American Association for Cancer Research
95th AACR Annual Meeting
March 27-31, 2004
Orange County Convention Center
Orlando, Florida

3300 The KLK5-splice variant-2 is a new biomarker for ovarian cancer.

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The presence of more than one mRNA form for the same gene is common among kallikreins and many of the kallikrein splice variants may hold significant clinical value. The human kallikrein gene 5 (KLK5) is a member of the human kallikrein gene family on chromosome 19. It has been shown to be differentially expressed in a variety of endocrine tumors including ovarian, breast and prostate cancer. Utilizing Expressed Sequence Tag database analysis and RT-PCR, we identified a new alternatively-spliced form of KLK5 (KLK5 splice variant 2, KLK5-SV2). This variant is formed of 1438 bp, 195 bp of 5' untranslated region, followed by 882 bp of protein coding sequence, then a 3' untranslated region of 361 nucleotides. Nucleotide sequence of this variant forms 7 exons, the first two of which are untranslated, and 6 intervening introns. It is different from the classic form of the KLK5 mRNA in its 5' untranslated region. The first 5'untranslated exon of the classical form is split into 2 exons with an intervening intron of 135 nucleotides. It also differs from splice variant-1 by having an extra 5' untranslated exon 68 nucleotides in length. KLK5-SV2 is expressed in a variety of tissues, with higher levels of expression in the mammary gland, cervix, salivary gland and trachea and lower levels in many other tissues. The receptor-positive breast cancer cell line BT-474 was used to examine the effect of different steroids of the expression levels of KLK5-SV2. Expression levels were significantly higher 24 hours after stimulation with androgens but not estrogen, progestins, alddosterone or corticosteroids. While high levels of expression were found in all normal breast tissues, no expression was detected in 16 cancer tissues, and expression was significantly lower than normal in the remaining four cancers. No expression was detected, under same conditions, in the BT-20 and BT-474 (unstimulated) breast cancer cell lines, and a weak expression was observed in the MCF-7 cell line. KLK5 SV-2 was not detectable in any of the 10 normal ovarian tissues examined. The variant was, however, expressed at high levels in 10 out of 20 ovarian cancer tissues, and lower levels were found in 4 other cancers. No expression was detected in the remaining 6 cancers. High expression levels were also detected in the HTB-75 ovarian cancer cell line. We conclude that KLK5-SV2 is a potential biomarker for breast and ovarian cancer.

Citation information: Proceedings of the AACR, Volume 45, March 2004