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UGT2B7 is not expressed in normal breast

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To the editor:

It has been previously proposed that UDP-glucuronosyltransferase 2 family, polypeptide B7 (UGT2B7) is expressed in normal and cancerous breast tissue and that it plays an important protective role in the development of breast cancer [1-7]. However, a reappraisal indicated that UGT2B7 is not expressed in breast. The original investigation [1] as well as a more recent one [8] reported UGT2B7 expression in breast on the basis of RT-PCR. However, in both cases the RT-PCR primers were improperly located in the first exon, which could not rule out the possibility of contamination from genomic DNA. We tried to replicate the above finding, but set the two primers in different exons (forward 5'-TGCTTTACTTTGACTTTTGGTTTCG-3' and reverse 5'-CCAGGAGTTTCGAATAAGCCATAC-3'). Using this strategy, the *UGT2B7* transcript could not be amplified in normal breast cDNA (Fig 1), thus indicating that this gene is not expressed or is expressed below the detectable level. This result was confirmed by real time PCR using the same primer pair in a cohort including 81 normal breast cDNA (result not shown). Since *UGT2B7* was not detected also in a cell line derived from breast cancer [9], the probability that the *UGT2B7* transcript is present in cancer tissues is low. UDP-glucuronosyltransferase activity on 4-hydroxyestrone (4-OH-E₁) were also detected in both normal and cancer tissues in previous report [1]. In light of the absence of UGT2B7 in breast, we proposed that this activity originates from other UGT members, especially UGT2B15, which shows relatively high glucuronidation activity on 4-OH-E₁ [9] and is highly expressed in breast [7].

Given that *UGT2B7* is not expressed in breast tissue, it is still necessary to explain the positive result in the immunoblot experiment of Gestl and colleagues [1]. One possibility is that the signal originated from other members of the UGT2B family. Gestl and colleagues verified the specificity of their antibody by blot with three other UGT2B members [1]. However, two proteins that are also expressed in the breast, UGT2B17 and UGT2B28 [7], were not tested. Alternatively, the positive immunoblot result may come from a splicing variant of UGT2B7. If a splicing variant skipped some exons, but kept the open reading frame for the C-terminal domain, it would not be distinguished from the complete type by their antibody, which was developed on the basis of the last 11 amino acids [1]. Recently, we identified one such splicing variant, designated as *UGT2B7_v4*, in lymphoblastoid cell line. It includes at least exon 1A and 1B [10] instead of exon1, and the exon 2-6 (Fig 2; amplified by primer 5'-AGCCAGCCTGAGTGACAT-3' and 5'-TGGAATAAACTGAAGTAGTCTCAC-3' and sequenced; the 5' and 3' end still unknown). This splice variant was predicted to encode a protein that is identical to amino acid 292-529 of the full-length UGT2B7 and might be recognized by the antibody used by Gestl and colleagues. Although we did not detect this splicing variant in breast by RT-PCR, it cannot be ruled out that a similar but unknown splicing isoform exists in breast.

Since steroid hormones play a central role in breast cancer risk and the UGT family is essential in the metabolism of steroid hormones and other carcinogens, it has long been proposed that UGTs are involved in breast cancer risk. Our results strongly suggested that UGT2B7 is not expressed in normal breast tissue. In light of this, it appears that if UGT2B7 indeed plays a role in breast cancer biology and susceptibility, it must be through its expression in the liver rather than the breast, which in turn is likely to affect systemic levels of steroid hormones.

Acknowledgments

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Fig 1. Multiplex RT-PCR of cDNA from liver and breast. The different lanes in the gel represent cDNA samples from different individuals. M indicates the marker and 330bp and 100bp were shown with arrows. Primer for β -actin comes from reference 10.

Fig 2.

Schematic gene structure of *UGT2B7* and *UGT2B7_v4*. More detail about exon 1A and 1B can be found in reference 10.