HUMAN TISSUE KALLIKREINS AS BIOMARKERS FOR BREAST, OVARIAN, AND OTHER MALIGNANCIES

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Human tissue kallikreins are secreted serine proteases, encoded by 15 genes that are tandemly localized on human chromosome 19q13.4. One tissue kallikrein, prostate-specific antigen or human kallikrein 3 (hK3) is the premier biomarker for prostate cancer diagnosis and management. We speculated that other members of this newly discovered class of serine proteases may also represent promising biomarkers for other types of cancer. We developed recombinant proteins, monoclonal antibodies and ELISA-based assays for quantification of human kallikreins 4, 5, 6, 7, 8, 10, 11, 13, and 14. By using these assays, we screened large numbers of serum samples from various malignancies to establish if any of these are promising biomarkers for cancer. We identified multiple kallikreins (hK5, hK6, hK7, hK8, hK10, hK11, and hK14) as promising biomarkers for ovarian carcinoma. In addition, two kallikreins, hK5 and hK14, were elevated in serum of approximately 40% of breast cancer patients. In studying the specificity of these enzymes, we confirmed (by using combinatorial library screening and phage-display) that most of them have trypsin-like activity, while some have chymotrypsin-like activity. We also verified that many of these enzymes can cleave efficiently extracellular matrix components, such as collagen, laminin, fibronectin, etc.

We conclude that at least two members of the human kallikrein family, hK5 and hK14, are promising biomarkers for breast carcinoma. Previously, we have shown that human kallikrein 3 or PSA is also a prognostic and diagnostic marker for breast carcinoma. Moreover, the ability of these enzymes to cleave extracellular matrix components may implicate them in tumor progression and metastasis. These enzymes may represent novel therapeutic targets for breast cancer.

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