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5258 Kallikrein gene down-regulation in breast cancer.

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Recent evidence suggests that many members of the human kallikrein gene family are differentially regulated in breast cancer and other endocrine-related malignancies. In this study, we utilized the Serial Analysis of Gene Expression (SAGE) and Expressed Sequence Tag (EST) databases of the Cancer Genome Anatomy Project to perform in-silico analyses of the expression pattern of the 15 human kallikrein genes in normal and cancerous breast tissues and cell lines using different analytical tools such as Virtual Northern blotting (VNB), Digital Differential Display (DDD) and X-profiler. Our results indicate that at least 4 kallikrein genes (KLK5, 6, 8, 10) are down-regulated in breast cancer. Probing 8 normal and 24 breast cancer SAGE libraries with gene-specific tags for each of the above kallikreins indicated moderate to high expression densities in normal breast (27 –319 tags per million; tpm, in 2-5 out of 8 libraries), compared to no or low expression (0 – 34 tpm in 0-2 libraries out of 24) in breast cancer. These data were verified by screening the EST databases, where all mRNA clones isolated for these genes, except for one in each, were from normal breast libraries, with no clones detected from breast cancer tissues or cell lines (with the exception of KLK8). X-profiler comparison of two pools of normal and breast cancer libraries further verified the presence of significant down-regulation of expression levels of 4 of the kallikreins genes (KLK5, 6, 10, 12). We experimentally verified the down-regulation of these 4 kallikreins (KLK5, 6, 8, 10 and 12) by RT-PCR analysis. While KLK5 was expressed at high levels in all normal breast tissues, it was only detectable in 3 out of 14 cancerous breast tissues examined. KLK6 was strongly positive in normal breast tissue, but was not expressed in 9 out of 14 tumor tissues, lower than normal in 3 and comparable to normal in two. KLK8 also showed a strong band in normal tissues, compared to undetectable expression in 5 tumor tissues, lower than normal in 7 tumors and comparable to or more than normal in two. KLK10 showed no expression in 8 tumors, lower than normal in 5 and comparable to normal in one tumor. While KLK12 was detectable in 3 out of 4 normal breast tissues, it was expressed at relatively lower levels in 6 out of 14 cancers.

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