96. THE PSA-RELATED KALLIKREIN ENZYMES AND HORMONE-DEPENDENT CANCERS

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The human tissue kallikreins are a multigene family of 15 serine proteases, which are expressed in hormone-dependent cancers. Prostate-specific antigen or PSA, a member of this family, is the current serum biomarker for detection and monitoring of prostate cancer. Other kallikreins are being investigated as potential diagnostic/prognostic markers, particularly for prostate (KLK2) and ovarian cancer (KLKs 4-11 & 14, 15), the latter specifically as biomarkers for serous epithelial ovarian carcinomas. Interestingly, some ovarian KLKs (8, 9, 14 & 15) appeared to be useful indicators of good prognosis whereas others (KLKs 4, 5, 6, 7, 10 & 11) indicated a poor outcome. One novel aspect of the human KLKs is the number of differentially-spliced transcripts that could encode truncated proteins devoid of protease activity. We have shown that some variant transcripts (for PSA, KLK2, KLK4, KLK5 & KLK7) are more highly expressed than full-length transcripts in malignant compared to benign tissues suggesting they may have potential as more cancer-specific biomarkers. Intriguingly, some KLK4 variants are localized to the nucleus, which is not a typical intracellular site for a protease that is normally secreted, emphasizing possible non-proteolytic functions of these variants. From biochemical studies, it appears that kallikreins are involved in a range of functional activities via the degradation of polypeptides (extracellular matrix proteins, IGFBPs) or polypeptide activation via hydrolysis of the pro-peptide (uPA, TGFβ). Although not yet proven, these observations suggest that kallikreins play a role in events associated with tumour progression. We have recently developed prostate cancer PC3 cell lines stably-transfected with prepro-PSA, -KLK2 and -KLK4. We have shown that PSA and KLK4 over-expression, but not KLK2, elicits a morphological change, increased migration to various chemo-attractants and increased attachment to extracellular matrix components (KLK4 only). The mechanisms underlying these changes are currently under investigation.

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