Promiscuous regulator of xenobiotic removal

The transcription factor SXR mediates drug, xenobiotic and steroid induction of a major drug–metabolizing enzyme. Drugs such as paclitaxel (Taxol) can bind and activate this transcription factor and therefore regulate their own metabolism and efflux from cells. Manipulation of this pathway might lead to new ways to improve therapeutic efficacy and to minimize toxicity (584-590).

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The body responds to drugs, environmental chemicals, endogenous steroids and bile acids by inducing the coordinated expression of a battery of drug-detoxification genes in tissues such as liver and intestine. These include the cytochromes P450 (CYPs), which are the enzymes responsible for oxidative, peroxidative and reductive metabolism of toxic compounds. Expression of drug transport proteins such as P-glycoprotein (encoded by *MDR1* and also known as MDR1 and ABCB1) leads to the efficient efflux these drugs from the body. Activation of drug transport can be beneficial in instances where it is important to remove toxins from the body, but detrimental in situations where it is important for a patient to retain effective levels of a therapeutic drug. In this issue, Snyold *et al.*[1] demonstrate that steroid xenobiotic receptor (SXR; also known as PXR), a transcription factor known to mediate drug, xenobiotic and steroid induction of the major liver drug metabolizing enzyme, can also regulate the expression of a drug efflux pathway, indicating a novel strategy to control drug clearance.

CYP3A4, the most abundant drug-metabolizing enzyme in the liver and intestine, is responsible for the metabolism of 50% of all drugs. Many drugs are substrates for both CYP3A4 and P-glycoprotein, a broad-specificity efflux pump protein encoded by the gene *MDR1*. It was first demonstrated in 1996 that *MDR1* expression is coordinated with expression of *CYP3A4*, with both gene products being induced by the same spectrum of drugs[2]. P-glycoprotein and CYP3A4 are colocalized in liver and intestine, and serve as a coordinated system for the absorption, metabolism and disposition of many drugs. Many drug–drug interactions arise from concurrent administration of drugs which are both substrates and inducers of *CYP3A4* and *MDR1* expression[3]. Long-term therapy with drugs that induce *CYP3A4* and *MDR1* increase the systemic clearance of some antileukemic agents, and such therapy has been shown to exert negative effects on survival while increasing cancer relapse[4]. Recent studies have shown that SXR, a member of the nuclear hormone receptor superfamily, regulates expression of *CYP3A* (ref. 5,6). SXR is activated by a pharmacopia of drugs, including antibiotics, statin cholesterol-lowering drugs, antiseizure medications, steroids such as glucocorticoids[5], some bile acids[7], environmental contaminants such as organochlorine pesticides and polychlorinated biphenyls[8], and herbal supplements such as St. John's wort[9].

Little is known about how certain drugs induce *CYP* and *MDR1* gene expression. Synold *et al.*[1] demonstrate that SXR is activated by paclitaxel (Taxol) and is responsible for inducing expression of not only *CYP3A* (previously shown to be induced by paclitaxel[10]) but also *CYP2C9* and *MDR1*. Paclitaxel is metabolized by both CYP3A4 and CYP2C9 (ref. 11) and transported by P-glycoprotein, and induction of all of these proteins leads to its enhanced clearance[12]. This indicates a broad role for SXR in the coordinated induction of multiple detoxification pathways.

Because concurrent administration of CYP3A4 and P-glycoprotein inducers (such as rifampicin) with drugs that serve as substrates for these proteins is a major basis of drug–drug interactions[5], pharmaceutical companies are now using SXR-binding and -activation assays to screen and predict which compounds will induce CYP3A expression and potentially cause drug interactions. These types of assays may also identify compounds that induce *CYP2C9* and *MDR1*, and cause auto-induction of their own clearance. It might be possible to someday create drugs that are 'SXR transparent' by minimizing or eliminating binding activity. In this regard, the report of Synold *et al.*[1] shows that docetaxel, unlike the structural analog paclitaxel, does not induce *CYP3A4* or *MDR1* expression because it does not activate SXR. This should result in superior pharmacokinetic properties relative to paclitaxel.

Synold *et al.*[1] demonstrate that Ecteinascidin-743 (ET-743), an antineoplastic agent, can antagonize SXR activation and inhibit *MDR1* expression. The authors suggest that SXR antagonists that downregulate the P-glycoprotein pathway of drug elimination could be exploited to improve drug retention. This approach should be undertaken cautiously, because clinical trials involving drugs that inhibit P-glycoprotein activity, given in an effort to reduce drug resistance, have had limited success and led to undesired pharmacokinetic side-effects[13]. *MDR1* expression 'modulators' should be carefully screened for their potential to inhibit or modulate metabolism of other medications taken by a patient. Given the knowledge that SXR has multiple detoxification genes as targets, antagonism of SXR might lead to increased drug toxicity.

Synold *et al.*[1] emphasize the feed forward pathways of drug clear-

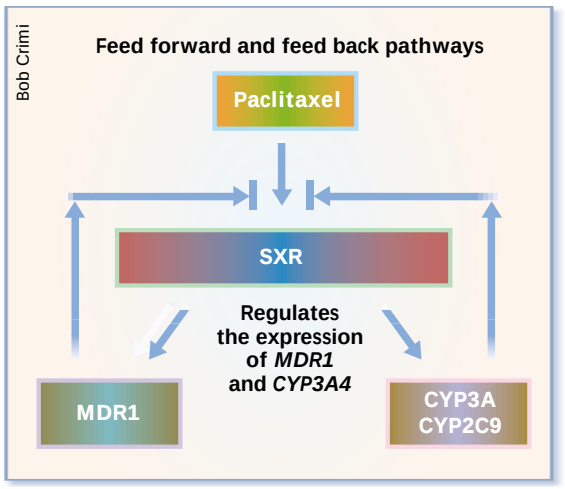

Fig. 1 Feedforward and feedback pathways of drug metabolism. Paclitaxel is a ligand for SXR, causing this nuclear receptor to activate transcription of the P-glycoprotein efflux pump protein encoded by *MDR1*, and the drug metabolizing enzymes CYP3A and CYP2C9. These pathways, however, mediate drug clearance and reduce paclitaxel activation of SXR in a feedback mechanism. Manipulation of this pathway may be used to prolong or reduce drug retention.

ance, in which paclitaxel binds and activates SXR, leading to expression of *CYP3A4*, *CYP2C9* and *MDR1*. Expression of these enzymes leads to paclitaxel metabolism and clearance (Fig. 1). There is also a feedback pathway where the gene products that are expressed as a result of SXR activation ultimately control the strength and duration of SXR response. For example, the level of CYP3A expression in response to a drug that is both an SXR ligand and P-glycoprotein substrate is determined by the cellular levels of the *MDR1* transporter[14]. Concurrently, paclitaxel activation of SXR is reduced by removal of parent compound by CYP3A4 and CYP2C9 metabolism, along with P-glycoprotein–mediated efflux. The *yin* and the *yang* of the opposing pathways remain in a self-maintained balance. Further study of this elegant system for coordinating the metabolism and excretion of compounds could lead to the development of more effective, less toxic drugs.

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VIP: A very important protein in arthritis

Many studies have shown that immune system modulation can be used to treat various forms of arthritis. A vasoactive intestinal peptide has recently been shown to have potent anti-inflammatory effects, indicating a new therapeutic approach for inflammatory arthritis (pages 563-568).

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Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting about 1% of adults[1]. The disease is usually marked by synovial inflammation and hyperplasia in the small joints of the hands and feet, although larger joints are frequently affected. Treatment of RA, though greatly improved in the last decade, remains an unmet medical need. Even with the advent of novel therapeutics like inhibitors of TNF-α and IL-1, a significant percentage of patients continue to exhibit signs and symptoms of synovitis. In this issue, Delgado *et al.*[2] describe how administration of the vasoactive intestinal peptide (VIP) suppresses inflammatory arthritis, providing new insight into the mechanisms of this disease.

The pathogenesis of RA is not fully understood and many different cell types are involved in the decades-long process of synovial of inflammation and joint destruction. Although macrophages and fibroblast-like synoviocytes are the primary sources of the pro-inflammatory cytokines and proteolytic enzymes that mediate joint damage, $CD4^+$ T cells probably have a key role in the initiation and perpetuation of disease. Over 10 years ago, studies of RA patients indicated that synovial T cells are relatively quiescent and produce surprisingly few cytokines compared with other T-cell–mediated chronic diseases[3]. More recently, low levels of several Th1 cytokines such as IFN-γ and IL-17 have been identified in RA synovium, whereas Th2 cytokines such as IL-4 are nearly absent[4]. The current paradigm proposes that in the rheumatoid synovium, a Th1 bias underlies chronic synovial inflammation. Conversely, a lack of Th2 cytokines, which antagonize many Th1 functions and can directly suppress effector molecule production by synoviocytes, leads to uncontrolled Th1-type responses[5]. Therefore, enhancement of Th2 function and suppression Th1 cells has been proposed as a therapeutic approach to RA.

The findings of Delgado *et al.*[2] support this hypothesis by demonstrating that VIP treatment dramatically suppresses clinical joint disease in murine collagen-induced arthritis (CIA). VIP regulates adaptive and innate immune responses[6], and also causes secretory diarrhea in patients with VIP-producing tumors. Although VIP is considered to be an immunosuppressant, it is now clear that VIP has multiple, complex functions. Its pleotropic actions have a salutary effect on both inflammation and immunity in the CIA model. For example, VIP suppresses Th1 cell function and differentiation, as demonstrated by the decreased IFN-γ expression. On the other hand, Th2 function is enhanced in VIP-treated mice, as determined by the observed increased in IL-4 production. VIP-treated mice produced lower levels of anti-type II collagen antibodies, indicating a downregulation of B-cell responses.

Delgado *et al.*[2] also report that VIP treatment suppresses production of pro-inflammatory mediators, as well as expression of the metalloproteinase gelatinase (MMP-2). MMP-2 is believed to contribute to joint destruction in paws of arthritic mice. *In vitro* studies indicate that VIP may act directly on synoviocytes, although an indirect ac-