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## Review

## Mitochondria: The gateway for tamoxifen-induced liver injury

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## ABSTRACT

Tamoxifen (TAM) is routinely used in the treatment of breast carcinoma. TAM-induced liver injury remains a major concern, as TAM causes hepatic steatosis in a significant number of patients, which can progress toward steatohepatitis. Liver toxicity is generally believed to involve mitochondrial dysfunction and TAM exerts multiple deleterious effects on mitochondria, which may account for the hepatotoxicity observed in patients treated with TAM. Endoxifen (EDX), a key active metabolite of TAM that is being investigated as an alternative to TAM in breast cancer therapy, slightly affects mitochondria in comparison with TAM and this demonstration well correlates with the absence of alterations in the clinical parameters of individuals taking EDX. The steady-state plasma concentrations of TAM and its active metabolites EDX and 4-hydroxytamoxifen (OHTAM) in patients taking TAM are highly variable, reflecting genetic variants of CYP2D6 involved in TAM metabolism. Besides de genetic polymorphisms, the intake of drugs that influence the enzymatic activity of CYP2D6 compromise the therapeutic efficiency of TAM. The knowledge of the impact of the variability of TAM metabolism in the breast cancer treatment explains the discrepant outcomes observed in patients taking TAM, as well as the individual variability of idiosyncratic liver injury and other sides effects observed. Therefore, and contrarily to the clinical use of EDX, the need of therapeutic drug monitoring and a regular assessment of liver function biomarkers should be considered in patients under therapies with TAM. In this review we focus on the mitochondrial effects of TAM and its metabolites and on the role played by mitochondria in the initiating events leading to TAM-induced hepatotoxicity, as well as the clinical implications.

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## Contents

1. Introduction .....	00
2. Overview of mitochondrial functions .....	00
2.1. Bioenergetic functions .....	00
2.2. Mitochondrial permeability transition .....	00
3. Effects of tamoxifen and its active metabolites on mitochondrial bioenergetics .....	00
3.1. Tamoxifen exerts multiple effects on bioenergetic functions .....	00
3.2. Tamoxifen active metabolites slightly affect mitochondrial bioenergetics in comparison with the prodrug .....	00
4. Tamoxifen and its metabolites inhibit mitochondrial permeability transition pore opening .....	00
5. Concluding remarks .....	00
Conflicts of interest .....	00
Transparency document .....	00
Acknowledgments .....	00
References .....	00

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## 1. Introduction

The antiestrogen tamoxifen (TAM) is the hormonal therapy of choice for patients who exhibit estrogen receptor positive breast cancer. In the adjuvant setting, TAM reduces the risk of recurrence and death from breast cancer and offers palliation for patients with metastatic disease as well (Yang et al., 2013). However, although relatively well tolerated compared with cytotoxic chemotherapy, TAM induces several adverse effects. TAM treatment is associated with an increased incidence of vaginal bleeding, endometrial polyps, endometrial thickening, and ovarian cysts (Baum, 2002). Moreover, according to several trials performed, hot flushes are reported by approximately 40% of the women taking TAM (Baum, 2002). Less common is the long-term risk of endometrial cancer and thromboembolic disease (Braithwaite et al., 2003). TAM has been associated with a decreased bone mineral density in premenopausal women, whereas an increase in postmenopausal women is observed (Ramaswamy and Shapiro, 2003). Moreover, TAM-induced liver injury remains a major concern (Ching et al., 1992; Oien et al., 1999; DeLeve, 2007). Adult female rats treated with TAM (10 mg/kg/day perorally) presented a significant increase in serum lipid profiles, liver enzymes, and bilirubin level (Ibrahim et al., 2013). TAM produced a significant increase in lipid peroxides level and a significant decrease in superoxide dismutase activity of hepatic tissue (Ibrahim et al., 2013). Indeed, relatively high concentrations of TAM and its metabolites were detected in the liver (Lien et al., 1991) and were shown to be positively correlated to age (Lien et al., 2013).

Liver toxicity is often revealed by different patterns of elevated liver enzymes. In TAM-treated ovariectomized female rats, alkaline phosphatase (ALP) and aspartate aminotransferase (AST) were significantly higher than in control females (Moreira et al., 2007). Using isolated perfused rat liver, TAM at 20  $\mu$ M was shown to promote the release of fumarate (mainly mitochondrial) and lactate dehydrogenase (mainly cytosolic), and these effects were much faster when higher concentrations of TAM (above 50  $\mu$ M) were used (Marek et al., 2011). Accordingly, patients taking both chemotherapy and TAM had a higher incidence of elevated transaminases than those on TAM alone, suggesting that chemotherapy may induce a higher degree of hepatocellular damage than does TAM individually (Liu et al., 2006).

In addition, hepatocytes treated with TAM presented hepatocyte steatosis and increased hepatocyte triglycerides and the expression of several proteins involved in the fatty acid synthesis were upregulated (Zhao et al., 2014). Accordingly, in 14 of 116 breast cancer patients on adjuvant TAM therapy at a dose of 10 mg twice daily, the triglyceride levels were significantly increased (above 400 mg/dL), but in 10 of 14 patients the triglyceride levels were lowered to a safer level after the dose of TAM was reduced to 10 mg once daily (Liu and Yang, 2003). A case of TAM-induced acute pancreatitis following alterations in serum lipid metabolism with positive rechallenge was also reported (Sakhri et al., 2010). A dose reduction was investigated as an attempt to decrease the adverse effects without compromising its activity in reducing breast cancer risk, since the triglyceride levels were shown to have a trend to increase in a dose-dependent manner (Decensi et al., 1999).

In mice treated with TAM (0.5 mmol/kg daily), hepatic steatosis was absent at 5 days, mild at 12 days, and moderate at 28 days (Larosche et al., 2007) and more than 30% of patients taking TAM develop fatty liver (Günel et al., 2003; Nishino et al., 2003; Liu et al., 2006). In the study conducted by Liu et al. (2006), TAM-induced fatty liver persisted for 48 months after discontinuing TAM in 20% of patients who developed it, pointing out that long-term follow-up of these patients is warranted. On a different study, TAM was associated with an increased risk of developing fatty liver disease,

but this association was restricted to overweight women; other predictors of fatty liver included hypercholesterolaemia and hypertension (Bruno et al., 2005). Nonalcoholic steatohepatitis (NASH) was present in 2.2% of the patients with breast cancer treated with TAM (Saphner et al., 2009). Some patients also develop hepatic fibrosis, cirrhosis and hepatic necrosis (Oien et al., 1999; Storen et al., 2000; Farrell, 2002). The elevation of alanine aminotransferase (ALT) up to  $\geq 1.5$  times the normal upper limit in women receiving TAM was shown to accurately predict the presence of fibrosis at histology, thus reducing the need for liver biopsy (Bruno et al., 2005). The pathogenesis of NASH is not fully understood, but it is thought that a baseline of steatosis requires a second hit capable of inducing inflammation, fibrosis or necrosis for NASH to develop (Osman et al., 2007). It is possible that TAM may act as the second hit by increasing serum triglyceride levels and reducing hepatic lipid  $\beta$ -oxidation, this way enhancing hepatic fat content (Osman et al., 2007). In fact, TAM induced hepatotoxicity is especially frequent in breast cancer patients with pre-existing liver steatosis (Floren et al., 1998; Elefsiniotis et al., 2004). In addition, serum leptin levels were found to be significantly elevated in patients with hepatic steatosis after TAM treatment (Günel et al., 2003).

Although TAM is a drug capable of inducing hepatotoxicity caused by mitochondrial dysfunction, it was not withdrawn from the market considering the favorable benefit-risk ratio, but it has received a Black Box warning from drug agencies (Labbe et al., 2008). Therefore, the mechanisms underlying TAM-induced liver injury deserve a closer look.

It is generally believed that mitochondrial dysfunction is a major mechanism whereby drugs can promote liver toxicity (Labbe et al., 2008; Nadanaciva and Will, 2011a,b; Naven et al., 2013). Indeed, the evaluation of drug-induced mitochondrial damage has received considerable attention in the last years, as the study of the effects of drugs on mitochondria allows for a better understanding of the pharmacological and toxicological mechanisms underlying the mode of action of drugs. Isolated mitochondria fractions have been shown to predict drug safety, while decreasing the number of laboratory animals and the costs of preclinical studies. Moreover, considering the exposure to high concentrations of drugs, the liver is often a target of mitochondrial toxicity (Nadanaciva and Will, 2009). Drugs can damage hepatic mitochondria in some individuals but not in others, and our current knowledge does not allow to predict the idiosyncratic liver injury related with drug-induced mitochondrial dysfunction (Hewitt et al., 2013). Interestingly, it was recently reported a gene expression signature in rat liver for detecting a specific type of oxidative stress related to reactive metabolites (OS/RM), which the authors suggest that may be useful to avoid idiosyncratic hepatotoxicity (Leone et al., 2014). TAM was identified as a drug capable of inducing OS/RM (Leone et al., 2014). It seems that genetic, metabolic and environmental factors that impair mitochondrial function can add their effects to those of mitochondria-targeting drugs, compromising mitochondrial function to an extent where hepatic manifestations start to occur (Labbe et al., 2008). In addition, drug-induced mitochondrial dysfunction can also trigger extrahepatic or general manifestations. The syndromes associated to mitochondrial toxicity are not uncommon and include lactic acidosis, myopathy, peripheral neuropathy, rhabdomyolysis and pancreatitis (Scatena et al., 2007; Labbe et al., 2008; Nadanaciva and Will, 2009, 2011b).

Since TAM largely accumulates inside mitochondria (Larosche et al., 2007; Theodossiou et al., 2012) and it is known to induce several effects on mitochondria (Hewitt et al., 2013), this review focus on the effects of TAM and its metabolites on mitochondrial functions and the mechanistic rationale underlying the initiating events leading to hepatotoxicity is discussed.

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