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Taxane Pathway

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Overview

Taxanes, such as paclitaxel and docetaxel, are widely prescribed chemotherapeutic drugs [1-3]. They have been used to treat many forms of cancer including breast, ovarian and lung cancers [1]. Paclitaxel was isolated from the Pacific yew in 1971 and docetaxel, a second generation taxane, is a semi-synthetic taxane analogue from the European yew identified approximately 20 years later [2]. The pathway above depicts the known candidate pharmacogenes involved in the pharmacokinetics and pharmacodynamics of taxanes.

Microtubules display a form of non-equilibrium dynamics referred to as dynamic instability that is essential to cell division [3]. Dynamic instability is regulated by microtubule-associated proteins (MAPs) including *MAPT*, *MAP2* and *MAP4* [3]. In an un-phosphorylated state, the MAP proteins bind and stabilize microtubules, leading to cell death [3].

Microtubules are composed of α -tubulin and β -tubulin heterodimers [1]. Taxanes block cell division by binding to β -tubulin, stabilizing the microtubules, leading to cell death [1,4]. A 3.5Å structure of bovine β -tubulin, with bound paclitaxel, can be found in the Protein Data Bank [5], entry 1JFF [6]. In addition, *in vitro* studies have shown taxanes to induce *BCL2* phosphorylation and apoptosis, with docetaxel doing so at much lower concentrations than paclitaxel [7,8].

While paclitaxel and docetaxel share many common structural features, their pharmacology and pharmacokinetics differ somewhat. Consequently, in some patients, solid tumors with resistance to paclitaxel have been shown to be sensitive to docetaxel [9,10].

The pharmacokinetics of taxanes are complex and are complicated by their different formulations [11]. Both taxanes are primarily metabolized in the liver and their primary route of elimination of the parent drug and hydroxylated metabolite is through biliary excretion via feces [2]. Early work found that docetaxel had linear pharmacokinetics but paclitaxel did not [2,12]. However, the two taxanes have different formulations: paclitaxel is dissolved in Cremaphor EL (CrEL, poly-oxyethyleneglycol triricinoleate 35)/ethanol (1:1)

whereas docetaxel is dissolved in polysorbate 80 (Tween 80) [13]. Tween 80 was found to alter the fraction of unbound docetaxel in patients [13] and another study found that in the absence of CrEL, the bioavailability of intraperitoneal paclitaxel was significantly increased [14]. Various other studies have shown that CrEL alters the pharmacokinetic behavior of many drugs, including paclitaxel [13,15]. Finally, a small study of the recently available, 130-nm albumin-bound (nab) particle formulation of paclitaxel, devoid of solvents, found that the disposition of paclitaxel is subject to considerable variability, depending upon the formulation used [16].

Both paclitaxel [17,18] and docetaxel [17,19-21] are metabolized by *CYP3A4*. Paclitaxel is also metabolized by *CYP2C8* [22,23], while docetaxel is also metabolized by *CYP3A5* [21]. In an *in vitro* study, a highly significant induction level of PXR (gene *NR1I2*) -mediated *CYP3A4* expression was observed for paclitaxel, whereas docetaxel only moderately increased *CYP3A4* expression [24]. In another study, paclitaxel activated PXR, but docetaxel did not [25]. Paclitaxel was also found to activate PXR and enhances P-glycoprotein (*ABCB1*) mediated drug clearance [25] and *ABCB1* expression [26] as well as *CYP2C8* expression [27].

Both paclitaxel and docetaxel are substrates for the ATP binding cassette multidrug transporters *ABCB1*, *ABCG2*, *ABCC1* and *ABCC2* [28-34]. OATP1B3 (*SLCO1B3*) was identified as the most efficient influx transporter for docetaxel [35] and identified as a key regulator of paclitaxel hepatic uptake [36,37]. OAT2 (*SLC22A7*) was found to transport paclitaxel in *in vitro* experiments [38].

Taxane resistance is frequent [3,39,40]. Possible mechanisms for such resistance are many, but definitive data for the causes of resistance remain unclear. There are several genes that encode α - and β -tubulins and different tubulins also arise from different post-translational modifications [41]. Such structural diversity makes comparative analysis between tubulins in drug-sensitive and drug-resistant cell lines difficult [42]. Exposure to taxane creates somatic mutations in tubulins, but the relationship of somatic mutations to resistance remains unclear, even for those mutations near the taxane binding site [43]. While an early study found a relationship between mutations in the tubulin-encoding *TUBB* gene and paclitaxel treatment response and clinical outcome (in tissue samples of patients with advanced non-small-cell lung cancer) [44], numerous other genetic and mutational analysis of the gene in cell lines and patients with lung cancer, breast cancer and ovarian cancer did not find such a relationship [45-54], suggesting that mutations in *TUBB* do not play a role in taxane resistance. Genetic and mutational analysis of the *TUBB* gene has been complicated due to the presence of several pseudogenes with high homology to the wild type gene [52,53]. Increased expression level of tubulins as a mechanism for resistance remains contradictory, although there is growing evidence that this does lead to resistance for particular tubulins [43]. Recently, high levels of chromosomal instability, and the genes involved in this instability, have been found to be related to taxane resistance [55]

Pharmacogenetics

The impact of genetic variants on taxane response is unclear: several studies did not find relationships between polymorphisms of genes in the taxane pathway, while others did. For example, in a large study (n=914) of ovarian cancer patients from the Scottish Randomized Trial in Ovarian Cancer (SCOTROC) phase III trial who were treated at presentation with carboplatin and taxane regimens, no association between polymorphisms of genes in the pathway and taxane response was found [56]. This study assessed polymorphisms in 11 genes (*ABCB1*, *ABCC1*, *ABCC2*, *ABCG2*, *CDKN1A*, *CYP1B1*, *CYP2C8*, *CYP3A4*, *CYP3A5*, *MAPT*, and *TP53*) and found no reproducible significant associations between genotype and

outcome or toxicity [56]. Similarly, in two other studies, no significant association was seen between *ABCB1*, *ABCG2*, *CYP1B1*, *CYP3A4*, *CYP3A5* and *CYP2C8* genotypes and paclitaxel clearance or *ABCB1*, *CYP2C8*, *CYP3A4* and *CYP3A5* and paclitaxel clearance [57,58].

In contrast, other studies of genes in the taxane pathway did find associations between polymorphisms of the genes and either patient survival or drug response. With respect to survival, one study found rs1056836, *CYP1B1**3 (4326 C>G; L432V) allele, was significantly associated with progression-free survival, independent of paclitaxel clearance [57]. The same SNP was also associated with survival in patients receiving docetaxel [59]. In a recent study of patients with metastatic breast cancer, the synonymous variant rs1045642 (*ABCB1*: 3435 C>T), showed a significantly lower disease control rate and lower overall survival rate than the CC genotype for the variant allele [60].

Other small studies have found associations between variants of *ABCB1* and taxane pharmacokinetics. One small study of Japanese patients found associations with *ABCB1* polymorphisms, including paclitaxel pharmacokinetics and *ABCB1* variants [61]. Another small study of Japanese patients found that those with the *ABCB1*:3435C>T (rs1045642) allele had a significantly higher AUC of a paclitaxel metabolite when compared to those possessing the 3435C allele [62]. Other studies associated *ABCB1*: 2677G>T/A with response to paclitaxel [63], response to taxane- and platinum-based chemotherapy [64] and gastrointestinal toxicity [64]. A combination of *ABCB1*:2677G>T/A and *ABCB1*:3435C>T (rs1045642) genotypes have been associated with neutropenia from paclitaxel therapy [65]. A recent small study of Caucasian patients found that the interindividual variability in paclitaxel clearance to be related to variants in *ABCB1*; in particular, patients heterozygous for G/A in position 2677 in *ABCB1* had a significantly higher clearance of paclitaxel than most other *ABCB1* variants [66].

That same study found variability in paclitaxel clearance to also be related to *CYP2C8* genotype; the *CYP2C8**3 had lower clearance of paclitaxel [66]. Another recent small study of docetaxel clearance found greater clearance with patients with the *CYP3A4**1B and *CYP3A5**1A alleles [35]. Most of these findings remain to be validated.

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