

Hidden Markov Models-Based Gene Expression Analysis Reveals New Features of PTHrP Peptide Impact on Cancer Pathogenesis and Progression***Tsigelny, I.F., Sharikov, Y., Burton, D., Hastings, R., Deftos, L.******University of California at San Diego; San Diego Supercomputer Center; Departments of Medicine, Anesthesiology, and Pharmacology; San Diego VA Medical Center, San Diego, CA, USA***

Parathyroid hormone-related protein (PTHrP) is commonly expressed in many cancers and influences a number of cancer-related signaling pathways in these malignancies. The varied and complex effects of PTHrP in cancer are mediated by its processed peptides. These peptides can differentially activate paracrine, autocrine, and intracrine pathways and correspondingly regulate proliferation, differentiation, and apoptosis. Such effects depend on known and putative cell-surface receptors as well as on nuclear localization and actions of these peptides. The mechanisms of action that mediate the effects of the many PTHrP-derived peptides in cancer cells have not been fully defined. We undertook a novel approach to elucidate the complex regulatory interactions that mediate PTHrP's multiple effects in many cancers.

We studied gene expression profiles in cancer cells respectively transfected with PTHrP forms, including PTHrP 1-173 and PTHrP 36-173, using Affymetrix oligonucleotides based matrix U133A. For data analysis, we developed and applied a program based on hidden Markov models (HMM). This program made it possible to identify effects of the different PTHrP forms at the chromosomal level. We were able to demonstrate unique chromosomal patterns of specific effects of the different functional domains of PTHrP on cancer cell gene expression. Our studies identified "amplicons" of neighboring genes in specific regions of chromosomes that were differentially regulated by different PTHrP forms. This novel approach can be used to study the complex patterns of gene expression in cancer that are regulated by PTHrP and its processed peptides. The methodology may be extended to studies of molecular mechanisms that have both basic and clinical importance.