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Celecoxib pathways: pharmacokinetics and pharmacodynamics

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Background

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgestic, and antipyretic properties. It is approved for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute pain [1-3]. Celecoxib has also shown promise in prevention of cancer, and has been used as an adjunct to surgery to reduce the number of adenomatous colorectal polyps in patients with the hereditary colon cancer susceptibility syndrome, familial adenomatous polyposis (FAP) [4-6]. The anti-inflammatory and pain-relieving properties of celecoxib result from inhibition of prostaglandin (PG) synthesis by selective inhibition of PG G/H synthase-2 (encoded by gene *PTGS2*). The two PTGS isoforms, PTGS1 and PTGS2, are bisfunctional enzymes with both cyclooxygenase (COX) and hydroperoxidase activities, but they are commonly referred to as COX; see 'Pharmacodynamics' section) [1,7,8]. Celecoxib is a member of the subclass of NSAIDs, which were purposefully designed as COX-2-selective inhibitors (pdCOX-2 inhibitors) and that are frequently called coxibs [9,10]. Most traditional NSAIDs (tNSAIDs) inhibit both COX isoforms; however, some of them show a degree of COX-2 selectivity that is similar to that of celecoxib, although they were developed before COX-2 was discovered [11]. pdCOX-2 inhibitors provide anti-inflammatory effects that are comparable with tNSAIDs that inhibit both COX isoforms while reducing the risk of serious gastrointestinal toxicity.

Following its introduction to US market in December 1998, celecoxib quickly became one of the most frequently prescribed drugs for the relief of pain and inflammation [12],

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Conflicts of interest
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although the data supporting a favorable gastrointestinal toxicity profile were much weaker than those of other compounds within the class [13]. Celecoxib, as well as other selective and nonselective NSAIDs, have been under intense scrutiny since 2004, when two pdCOX-2-selective inhibitors, rofecoxib (VIOXx) and valdecoxib, were withdrawn from the market due to an increased risk of cardiovascular events including myocardial infarction [14-16]. Etoricoxib and lumiracoxib were never approved in the US due to cardiovascular safety concerns. Celecoxib is the only pdCOX-2 inhibitor currently available in the US. For many patients with both severe arthritis and intolerance to nonselective NSAIDs due to gastrointestinal side effects, pdCOX-2 inhibitors provide significant clinical benefit. The clinical care of patients requiring anti-inflammatory pain therapy, as well as those at high risk of colorectal adenomas, would be greatly aided by measurements that identify the patients who will benefit from celecoxib, yet not suffer adverse events. This summary briefly reviews the pharmacokinetics of celecoxib (Fig. 1) and discusses the candidate genes mediating the diverse pharmacological profile of celecoxib (Fig. 2). Knowledge of the pharmacogenomics of these pathways may help to achieve personalization and optimization of celecoxib therapy.

Pharmacokinetics

After oral administration, celecoxib is rapidly absorbed and achieves peak serum concentration in approximately 3 h. It is extensively metabolized in the liver, with very little drug (< 3%) being eliminated unchanged [17]. The major routes of excretion for celecoxib are feces and urine [18]. Celecoxib is metabolized primarily through methyl hydroxylation to form hydroxycelecoxib. This reaction is largely catalyzed by CYP2C9, although CYP3A4 also plays a minor (< 25%) role [7,17,19] (Fig. 1). Hydroxycelecoxib is further oxidized to form carboxycelecoxib by cytosolic alcohol dehydrogenases ADH1 and ADH2 [19], then conjugated with glucuronic acid by UDP glucuronosyltransferases to form the 1-*O*-glucuronide. None of the metabolites are pharmacologically active [7].

As celecoxib metabolism is predominantly mediated by CYP2C9, polymorphisms in CYP2C9 are likely to have a direct impact on celecoxib pharmacokinetics and variability in drug responses. Individuals who are poor metabolizers of CYP2C9 substrates (e.g. CYP2C9*3 allele carriers) have an increased exposure to celecoxib when compared with those with normal CYP2C9 activity [19-21] (see ‘Pharmacogenomics’ section). Drugs that inhibit CYP2C9 should therefore be used with caution in patients taking celecoxib.

Although not a substrate of CYP2D6, celecoxib inhibits this metabolic enzyme [22]. Drugs that are metabolized by CYP2D6 (e.g. metoprolol [22]) should also be used with caution in patients receiving celecoxib due to a potential risk of drug interaction.

Pharmacodynamics

Celecoxib exerts its anti-inflammatory and analgesic activities through blocking the synthesis of various inflammatory prostanoids (PG) [7,8,23]. The prostanoids, which include PGs and thromboxane, are the end products of fatty acid metabolism produced by tissue-specific COX enzymatic activity. These products are important physiological and pathological mediators that are involved in a wide range of biological processes including inflammation, pain, cancer, glaucoma, osteoporosis, cardiovascular diseases, and asthma [24]. The production of the prostanoids (PG) is dependent on the availability of arachidonic acid (AA). Following stimulation of the cell membrane by inflammatory or mitogenic signals, the first step in PG synthesis is the release of AA from the cellular phospholipids through the action of either secretory (sPLA2, encoded by gene *PLA2G2A*) or cytoplasmic ($cPLA_2$, encoded by gene *PLA2G4A*) phospholipases. Once AA is released, the two isoenzymes, COX-1 (encoded by *PTGS1*) and COX-2 (encoded by *PTGS2*), catalyze the

production of the prostanoids (Fig. 2) [25]. As indicated above, this involves two sequential reactions. The initial COX reaction converts AA into PGG_2. The second reaction reduces PGG_2 to PGH_2. PGH_2 is then converted into active metabolites PGE_2, prostacyclin (PGI_2), thromboxane ($T\times A_2$), PGD_2, and $PGF_{2\alpha}$ by the action of tissue-specific PG synthases [26,27]. These active metabolites interact with specific prostanoid G-protein-coupled receptors to mediate diverse physiological responses, such as inflammation, fever, blood pressure regulation, clotting, and gastrointestinal protection.

The COX-1 and COX-2 enzymes exhibit distinct expression profiles and roles in physiological processes. COX-1 is constitutively expressed in many cell types and is the major COX isoform in gastric tissue. It is responsible for the protection of the gastric mucosa, which led to the development of the 'COX-2 hypothesis' that drugs targeted against COX-2 only would have reduced upper gastrointestinal toxicity [8]. Although COX-2 is highly inducible by inflammatory stimuli such as cytokines, growth factors, and tumor promoters [28-31], it is also constitutively expressed in some tissues, such as the vessel wall, the kidney, or the heart. Indeed, the depression of the physiological formation of COX-2-dependent prostanoids in these tissues has been identified as the molecular mechanism underlying the thrombotic cardiovascular complications of COX-2 inhibition [16]. Seven placebocontrolled, randomized trials with three chemically distinct pdCOX-2 inhibitors, including celecoxib, have documented the cardiovascular risk. Of note, celecoxib is now used at lower doses than in the trials that showed its cardiovascular hazard. Celecoxib has 30-fold greater inhibitory activity against COX-2 compared with COX-1, and inhibits COX-1 only minimally at therapeutic concentrations [32,33]. Although the selectivity for COX-2 measured *in vitro* is lower for celecoxib compared with other drugs in the coxib class (e.g. rofecoxib, valdecoxib, lumiracoxib, and etoricoxib), it is very similar at therapeutic concentrations *in vivo*. Celecoxib also retains more ability to inhibit COX-1 compared with other coxibs; however, the consequences of this with regard to its therapeutic efficacy and toxicity are not well understood [34-36].

Antineoplastic actions

Selective COX-2 inhibitors, especially celecoxib, have been evaluated as a potential cancer chemopreventive and therapeutic agent in clinical trials for various malignancies. Nonselective NSAIDs such as sulindac have been used since the 1980s as adjuncts to surgery for prevention of intestinal tumors in patients with FAP, a genetic condition that often leads to colorectal cancer [6]. Celecoxib has been shown to significantly reduce the number of colorectal polyps in patients with FAP as well as those with sporadic colorectal adenomas [4-6]. Celecoxib has also demonstrated anticancer effects in established invasive tumors, including colon carcinoma, lung carcinoma, and prostate cancer, both *in vitro* and *in vivo* [8,37-42]. The exact mechanisms for its anticancer activity are not clear and may involve both COX-dependent and COX-independent mechanisms [41,43,44]. A wide range of tumor-associated molecular events are modulated by celecoxib in in-vitro assays, but these have yet to be placed within a coherent context that clearly describes clinical responses and most COX-independent effects were only observed at supratherapeutic concentrations *in vitro* (reviewed by Grosch *et al*. [44]). Figure 2 shows that the candidate genes involved in the proposed anticarcinogenic mechanisms of celecoxib include induction of apoptosis, cell cycle arrest, regulation of angiogenesis, and induction of endoplasmic reticulum (ER) stress. Celecoxib-mediated inhibition of cell cycle progression has been observed in cell culture experiments along with an increased expression of cell cycle inhibitors, p21 (encoded by gene *CDKN1A*) and p27 (encoded by gene *CDKN1B*), and/or decreased expression of cyclins (encoded by gene *CCNA1*, *CCNB1*, and *CCND1*) [40,45-47]. Increased degradation of the oncoprotein, β-catenin (encoded by gene *CTNNB1*) is also observed in celecoxib-treated human colon cancer cells, and this is associated with marked reductions in tumor cell

proliferation [48]. Again, a major caveat is that these studies were conducted at concentrations *in vitro* that were 10–100 times higher than plasma concentrations measured in humans. Induction of apoptosis by celecoxib is associated with activation of proapoptosis molecules such as caspases and CHOP (encoded by gene *DDIT3*) [49], as well as inhibition of antiapoptotic molecules, such as PDK1 (encoded by gene *PDPK1*) and its downstream target AKT1 [38,50-52]. Finally, inhibition of angiogenesis and tumor cell invasiveness may also contribute to the antitumor activity of celecoxib. Celecoxib treatment decreased the expression of vascular endothelial cell growth factor [53-55] and inhibition of matrix metalloproteinase 9 [56] in cancer tissues and cell lines.

Besides COX-2, celecoxib can directly bind to and inhibit a few other targets that may play important roles in the antitumor response mechanism. PDK1 is a direct target of celecoxib and inhibition of PDK1/Akt signaling correlated with celecoxib-induced apoptosis in both colon and prostate tumor cell lines [38,50]. However, significantly higher concentrations of celecoxib (IC_{50} in micromolar range) are required for inhibition of PDK1 compared with that required to inhibit COX-2 (IC_{50} in nanomolar range). Celecoxib also binds to and inhibits sarcoplasmic/ER calcium ATPase [57]. This binding can lead to rapid leakage of calcium into the cytosol, triggers ER stress, and ultimately leads to apoptosis [58]. This activity is highly specific for celecoxib and has not been associated with other COX inhibitors. Carbonic anhydrases (CA), enzymes that catalyze the reversible hydration of carbon dioxide, are also inhibited by celecoxib (IC_{50} in the low nanomolar range) [59,60]. Some of the CAs (e.g. CA9 and CA12) are associated with tumor development [61,62]. However, no study has clearly demonstrated the relationship between inhibition of CAs and anticancer activity of celecoxib, and celecoxib used at therapeutic concentrations also did not appear to have a clinically significant inhibitory action on renal CAs [63].

Cardiovascular toxicity

Data from clinical trials and case–control studies have associated the use of selective COX-2 inhibitors, rofecoxib, valdecoxib, and celecoxib with an increased incidence of myocardial infarction, stroke, and death due to cardiovascular causes [5,64-67]. These toxicities were uncovered as secondary endpoints during trials testing coxibs for colorectal adenoma prevention and arthritis treatment. The US Food and Drug Administration currently mandates black-box warnings of increased cardiovascular hazards for the entire NSAIDs class. Available data suggest that this risk may increase with the duration of use and may also vary by a patient's individual baseline cardiovascular risk [16].

For celecoxib, the increased cardiovascular risk seems to be exposure dependent; both the dose and the dosing interval may be important factors in cardiovascular risk. In the Adenoma Prevention with Celecoxib (APC) trial, celecoxib 400 mg twice a day exhibited a greater than three-fold risk for combined endpoints of cardiovascular death, myocardial infarction, stroke, or heart failure compared with placebo, and 200 mg twice a day with a greater than two-fold risk [5,67]. Patients with higher baseline cardiovascular risk factors also tended to exhibit an increased risk. An evaluation of 5-year outcome data from the APC trial found a significant association between baseline cardiovascular risk factors and celecoxib-associated cardiovascular events [67]. The prevention of colorectal sporadic adenomatous polyps trial showed that the risk for cardiac disorders was higher in those taking celecoxib 400 mg once daily than in those on placebo [4,68]. In contrast, a number of clinical studies and a meta-analysis failed to demonstrate clear evidence of an increased thrombotic cardiovascular risk with celecoxib doses of less than or equal to 400 mg daily compared with placebo [42,69,70]. These analyses included data comparing coxibs with other nonselective NSAIDs. It is unclear whether nonselective NSAIDs also increase cardiovascular risk; therefore, these data cannot assess the relative safety of coxibs. In a more conclusive study, a pooled analysis of six randomized trials comparing celecoxib with

placebo concluded that cardiovascular risk for celecoxib-treated patients increases with dose, and that a once-daily dose is associated with lower cardiovascular risk than the twice-daily dose [18,71]. Patients in the high baseline cardiovascular risk group exhibited a disproportionately higher risk of an adverse event, whereas celecoxib did not cause a significant increase in cardiovascular events in the low-risk group, suggesting the importance of considering baseline cardiovascular risk for appropriate patient selection. In response to these data, the American Heart Association recommends that patients treated with celecoxib use the lowest effective dose for the shortest duration to minimize the potential risk for an adverse cardiovascular event. Patients with existing cardiovascular disease or risk factors for cardiovascular disease may be at greater risk and alternative therapy should be considered.

The mechanism underlying the increased cardiovascular risk of COX-2 inhibition has been studied extensively. The clinical events associated with coxib cardiovascular toxicity are primarily thrombotic in nature. The depression of COX-2-derived cardioprotective PGs, particularly PGI_2, and perhaps PGE_2, by the coxibs removes a physiological restraint on mediators that induce thrombosis, increase blood pressure, and promote atherogenesis [8,16,24,72-74]. One of these mediators is TxA_2, which is synthesized by COX-1 action in platelets. Long-term treatment with COX-2-specific inhibitors may create a prothrombotic environment and predispose patients to elevated cardiovascular risk. This may be particularly harmful for patients already predisposed to thrombosis due to the presence of atherosclerotic plaques in coronary or cerebral arteries. It is likely that the clinical safety of celecoxib may depend on a fine balance of multiple factors, especially given the complexity of the molecular system regulating atherothrombotic processes [75]. Inter-individual variability in drug metabolism, differences in the half-life of the drug, the effect on blood pressure [76], or endothelial function [77] may all contribute to the toxicity profile of coxibs or other NSAIDs. Simultaneous COX-1 inhibition may ameliorate the cardiovascular hazard of COX-2 inhibition [16]. For example, compared with other more selective COX-2 inhibitors (e.g. rofecoxib and valdecoxib), celecoxib has some activity against COX-1 and also seems to exhibit a relatively safer cardiovascular profile in randomized-controlled trials, especially when used at lower than 400 mg daily [69,78]. Observational studies suggest that the cardiovascular risk of the tNSAIDs is heterogeneous. Indeed, some tNSAIDs may have cardiovascular toxicity similar to that of the coxibs [79]. In addition to a simple dose–effect relationship, COX-independent ‘protective’ mechanisms have been discussed. For example, experiments showed that celecoxib, but not rofecoxib, caused a reduction in the excitability and contractility of cultured vascular smooth muscle cells and decreased vascular tone *in vitro*, by opening the voltage-gated KCNQ5 K + channels and blocking the L-type calcium channels [80,81]. However, research is needed to assess whether effects on ion channel can be observed *in vivo* and indeed result in vasodilation and reduced systemic blood pressure.

Pharmacogenomics

Multiple reports have shown that there is considerable variability both within and between individuals in the pharmacokinetic and pharmacodynamic responses toward celecoxib [34,35]. A large portion of the variability may be attributable to stable host factors including genetics. For example, polymorphisms in celecoxib-metabolizing enzymes or targets may affect its efficacy or toxicity. Several studies have reported associations between genomic variations of CYP2C9 and plasma drug levels of celecoxib, and a few have explored the role of other metabolizing enzymes and pharmacodynamic candidate genes/variants in drug efficacy, resistance, and adverse drug reactions. On the basis of data described below, celecoxib was one of the first drugs for which the manufacturers’ drug information recommended caution on the basis of pharmacogenetic information. The caution is raised for patients who are known or suspected to be poor CYP2C9 metabolizers and specifically

states that clinicians should 'consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e. CYP2C9*3/*3), and consider using alternative management in patients with juvenile rheumatoid arthritis who are poor metabolizers' (CELEBREX^{R} Package Insert, http://pfizer.com/files/products/uspi_celebrex.pdf).

CYP2C9 and pharmacokinetics

Celecoxib is metabolized primarily by CYP2C9, a phase I metabolizing enzyme responsible for the clearance of many drugs. The gene encoding the CYP2C9 enzyme is highly polymorphic, including several functional variants of significant pharmacogenetic importance [82,83]. Among individuals of European ancestry, the two most common variants associated with reduced enzyme activity are *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910) [82-84]. Both in-vitro and in-vivo studies found that celecoxib pharmacokinetics are altered in individuals carrying the *CYP2C9* variant alleles [19-21,85,86]. In-vitro study showed that CYP2C9-dependent methyl hydroxylation of celecoxib decreased by 34 and 90% in the presence of cDNA-expressed CYP2C9*2 and CYP2C9*3, respectively [21]. In human liver microsomes, the rate of celecoxib hydroxylation decreased in cells with heterozygous *CYP2C9*1/*3* (59% decrease) and CYP2C9*1/*2 (47% decrease) genotypes compared with those with *CYP2C9*1/*1* [21]. There was also a marked reduction (up to 5.3 times) in hydroxycelecoxib formation in a liver sample with a homozygous *CYP2C9*3/*3* genotype [20,21,86]. From two single-dose clinical studies (100 and 200 mg, respectively), the area under the curve (AUC) of celecoxib in individuals with *CYP2C9*1/*3* and *CYP2C9*3/*3* genotypes was more than or equal to two-fold higher than in those with the *CYP2C9*1/*1* genotype [20,21]. Similar results were observed in a steady-state pharmacokinetic study with twice-daily doses of celecoxib (200 mg) [85]. Yet another study showed that the AUC in a pediatric patient with the *CYP2C9*3/*3* genotype was more than 10-fold higher than that from two *CYP2C9*1/*1* patients following a single celecoxib dose (250 mg/m^2) [86]. The effect of *CYP2C9*2* on celecoxib pharmacokinetics seems to be much weaker than that of *CYP2C9*3* in most systems examined so far. Three studies showed that the *CYP2C9*1/*2* genotype had minimal impact on celecoxib hydroxylation and clearance *in vivo* [20,21,85] and the two studies found that the AUC of celecoxib in *CYP2C9*2/*2* patients did not differ statistically from the ones with the *CYP2C9*1/*1* genotype [20,85]. Surprisingly, a placebo-controlled crossover study showed that the *CYP2C9*2* variant was associated with elevated plasma concentrations of celecoxib (200 mg) 4 h after administration, whereas the *CYP2C9*3* variant had no effect on plasma concentrations [34]. The impact of other *CYP2C9* polymorphisms, such as *5, *6, *9, and *11, on the pharmacokinetics of celecoxib has not been evaluated.

CYP2C9 and clinical outcomes

Although the data presented above include some inconsistencies, it appears that the enzyme coded by the **2* allele, *CYP2C9*2*, shows a moderate decrease in activity, whereas the enzyme coded by the **3* allele, especially in the homozygous state, leads to a more marked decrease in activity when compared with the wild-type *CYP2C9* (also called *CYP2C9*1*) [87]. Patients expressing one or more reduced function alleles of the enzyme may have reduced celecoxib clearance, resulting in increased drug exposure and a greater risk for side effects [84]. The strongest data for a clinically relevant association between the CYP2C9 genotype and celecoxib activity come from the APC trial. This study randomized 2035 patients with a high risk of colorectal adenoma formation to either low-dose celecoxib (200 mg, twice daily), high-dose celecoxib (400 mg, twice daily), or placebo. The primary endpoint of the trial was the occurrence of one or more colorectal adenomas during a 3-year on-treatment interval. This trial also evaluated the influence of *CYP2C9*2* and *3 variants on celecoxib response [88]. Among all genotypes, celecoxib was associated with a dose-dependent reduction in adenoma, with high-dose celecoxib yielding a 5.6% greater reduction

in the 3-year cumulative incidence of adenoma compared with low-dose celecoxib. However, the additional benefit of the higher dose was restricted to those with the *CYP2C9*3* genotype (relative risk = 0.51; confidence interval = 0.30–0.87). Patients with the *CYP2C9*3* genotype treated with high-dose celecoxib showed a 19.7% greater reduction in adenoma incidence than those treated with low-dose celecoxib. In contrast, the high dose was not associated with significant risk reduction among patients with *CYP2C9*2* or wild-type genotypes. These data, therefore, showed that the beneficial effect of higher drug dose was realized only in the slow metabolizers.

There is limited evidence linking *CYP2C9* genotypes to variability in celecoxib-induced toxicity, such as gastrointestinal bleeding and cardiovascular toxicity. In patients using celecoxib for acute arthritis management, the presence of *CYP2C9*3* and *CYP2C9*2* alleles was associated with a significantly higher risk of developing gastrointestinal bleeding [89-92]. However, these data were not conclusive, because the sample size of celecoxib users among all NSAIDs users included in these studies was small. There was no relationship found between the *CYP2C9* variant genotype and the risk of gastrointestinal bleeding in patients from the large APC trial, which had the advantage of a placebo comparison arm [88]. The APC trial also examined the relationship between the CYP2C9 genotype and celecoxib-associated cardiovascular toxicity. Compared with placebo, a higher incidence of cardiovascular and thrombotic events was observed for those with the CYP2C9 variant genotype using high-dose celecoxib. Despite the considerable size of the trial, however, the overall cardiovascular toxicity event rate was low, making it impossible to determine whether or not the CYP2C9 genotype affected either the event rate or the dose response.

Pharmacodynamic candidate genes

There are limited data with regard to the impact of pharmacodynamic candidate genes on celecoxib response and toxicity. A study with 50 healthy volunteers showed that the Pro17Leu variant in the signal peptide of the COX-1 enzyme was associated with a failure by either celecoxib or rofecoxib to inhibit thromboxane formation [34]. Variants in COX-2 (*PTGS2*), the primary target of celecoxib, were also examined for their impact on celecoxib response in this study; however, no association was found between variant rs5273 in *PTGS2* and any phenotype [34]. Another variant in *PTGS2*, − 765G > C (rs20417), did not modulate celecoxib effects on PG production in an ex-vivo whole blood assay [93]. Finally, 15-hydroxyprostaglandin dehydrogenase (15-PGDH, encoded by gene *HPGD*), an enzyme responsible for the metabolism of PGs and an inhibitor of the colonic COX-2 pathway, has been associated with resistance to celecoxib [94]. In mice lacking 15-PGDH, celecoxib adenoma preventive activity is abrogated. 15-PGDH levels are variable among adenoma patients, and low 15-PGDH levels correlated with celecoxib resistance in a small subset of patients with recurrent colon adenomas from the APC trial. Further work is needed to validate this result and uncover the genomic determinants of 15-PGDH expression.

Summary

The selective COX-2 inhibitor, celecoxib, shows a complex but important pharmacogenomics profile. The use of this highly effective anti-inflammatory and antitumor drug is limited by concerns about its potential for increased cardiovascular risk. Although the mechanism of action of celecoxib is well studied and many large clinical trials have examined its efficacy, we still lack a complete understanding of the sources of variability in the occurrence of adverse effects as well as the differential risk profile for all drugs in the NSAID class. Preliminary work showed that genetic factors influence response to celecoxib and may be useful in selecting individuals at risk for adverse events. However, the existing pharmacogenetic studies of celecoxib toxicity are still exploratory, with limited sample size

and limited number of events. NSAIDs are widely used, and the lower gastrointestinal toxicity of the coxibs represents an important potential advantage over nonselective NSAIDs, as long as we can identify those at an increased risk for cardiovascular toxicity. Larger outcome trials and comprehensive analysis of both pharmacokinetic and pharmacodynamic candidate genes are needed to identify genetic markers to predict variations in response and celecoxib-induced adverse events.

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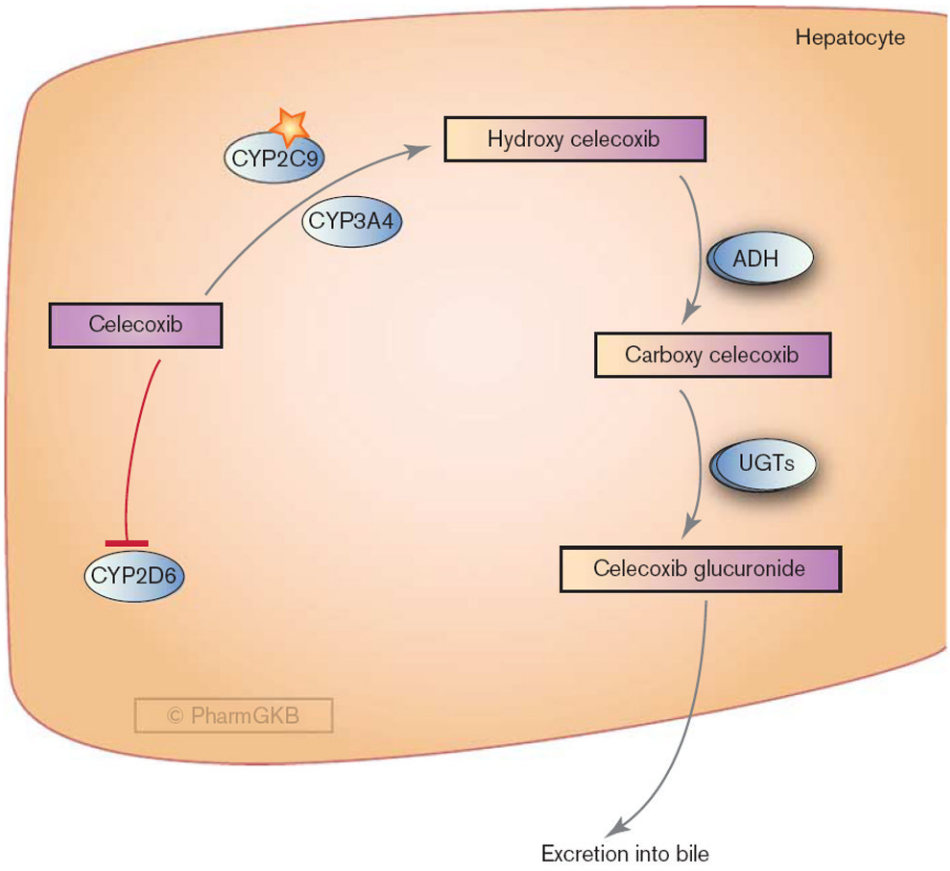

Fig. 1.

Hepatic metabolism of celecoxib. ADH, alcohol dehydrogenases; UGTs, UDP glucuronosyltransferases. A fully interactive version is available online at http://www.pharmgkb.org/pathway/PA165816736.

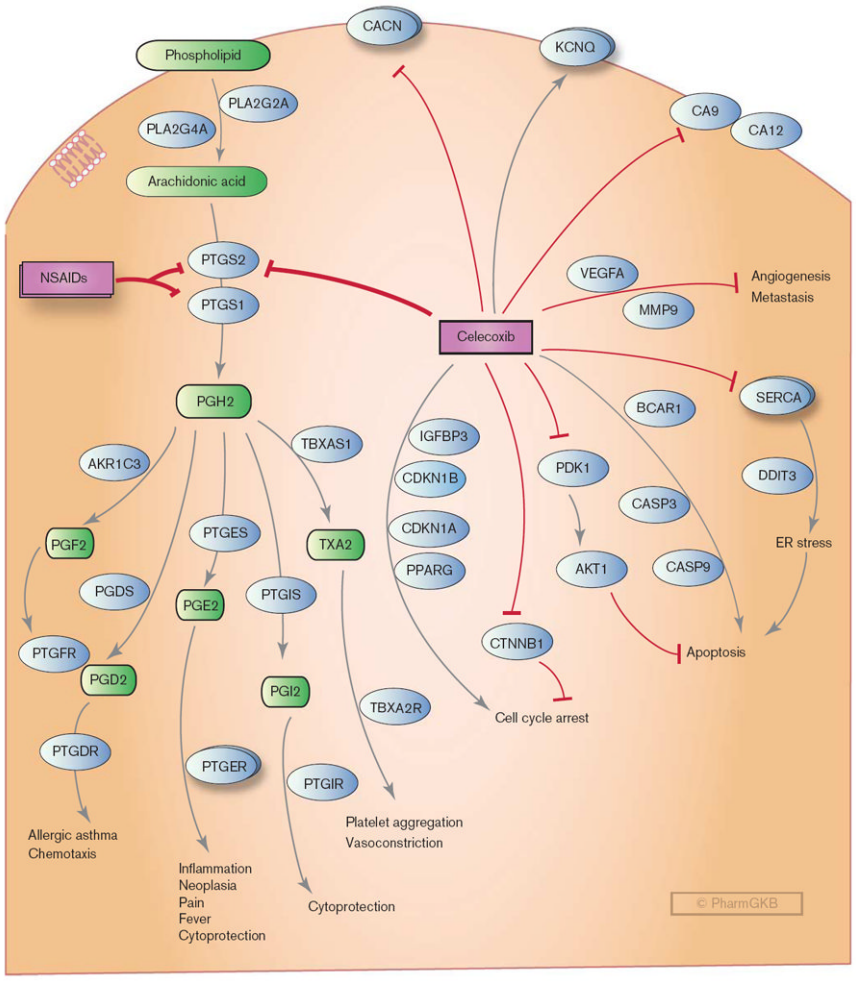

Fig. 2.

Stylized cell depicting the mechanism of action of celecoxib and candidate genes interacting with celecoxib and involved in the proposed anticancer mechanisms of celecoxib, including induction of apoptosis, cell cycle arrest, regulation of angiogenesis, and induction of endoplasmic reticulum (ER) stress. CACN: L-type calcium channels; KCNQ: voltage-gated potassium channels; MMP9, metalloproteinase; NSAIDs, nonsteroidal anti-inflammatory drugs; PGH2, prostaglandin H2; PGE2, prostaglandin E2; PGI2, prostacyclin; PGD2, prostaglandin D2; PGF2, prostaglandin F2; PTGER, prostaglandin E receptors; SERCA, sarcoplasmic/ER calcium ATPases; TXA2, thromboxane A2; VEGFA, vascular endothelial cell growth factor. A fully interactive version is available online at http://www.pharmgkb.org/pathway/PA152241951.