ELSEVIER

EJC Supplements Vol 2 No. 9 (2004) 24–25

EJC Supplements

www.ejconline.com

E5. Selective oestrogen receptor modulator's (SERM's) added to the list of human carcinogens

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In 1996, tamoxifen, a selective oestrogen receptor modulator (SERM)-type drug and one of the most successful and widely prescribed anti-neoplastic agents worldwide, was classified by International Agency for Research on Cancer-World Health Organisation (IARC-WHO) as a 'group-one' human carcinogen [1]. Similar carcinogenic qualities are now emerging for toremifene, a fellow SERM. The mechanistic basis for tamoxifen carcinogenicity has been explored by numerous researchers and has largely focused upon the potential, as seen in experimental animals, for the drug to be metabolised to genotoxic species that bind covalently to DNA and cause mutation. The presence of such DNA adducts in human tissues and, most importantly, in the target tissue, the endometrium, has been the source of considerable debate. Initial studies, seeking the presence of tamoxifen-DNA adducts in patients treated with the drug and analysed by the ^{32}P-post-labelling technique, failed to find any evidence of genotoxic damage [2]. This was also supported by an analysis of endometrial explant cultures treated with tamoxifen and subsequent high performance liquid chromatographic (HPLC) analysis of ^{32}P-post-labelled endometrial DNA from a further cohort of patients. However, some subsequent studies have since suggested that adducts may be detectable in the human endometrium in women on tamoxifen therapy, although inter-laboratory validation of these claims needs to be performed [3]. Hence, the debate continues as to whether the drug is a genotoxic carcinogen in humans or not. However, regardless of the presence or absence of DNA adducts, tamoxifen is often responsible for rapid and benign changes in endometrial pathology, such as hyperplasia and polyps. This has been attributed to the oestrogen agonist activity of tamoxifen in this tissue, but rapid tamoxifen-specific induction of adenomyosis in mice and endometrial tumours in neonatal rats in the absence of oestrogenic hyperplasia, suggest that tamoxifen has qualities beyond oestrogen agonist activity [4] that may contribute to an epigenetic and non-genotoxic mechanism of carcinogenicity. For example, we have reported that tamoxifen can induce a mitogenic environment in the human endometrium based on dysregulation of transforming growth factor beta and cognate receptors. To consider tamoxifen as an adduct-forming genotoxin is an oversimplification of the carcinogenic profile of this drug. A more complete understanding of these processes is required to assist in future SERM development and safety assessment. To this end, we have sought to compare and characterise the transcript profile of tamoxifen, raloxifene and the agonist oestradiol in human endometrial cells. Using primary cultures of human endometria, to best emulate the *in vivo* responses in a manageable *in vitro* system, we have shown 230 significant changes in gene expression for epithelial cultures and 83 in stromal cultures, either specific to 17β-oestradiol, tamoxifen or raloxifene, or changed across more than one of the treatments. Considering the transcriptome as a whole, the endometrial responses to raloxifene or tamoxifen were more similar than either drug was to 17β-oestradiol. Treatment of endometrial cultures with tamoxifen resulted in the largest number of gene changes relative to control cultures and a high proportion of genes associated with regulation of gene transcription, cell-cycle control and signal transduction. Tamoxifen-specific changes that might point towards mechanisms for its proliferative response in the endometrium included changes in retinoblastoma and c-myc binding proteins,

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1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2004.08.005

the *APCL*, *DHFR* and *E2F1* genes and other transcription factors. Tamoxifen was also found to give rise to the highest number of gene expression changes common to those that characterise malignant endometria [5]. It is anticipated that this study will provide leads for further and more focused investigation into SERM carcinogenicity.

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