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Is nuclear factor kappa-B the missing link between inflammation, cancer and alteration in hepatic drug metabolism in patients with cancer?

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ABSTRACT

In the last few years, several studies have provided a causal link between constitutive activation of nuclear factor kappa-B (NF-κB) and the initiation and development of cancer. More recently, it appears that a cancer-induced inflammatory response may be an important factor in the inter-individual variability of the response to and toxic effects of cancer chemotherapy, as well as in the alteration of drug metabolism enzyme expression in patients. The relationships between chronic inflammation (or infection), cancer and drug metabolism are many: chronic infections lead to inflammation, inflammation may lead to cancer, cancer usually leads to an inflammatory syndrome, and inflammation alters the expression of drug metabolising enzymes and thus of the efficiency of cancer chemotherapy. This review focuses on the functional consequences of NF-κB activation during oncogenesis and on the expression of the major cytochrome P450s (CYP) involved in anticancer therapies. Finally, the potential role of NF-κB as the missing link between inflammation, cancer and alteration in hepatic drug metabolism in patients with cancer is discussed.

1. Introduction

The clinical efficacy of anticancer therapy is severely limited by an inability accurately to predict the outcome for the patient in terms of both tumour response and toxicity. This lack of prediction is of even greater clinical significance with anticancer agents due to their narrow therapeutic index. Despite advances in molecular medicine resulting in new drugs with specific cellular targets, there are still major issues outstanding related to drug resistance and individual patient variability. Most anticancer drugs are cleared primarily by the liver.[1] Drug metabolising enzymes, such as the cytochrome P450 (CYP) subfamilies 2 and 3 play a key role in the activation and deactivation of drugs, including a number of cytotoxic drugs, and can therefore influence the susceptibility of organs and tissues to their therapeutic and toxic effects. CYP suppression can result in increased clinical toxicity of drugs with a low therapeutic index. Conversely, some drugs must be converted to their pharmacologically or toxicologically active metabolites by CYPs, and suppression of their metabolism can lead to a reduced therapeutic or toxic effect.

The major CYPs involved in the metabolism of cytotoxic agents belong to the CYP2 and CYP3 families. The CYP2 family is large, comprising the subfamilies 2A, 2B, 2C, 2D and 2E, but

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only CYP2B6 has been well studied with regard to tumour metabolism. CYP2B6 is responsible for the bioactivation of cyclophosphamide and ifosfamide through 4-hydroxylation.[2] Local CYP2B6 enzyme expression in cancer cells may constitute a relevant factor for the outcome of therapy, and recombinant retroviruses have been used successfully to deliver the CYP2B6 gene to malignant cells, resulting in an enhancement of their sensitivity to cyclophosphamide.[3] The CYP2C subfamily, which metabolises approximately 20% of clinically used drugs,[4] is responsible for the metabolism of several cytotoxic drugs: CYP2C8 catalyses the metabolism of paclitaxel, while CYP2C9 and CYP2C19 both catalyse the activation of cyclophosphamide and ifosfamide. Finally, members of the CYP3A subfamily are among the most important of all human drug metabolising enzymes; approximately 55% of all drugs are metabolised by CYP3A4,[5] especially the newer cytotoxic agents such as the taxanes (paclitaxel, docetaxel) and camptothecins (irinotecan, topotecan), but also older agents such as the vinca alkaloids (vincristine, vinblastine, and vinorelbine), cyclophosphamide, etoposide and tamoxifen.

An inflammatory response is a prominent feature in clinical oncology and it is well known that a long-lasting inflammatory response is equally common in almost all types of solid tumour.[6] Indeed, the level of pro-inflammatory cytokines and acute phase reactants is increased in many patients with advanced cancer.[7–9] Moreover, chronic inflammation is an important risk factor in carcinogenesis, and it has been estimated that >15% of all malignancies are initiated by inflammation.[10] In addition, it is well known that an inflammatory response generally results in decreased expression of mRNA and thus protein synthesis of CYPs, leading to decreased microsomal metabolism and drug clearance.[11] Even if the molecular mechanisms are not well understood, this possibility raises the concern that patients with cancer who develop an inflammatory response may have reduced tumour chemosensitivity. Recently, we reported that pro-inflammatory cytokines (IL-6, IL-1β) and molecules (lipopolysaccharides, LPS), or the activation of pro-inflammatory transcription factor such as NF-κB inhibit the expression of constitutive androstane receptor (CAR) and pregnane X receptor (PXR), two key nuclear receptors involved in CYP2 and CYP3 gene regulation.[12] These xenosensors are activated by a variety of xenobiotics and drugs, and they regulate the expression of genes involved in detoxification, such as CYP3A4, 2B6 and 2Cs. These results provide a new view on the interplay between inflammation, cancer and the alteration of drug metabolism.

2. Cancer, inflammation and NF-κB

2.1. *Inflammation and cancer initiation*

Tumours have been linked with inflammation since 1863, when Rudolf Virchow discovered leukocytes in neoplastic tissues and first made the connection between inflammation and cancer.[13] Since then, a substantial body of evidence has been published to support the conclusion that chronic inflammation represents a key risk factor for cancer. Indeed, chronic inflammation is caused by a variety of factors, including bacterial, viral and parasitic infections, chemical irritants and non-digestible particles. The longer the inflammation persists, the higher the risk of associated carcinogenesis. Examples of such association include the human papilloma virus (HPV) and anal or cervical cancer,[16] bacterial infection by *Helicobacter pylori* and gastric adenocarcinoma,[17] Hepatitis B/C virus and hepatocellular carcinoma,[18] *Schistosoma haematobium* and cancer of the bladder,[19] asbestos induced inflammation and bronchogenic carcinoma or mesothelioma in humans.[20] Disturbances in homeostasis due to malignant disease induce systemic and metabolic changes that make up the acute phase response.[13] The response includes an increase in neutrophils, changes in metabolism (carbohydrate, protein, lipids and amino acids), activation of complement and coagulation pathways, and production of acute-phase proteins. Various cytokines are involved in inflammation and the acute phase response. Pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α) and interleukins IL-1β and IL-6 are among the most important. These cytokines modulate gene expression via the janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase, and NF-κB pathways. A hypothesis is that the tumour growth, invasion, necrosis and metastasis stimulate immune cells with the release of inflammatory cytokines, so that the IL-1β or IL-6 levels may reflect the tumour's aggressivity and, consequently, a less favourable prognosis. Alternatively, it has been observed that increased IL-6 levels in cancer may be related to its synthesis and release by tumour cells,[14] and so represent their proliferative activity.[15]

In addition, chronic inflammation is implicated in the anorexia–cachexia syndrome, which is characterised by progressive wasting, lack of response to treatment, and a poor prognosis. Mantovani and colleagues[21] reported higher serum concentrations of some cytokines, including IL-1β, IL-6 and TNF-α, in patients with anorexia–cachexia. It is well known that IL-1β and IL-6 play a key role in regulation of the inflammatory acute-phase response,[22] and particularly in the regulation of C-reactive protein (CRP) synthesis by hepatocytes.[23] Raised concentrations of serum IL-6 and CRP seem to be strong independent prognostic factors for survival in severe malignant disorders including myeloma, melanoma, ovarian cancer, renal-cell carcinoma, and gastrointestinal cancers, but are not yet routinely incorporated into staging criteria.[6]

Chronic inflammation occurs due to environmental stress around the tumour and this generates a shield protecting it from the immune system. It has recently been demonstrated that the micro-environment of the tumour highly resembles an inflammation site, with a significant advantage for tumour progression. This results from enhancement of the levels of cytokines, chemokines, leukocytes, lymphocytes and macrophages, which contribute to vessel dilatation and neovascularisation for increased blood flow, to the immunosupp- ression associated with the malignant disease, and to tumour metastasis.[24] Furthermore, this inflammatory micro-environment of the tumour, apart from its significant role in cancer progression and protection from the immune system, has a considerable adverse effect on the success of the various current cancer treatments. It has recently been proposed that the inflammatory response to cancer may affect the disposition and compromise the pharmacodynamics of chemotherapeutic agents.[25]

2.2. NF-κB in inflammation and cancer

A key player in inflammatory processes is transcription factor NF-κB,[26] which consists of a number of closely related protein dimers that bind a common sequence motif.[27] NF-κB is a homo- or hetero-dimeric transcription factor consisting of one or two of five members of the Rel family of transcription factors: p65 (RelA), RelB, c-Rel, NF-κB1 (p105–p50) and NF-κB2 (p100–52). In resting non-stimulated cells, NF-κB dimers are cytoplasmic, but translocate to the nucleus in response to a variety of pro-inflammatory stimuli. Two major pathways account for nuclear translocation (i.e. activation) of NF-κB. The canonical NF-κB activation pathway, applies to dimers composed of RelA, c-Rel and p50, which are retained in the cytoplasm by specific inhibitors, the IkB proteins.[28] This pathway is normally triggered in response to microbial and viral infections and to pro-inflammatory cytokines, all of which activate the IkB kinase (IKK) complex. IKK phosphorylates NF-κB bound IkBs and target them for ubiquitin-dependent degradation, allowing liberated NF-κB dimers to enter the nucleus.[29] IkB phosphorylation depends mainly on the IKKβ catalytic subunit of the IKK complex.[30] In the alternative pathway, the NF-κB2 precursor protein, preferentially binds RelB in the cytoplasm, resulting in the release of RelB:p52 dimers.[28] This pathway depends on the IKKα subunit [31] and is IKKβ-independent.[32] Both pathways ultimately lead to transcription of distinct sets of target genes, mediating different biological functions. Recently, it has been reported that NF-κB can also be activated by DNA-damaging drugs or ultraviolet light, without apparent IKK activation, thereby providing a third NF-κB pathway.[33]

The involvement of the NF-κB pathway in acute inflammation and cell survival is well established.[34] In addition to inflammation, persistent NF-κB activation has been suggested to contribute to cancer.[35] For example, chromosomal rearrangements leading to constitutive NF-κB activation (avian c-Rel), or overexpression of NF-κB subunits have been detected in lymphoid malignancies.[36,37] Furthermore, mutations in c-Rel, p100 and IKKα, and constitutive IKK1 activation are associated with leukaemia and lymphoma.[38] Activated NF-κB was also detected in many solid tumours and its inhibition in tumour cell lines increases their sensitivity to chemotherapeutic drugs and radiation.[39] Indeed, NF-κB is known to activate genes whose products inhibit apoptosis,[40] which could be instrumental in tumour development. NF-κB has recently been proposed as the missing link between inflammation and cancer as it might activate signalling pathways in both cancer cells and tumour-associated inflammatory cells that promote malignancy.[41] New data obtained from two mouse models of inflammation-associated cancer now implicate NF-κB in cancer progression.[42,43] The data obtained suggest that the NF-κB pathway does not affect initiation but has a dual action on tumour promotion: first by preventing the death of cells with malignant potential, and second by stimulating the production of pro-inflammatory cytokines in inflammatory cells in the tumour mass. The pro-inflammatory cytokines then signal to initiated or otherwise 'damaged' cells to promote their survival and proliferation. It has been observed that preventing NF-κB activation in hepatocytes after 7 months of chronic inflammation was sufficient to inhibit the development of liver cancers, indicating that NF-κB is crucial for malignant conversion (by preventing apoptosis of pre-malignant cells) although not in the early stages of tumour development. At the same time, NF-κB activation in tumour-associated inflammatory cells contributes to tumour growth by inducing synthesis of tumour-promoting pro-inflammatory mediators.

Activation of NF-κB in response to chronic inflammation may be of particular relevance to gastrointestinal carcinogenesis, especially in gastric cancer, colitis-associated cancer and hepatocellular carcinoma. Activated NF-κB was detected in lamina propria macrophages and epithelial cells from biopsy specimens or cultured cells of patients with inflammatory bowel disease[44] as well as in colorectal cancer but not in adjacent normal tissue.[45–47] In addition, NF-κB activation is often observed in human hepatocellular carcinoma, particularly following hepatitis.[48] Recently, it has been observed that tissue-specific deletion of IKKβ in enterocytes and macrophages (the two cell types in which NF-κB is activated during colitis-associated cancer), can reduce the incidence and development of inflammation-associated cancer. In enterocytes, it has been observed that IKKβ contributes to tumour initiation and promotion by suppressing apoptosis through the mitochondrial pathway (IKKβ in these cells is required for induction of BCL-xl), while it is involved in production of inflammatory mediators that promote tumour growth only in myeloid cells.[43]

3. Impact of malignancy on CYP2B, CYP2C and CYP3A gene expression

3.1. Role of inflammation in drug metabolism in cancer patients

Hepatic phase I metabolism of drugs has been observed to be reduced in tumour-bearing animals relative to non-tumour-bearing animals.[49] In another study, rats with nitrosamine-induced tumours exhibited reduced activity of hepatic CYP2C, 2D and CYP3A, relative to controls.[50] In patients, Philip and colleagues reported a reduction in the expression of drug metabolising enzymes in primary and secondary hepatic tumours, relative to normal liver tissue.[51] In general, CYP2B6 expression is lower in tumours (breast[52] and gastro-intestinal tract[53]) relative to normal tissues, indicating a possible repression of transcription. Expression of the CYP2C subfamily was also reduced in gastrointestinal cancers.[54] Indeed, it has been demonstrated that inoculation with tumour cells induces similar changes to CYP enzyme activity, protein content and drug pharmacokinetics as those induced by inflammation in animals.[25] Finally, despite its importance in normal tissues, CYP3A4 transcription seems to be repressed in neoplastic tissues, notably in breast cancers[55] but also in human hepato-carcinomas (M.J. Vilarem, Inserm U632, Montpellier-France). In addition, studies have demonstrated that, in response to inflammatory mediators in patients with cancer, there is a reduction in the hepatic clearance of drugs, as confirmed by pharmacokinetic studies or indicated by markers of specific cytochrome activity. Among the factors that influence CYP3A activity in cancer patients, it has been observed that an acute-phase response in patients with advanced cancer is associated with reduced hepatic drug metabolism as measured by the erythromycin breath test.[56]

In addition, Baker and colleagues reported that CYP3A4 activity was inversely correlated with the inflammatory marker α1-acid glycoprotein (which is an acute phase reactant).[57] In the same way, the pharmacokinetics of cyclosporin (a CYP3A4 substrate) have been shown to parallel the kinetics of the inflammatory response after bone-marrow transplantation: the CYP-mediated formation of cyclosporin metabolites decreased with inflammation, as monitored by measurement of the CRP concentration.[58]

3.2. *NF-κB and CYP2B, CYP2C and CYP3A4 gene expression*

The pregnane X receptor (PXR, NR1I2) and the constitutive androstane receptor (CAR, NR1I3) are members of the nuclear receptor subfamily. Both CAR and PXR are activated by xenobiotics and act as master regulators of systems that are involved in the detoxification and elimination of steroids, bile acids and xenobiotics.[12] Genes induced by these receptors include: phase I cytochrome P450 enzymes (CYP2A6, CYP2B6, CYP2C8/9 and CYP3A4), phase II enzymes such as uridine diphospho-glucuronosyltransferases (UDPGT), glutathione-S-transferase (GSTs), and sulphotransferases (SULTs), and the phase III transporters such as the multidrug resistance-associated protein 2 (MRP2) and the multidrug resistance protein (MDR1). Since CAR and PXR share many ligands/activators[59] and induce specific but overlapping sets of genes,[60] they provide the cell with two overlapping and semi-redundant mechanisms for recognising and eliminating toxicants.

Very little is known about the regulation of CAR and PXR. We have previously reported that the induction of CYP3A4, CYP2B6 and CYP2C8/9 by rifampicin and phenobarbital can be blocked by interleukin 6, which reduces the expression of PXR and CAR in primary human hepatocytes.[61] Beigneux and colleagues also found that the inflammation-related decrease in the expression of these receptors blocked both basal and inducible CYPs expression in mice treated with lipopolysaccharides. A reduction in the transcription of the retinoid X receptor (RXR), the heterodimer partner for CAR and PXR, was also observed. The reduced expression of these nuclear receptors preceded the downregulation of CYP3A4, CYP2B6 and CYP2C8/9 mRNA.[62] In addition, significantly lower mRNA levels of cyp3a11 were found in endotoxin- or IL-6-treated mice, but not in PXR knock-out mice. Of note also is the fact that significantly lower levels of PXR mRNA and protein were detected in endotoxin- and IL-6-treated mice, suggesting that the downregulation of several hepatic proteins during inflammation is PXR-dependent.[63]

It has been known for more than 20 years that induction of CYP2B, CYP2C and CYP3A by xenobiotics such as phenobarbital and rifampicin in cultured rodent or human hepatocytes is potentiated by pre-treatment of cells with glucocorticoids such as dexamethasone. We have demonstrated that this effect is related to the induction of PXR and CAR by glucocorticoids.[64–66] Glucocorticoid control of cellular functions is mediated via the glucocorticoid receptor (GR), a well known transcription factor.[67] Unliganded GR resides in the cytosol, associated with a heat-shock protein complex. Following hormone binding, GR dissociates from the complex and migrates as a homodimer to the nucleus, where it binds to glucocorticoid-response elements (GRE) in target gene promoters.[67] GR acts via two different mechanisms: transcriptional regulation that requires DNA-binding and protein–protein interaction between GR and other transcription factors, such as NF-κB or AP-1, which is independent of DNA binding.[68] CAR and PXR appear to be primary glucocorticoid-responsive genes. This was confirmed recently by the identification of a functional glucocorticoid responsive element (GRE) in the human CAR promoter.[69] However, the presence of a functional GRE in the PXR regulatory region remains to be confirmed, even if the direct involvement of GR in PXR gene regulation has to be demonstrated.[64] These observations suggest the existence of a cascade of signal transduction GR-CAR/PXR-CYP2/3. Recently it has been shown in primary human hepatocytes and in vivo in mice, that pro-inflammatory mediators, such as IL-6, IL-1β and LPS, reduce the expression of both CAR and PXR at the transcriptional level, and concomitantly reduce the expression of CYPs and other drug metabolising systems regulated by these receptors.[61,62,70] It is known that GR interaction with NF-κB leads to a functional inhibition of NF-κB.[68,71] Indeed, interference with NF-κB signalling is also thought to be the major underlying mechanism of action of glucocorticoids, which are widely prescribed as anti-inflammatory and immunosuppressive drugs. One idea is that GCs increase the expression of IkBα, which prevents the nuclear translocation of NF-κB and therefore prevents NF-κB-dependent transcriptional activation.[72] This effect, however, might be cell specific. Furthermore, the glucocorticoid receptor interacts directly with p65 in the nucleus and thereby inhibits p65-dependent transactivation of target genes.[73,74] It has been shown that GR overexpression dramatically reduces NF-κB binding activity and the expression of NF-κB-responsive genes in skin.[75] In addition, GR plays a tumour-suppressor role in skin carcinogenesis induced by the ras oncogene, possibly through transrepression of NF-κB-dependent genes and alteration of the proliferation/apoptosis/differentiation balance in transformed keratinocytes.[76] Indeed, experiments with transgenic mice harbouring mutated GR, which cannot activate GRE containing promoters, clearly indicated that many important effects of glucocorticoids including their anti-inflammatory effect and blockage of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced response in skin depend on GR interaction with NF-κB and AP-1.[77,78] On the other hand, it is known that transcriptional co-regulators, such as p300/CBP or SRC-1, function as co-activators for both the GR and the NF-κB pathways.[79] These co-activators have been shown to possess histone acetyltransferase (HAT) activity. HAT activity is involved in chromatin remodelling, which is a key step in transcriptional activation. It is conceivable that there could be competition. Thus, when one pathway is activated, the other pathway would be repressed through competition for co-activator availability.

Transient transfection studies with human CAR promoter constructs linked to the luciferase-reporter gene indicated that LPS and IL1β-mediated repression of CAR gene expression occurred at the level of gene transcription. Moreover, several data suggested that NF-κB is a critical mediator of LPS- or IL-1β-mediated inhibition of CAR expression through the repression of ligand-activated glucocorticoid receptor action.[70] We observed that NF-κB p65 interferes with the enhancer function of the distal glucocorticoid response element of the CAR

promoter gene that we have recently identified. We observed that: (i) LPS, IL-1β or p65RelA overexpression downregulated GR induced CAR expression; (ii) these suppressive effects could be blocked both by pyrrolidine dithiocarbamate, which is known to inhibit NF-κB activation, or by the overexpression of NF-κB repressor (SRIkBα). Moreover, the glucocorticoid-induced histone H4 acetylation of the CAR promoter was markedly inhibited by LPS or IL-1β in human hepatocytes. These data suggest that NF-κB activation inhibits glucocorticoid-induced HAT activity around the CAR promoter gene. It is possible that this is due to inhibition of GR-associated HAT activity (co-activators competition) and/or recruitment of histone deacetylases (HDACs) to the GR complex by NF-κB.

4. Conclusion

Cancer-induced inflammatory response may represent an important factor in the inter-individual variability of the response to and toxic effects of cancer chemotherapy, and NF-κB may represent the causal link between cancer, inflammation and drug metabolism. Indeed, it has been reported that suppression of NF-κB activation by proteasome inhibitors restores chemosensitivity in various cell lines.[80,81] In the same way, small molecule inhibitors of the NF-κB pathway are considered as a promising new therapeutic option.[82] These results identify the NF-κB pathway as a rational target for anti-inflammatory and cancer therapy. Non-steroidal anti-inflammatory drugs (NSAIDs) represent promising possibilities for use in cancer chemoprevention and treatment. Indeed, anti-inflammatory therapy with NSAIDs reduces the risk of some cancers.[83] NSAIDs have been reported to inhibit the IKKβ-dependent NF-κB-signalling pathway,[84,85] in addition to their known ability to inhibit cyclo-oxygenases (COX) and prostaglandin synthesis.[86] Celecoxid for example, which suppresses NF-κB activation through the inhibition of IKK,[87] is effective in the treatment of breast, skin and bladder cancer.[87] The option of treating inflammation-associated cancer with NF-κB inhibitors seems attractive. However, it has to be kept in mind that NF-κB inhibition could also influence an immunological response to the tumour (e.g. T cell activation depends on NF-κB signalling). At present, it is not clear how NF-κB inhibition will affect immune surveillance. Should future anticancer strategies focus on regulating NF-κB activation? It is important to note that all organs are endowed with unique cell-death pathways, as well as with damage–response pathways that typically involve short-term activation of innate immune cells. In the skin, for example, keratinocytes die through 'terminal differentiation', and inhibiting NF-κB in initiated keratinocytes actually promotes one type of cancer by reducing terminal differentiation.[88]

On the other hand, several mechanisms have been implicated in the low efficacy of a drug in a tumour mass. Of relevance here is the observation that solid tumours are characterised by regions of hypoxia associated with poor vascularisation. The hypoxia state has wide-ranging consequences in terms of drug activity and intracellular reactions. Oxygen is required for the generation of cytotoxic radical species formed as a result of exposure to chemotherapeutic agents; consequently, tumoural hypoxia is often associated with resistance.[89] Oxygen is also a co-substrate required for all CYP catalysed mono-oxygenase reactions; hence, low oxygen concentrations have the potential to reduce the efficacy of anti-tumoural activation of pro-drugs and thus their therapeutic effect. The issue of tumoural hypoxia has not been comprehensively addressed. However, no difference has been observed in the metabolism of cyclophosphamide after transfection of hypoxic and non-hypoxic cells with the CYP2B6 and P450 reductase gene, suggesting that for this enzyme, the intra-tumoural oxygen concentration was sufficiently high for activity in hypoxic cells.[90] Now it is clear that tumours that have constitutive NF-κB activity usually show increased resistance to chemotherapy. One explanation might be the induction of the multidrug resistance P-glycoprotein MDR1, which seems to be an NF-κB-regulated gene product.[91] This could result in an enhancement of drug efflux from the cell and then a slow penetration of the drug into the tumour site. Recently, it has been observed that NF-κB transactivates a human mdr1 promoter luciferase construct. Moreover, an NF-κB binding site has been identified in the first intron of the human mdr1 gene and it has been demonstrated that NF-κB complexes can bind with this intronic site.[92] In addition, modification of drug metabolising enzyme expression, for example of CYPs which play a key role in the activation and deactivation of cytotoxic drugs.[93] can therefore influence the susceptibility of organs and tissues to the therapeutic and toxic effects of the drugs. As NF-κB inhibits the expression of key transcriptional factors (i.e. CAR and PXR) involved in CYPs gene regulation, this could represent another mechanism of modification of cytotoxic agent metabolism in patients with cancer. Indeed, this possibility raises the concern that patients with cancer and having inflammatory responses may have reduced metabolism and reduced tumour chemosensitivity (Fig. 1).

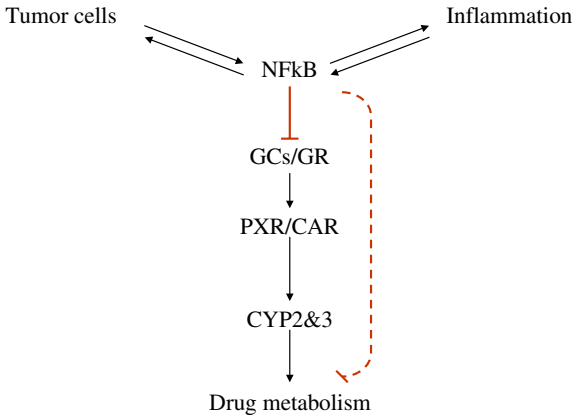

Fig. 1 – Inter-relation of nuclear factor kappa-B (NF-κB) activation in cancer, inflammation and modification of drug metabolism in cancer patients. GCs, glucocorticoids; GR, glucocorticoid receptor; CYP2&3, cytochrome P450 subfamilies 2 and 3.

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