3632  Differential expression of a novel KLK5 splice variant in ovarian and prostate cancer.

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Human tissue kallikreins are a group of serine proteases encoded by 15 structurally similar and hormonally-regulated genes that tandemly localize on chromosome 19q13.4. Some of these genes (e.g. prostate-specific antigen and human glandular kallikrein) are valuable biomarkers for prostate cancer. Another group of kallikreins (KLK 6, 7, 8, 10 and 11) are emerging biomarkers for ovarian carcinoma. Differential splicing is a common event among this multigene family and the alternative transcripts generated may possess physiological and prognostic significance. Our own data, and those already published in the literature, allowed us to identify over 50 splice variants as follows: KLK1 (2); KLK2 (4); KLK3 (9); KLK4 (5); KLK5 (4); KLK6 (5); KLK7 (2); KLK8 (4); KLK9 (1); KLK10 (1); KLK11 (3); KLK12 (2); KLK13 (8) and KLK15 (5). The most frequent events in differential splicing include incomplete or complete exon deletion, exon extension, differential splicing between exons and utilization of new transcription start sites. The classical KLK5 gene [previously known as KLK-L2 or human stratum corneum tryptic enzyme (HSCTE)] is differentially expressed and was shown to be a potential prognostic marker for a variety of hormone-dependent malignancies, including ovarian, breast, prostate and testicular cancers. More recently, the hK5 protein was shown to be a potential serum diagnostic marker for ovarian and breast cancer. We here identified a novel splice variant of the KLK5 gene denoted KLK5-SV1 with alternative splicing within the 5′ untranslated region. The variant has a different 5′splice site, but encodes the same protein product as the classical form. Variant-specific reverse transcription-polymerase chain-reaction analysis of this transcript in 29 human tissues indicated highest expression in the cervix, salivary gland, kidney, mammary gland and skin. Comparative analysis of the expression levels of KLK5-SV1, KLK5 splice variant 2 (KLK5-SV2), and the classical KLK5 form showed that out of all three mRNA transcripts, the classical form is predominantly expressed (found in more tissues and at higher expression levels) followed by KLK5-SV1. KLK5-SV1 is expressed at high levels in a variety of ovarian cancer cell lines including HTB 75 and ES2. The variant was also found to be expressed in 9/10 ovarian cancer tissues, compared to one normal ovarian tissue where it was completely absent. Furthermore, it showed significantly higher expression (61%) in normal prostate tissues compared to their matched prostate cancer tissue counterparts. As such, KLK5-SV1 may have clinical utility in various malignancies and should be further explored as a potential new biomarker for prostate and ovarian cancer.

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