60]. Rosenberger and colleagues present the hypothesis that physiologic regional hypoxia occurring in the dermal glands triggers a cycle involving HIF, VEGF and Akt activation [61]. They showed that HIF-1α mRNA is elevated in the epidermis of psoriatic skin and that HIFs are strongly activated in cell types that express pivotal angiogenic factors. This led to the theory that more severe skin hypoxia in psoriasis could lead to keratinocyte and HIF-mediated angiogenesis through upregulation of VEGF and Flt-1. Phospho-Akt in the dermal capillaries is thought likely to provide positive feedback to the HIF-VEGF system [61].

Inflammatory bowel disease

Links between hypoxia, HIF-1 and NFκB signalling have been demonstrated for chronic inflammation in murine models of colitis. In cells of the gastrointestinal tract, the effects of hypoxia on transepithelial permeability have been implicated in inflammatory bowel disease (IBD), which consists of Crohn's disease and ulcerative colitis [21]. Both the HIF-1 and NFκB pathways have been demonstrated to have protective roles in intestinal epithelial cells through the use of intestinal epithelial cell conditional knockout mice for HIF-1α and IKKβ [62-64]. Karhausen and colleagues showed that mice constitutively expressing HIF-1α in the colon were protected from hypoxia-induced permeability changes, as well as from trinitrobenzene sulphonic acid (TNBS) colitis [64]. Conversely, conditional knockout of HIF-1α in the gut resulted in more severe symptoms of colitis. Meanwhile, Greten and colleagues demonstrated that conditional knockdown of IKKβ in enterocytes resulted in increased apoptotic damage in a murine model of dextran sulphate sodium-induced colitis [63].

DMOG is a pan hydroxylase inhibitor that has been shown to activate both HIF-1α-dependent [65] and NFκB-dependent [11] gene expression *in vitro*, most probably through the inhibition of hydroxylation-dependent repression of both signalling pathways. In a recent study we demonstrated that DMOG is profoundly protective in a murine model of dextran sulphate sodium colitis [66]. We hypothesised this to be via induction of both HIF-1α and NFκB pathways, and proposed that its occurrence was at least in part due to the development of an anti-apoptotic phenotype. Inhibition of apoptosis by DMOG is hypothesised to be important in the maintenance of epithelial barrier function in murine colitis and to prevent mixing of luminal antigens with the submucosa that houses the mucosal immune system. Previous studies have

suggested that the regulation of intestinal epithelial cell apoptosis is crucial in the development of inflammation in the gut [67,68]. Further support for the above data is provided by Robinson and colleagues [69] who demonstrated in a TNBS-induced murine model of colitis that induction of HIF-1 α by FG-4497 (a novel PHD inhibitor) results in beneficial outcomes. This effect is likely due to a barrier-protective function.

Conversely, Shah and colleagues have suggested that HIF in fact augments experimental colitis through macrophage migration inhibitory factor-dependent signalling [70]. Their data show that a chronic increase in HIF signalling in colon epithelial cells results in increased expression of proinflammatory mediators, the levels of which were decreased by inhibition of the HIF target gene migration inhibitory factor. The perceived conflict between the above studies and this one may at least in part be explained by the fact that the proinflammatory phenotype of the $Vhl^{\Delta E}$ mouse model used by Shah and colleagues [70] was HIF-2 α mediated, while the protection observed by Karhausen and colleagues [64] was HIF-1 α mediated. This difference suggests that HIF-1 α and HIF-2 α may have distinct and separate roles in colon homeostasis. Other differences between the studies that may have contributed to the disparity in findings include (i) the specific promoter used to drive the intestinal epithelial cell knockout – Karhausen and colleagues [64] used mice expressing Cre-recombinase under the transcriptional control of a fatty acid binding protein promoter, while Shah and colleagues [70] used mice expressing Cre-recombinase under the control of the villin promoter – and (ii) the model of colitis employed – Karhausen and colleagues [64] used TNBS-induced colitis, while Shah and colleagues [70] used an irritant-based model of colitis.

Prolyl-hydroxylase inhibitors in inflammatory disease

The use and development of prolyl-hydroxylase inhibitors (PHDIs) in the treatment of disease is an area of intense research. Several recent studies have reported the potential for using PHDIs in animal models of ischaemia affecting the whole animal [71], the brain [72], the heart [73] and the kidney [74-76] as well as in IBD [66,69].

The difficulty in developing specific PHDIs suitable for use in the clinic centres on the current lack of specificity of PHDIs as well as isoform-specific roles for the different PHDs. Most available PHDIs act at the substrate binding interface and interfere with the PHD interaction with essential co-factors (2-oxoglutarate, Fe $^{2+}$, ascorbate). Structural mimetics of 2-oxoglutarate are amongst the most commonly used but other nonspecific compounds such as desferrioxamine and cobalt interfere with the iron/ascorbate balance. 2-Oxoglutarate analogues are essentially pan-hydroxylase inhibitors and inhibit prolyl and asparaginyl hydroxylases alike. Evidence from PHD3 $^{-/-}$ mice suggests a neuronal role for PHD3 in sympathoadrenal development [77]. Evidence from PHD1 $^{-/-}$

mice suggests a role for PHD1 in the regulation of basal metabolism [78]. PHD2 $^{-/-}$ mice are embryonic lethal [79]. Against this background, systemic administration of pan-hydroxylase inhibitors may be undesirable given the diverse functions of the individual PHD isoforms. Development of specific PHDIs will probably advance their potential as therapies in the future.

Development of specific PHDIs may be of particular use in the treatment of inflammatory disease, where recent studies using the PHDIs DMOG and FG-4497 resulted in profound protection from experimentally induced colitis in mice. In a study using dextran sulphate sodium-induced colitis, intra-peritoneal injection of DMOG significantly reduced the development of colitis [66]. Using the PHDI FG-4497, Robinson and colleagues demonstrated similar protection in their model of TNBS-induced colitis [69]. Future work is needed to determine the specific hydroxylase isoform target of the drugs *in vivo* or, indeed, whether the protective effect from colitis is only evident against a background of pan-hydroxylase inhibition. Similarly, the downstream effectors of hydroxylase inhibition that occasion the protection from colitis need to be fully elucidated. Studying the development of experimental colitis in isoform-specific PHD null mice will greatly enhance our understanding of the role of hydroxylases as possible therapeutic targets in inflammatory disease.

The colon is ideally suited to avail of the benefits of PHDI in inflammatory disease. HIF-1 α activation under conditions of hypoxia is known to activate a number of epithelial barrier-protective genes [49]. Maintenance of intestinal epithelial barrier integrity is of paramount importance in IBD such as ulcerative colitis and Crohn's disease. An intact epithelial barrier will prevent luminal antigenic material mixing inappropriately with the submucosa and will prevent inflammation. Targeted delivery of a PHDI that can activate NF κ B and HIF at the beginning of an IBD episode may therefore prove beneficial through maintenance of barrier integrity via IKK β -mediated suppression of enterocyte apoptosis [63] and HIF-1 α -mediated barrier protection [64]. The use of PHDIs in inflammatory conditions, however, should be approached with caution. Activating NF κ B via PHD inhibition – whilst potentially beneficial in the suppression of apoptosis and maintenance of epithelial barrier protection – could lead to inappropriate survival of cancer cells. Similarly, the addition of an NF κ B-activating PHDI in an inflammatory setting may seem counterintuitive given the body of evidence for NF κ B target genes contributing to inflammatory signalling [80,81]. The targeted delivery of a PHDI in the appropriate inflammatory condition will therefore be of paramount importance.

Activation of HIF in inflammatory disease via PHDIs also comes with caveats. While one subset of HIF target genes actively maintains the epithelial barrier as discussed previously, another subset of HIF-1-dependent proangiogenic genes may also be activated. This could potentially contribute

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to localised angiogenesis and may increase the risk of inflammation-associated cancer.

As a consequence, PHDIs may not be indicated in RA because of the central contribution of angiogenesis in the pathogenesis and invasiveness of that particular inflammatory condition. Similarly, the contribution of angiogenesis to the development of psoriatic plaques may preclude the use of PHDIs. The use of PHDIs in IBD does, however, show some promise. The profound protection from experimentally induced colitis seen with DMOG [66] and with FG-4497 [69], coupled with the pre-eminent role of the intestinal epithelial cell in preventing inflammation, makes the use of PHDIs an attractive potential therapeutic strategy in IBD.

Conclusions

Identification of the co-regulation of NFκB and HIF pathways by hydroxylase family members has enhanced our understanding of the mechanism of hypoxia-induced NFκB activity. The fact that the inhibitory action of hydroxylases is at the level of the IKK complex through suppression of catalytic activity means that microenvironmental hypoxia has the potential to modulate NFκB signalling elicited through a range of stimuli such as TNFα. The implication of such NFκB-inducing stimuli in the initiation of HIF-1α transcription highlights the importance of hypoxia and NFκB together and in isolation in the inflammatory response. The complicated cross-talk between these two signalling pathways means that even specific inhibitors of NFκB and HIF are likely to influence the other pathway. Notwithstanding this, exciting new evidence is emerging for the potential therapeutic application of hydroxylase inhibitors in a range of ischaemic conditions affecting the whole animal [71], the brain [72], the heart [73] and the kidney [74-76], and also in models of hypoxic inflammation such as IBD [66,69].

Competing interests

The authors declare that they have no competing interests.

Authors' information

Owing to space restrictions, it was not possible in the present article to reference every publication relevant to the role of hydroxylases in NFκB signalling.

Acknowledgements

The authors are funded by the Science Foundation Ireland (CTT and EPC) and by the Health Research Board (Ireland) (KMO)

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