Intracellular signaling pathways regulate expression of Prostate Specific Antigen and other kallikreins in human breast cancer cells

Miltiadis Paliouras and Eleftherios P. Diamandis

ABSTRACT

Human tissue kallikreins (KLKs) in breast cancer cell lines show both hormone-dependent and –independent expression, however the regulatory pathways which influence this are not yet understood. This study suggests that certain signal transduction pathways may influence regulation of both hormone-dependent and –independent KLK gene expression in breast cancer cell lines, T47D, and one hormone-independent cell line, MDA-MB-468. Changes in protein expression profiles upon inhibitor treatments. Cell signaling pathways are utilized by all steps of gene expression, and control the activities of various receptors, kinases, phosphatases, and co-factors/co-activators/co-repressors for individual and common genes. In turn, these pathways and the resulting gene expression contribute to cellular differentiation, development, and disease progression. In order to project this, we have utilized selective inhibitor treatment approach to specific cell signaling pathways that have been implicated in Prostate Specific Antigen (PSA) regulation in prostate cancer cell lines, to analyze the expression profiles of other coordinately expressed kallikreins in both prostate and breast cancer cell lines. Overall, carcinogenesis is a complex process that is a result in alterations in gene expression. One of the goals of cancer research is to identify potential therapeutic targets and to determine its effects on tumor phenotype. All KLK enzymes show differential expression patterns in many cancers (primarily endocrine or hormone-related cancers) at the mRNA and protein levels. Identifying gross genetic alterations within the kallikrein gene family is critical in understanding their role in promoting cell growth, invasion, and metastasis. Recently, it has been shown that the AR has an important role in the normal development and function of many organs, as well as in the pathogenesis of prostate cancer. A number of factors can alter the expression of these genes, in both cell culture and in vivo, have shown that most, if not all KLKs are under steroid hormone regulation. More recently, several studies suggest the possibility that signal transduction pathways may influence the hormonal regulation of kallikrein gene expression. The traditional understanding of androgen receptor (AR) mediated gene expression simply relied on the binding of the hormone to the receptor and binding of the complex to the AR responsive elements. We are now realizing that many signal transduction pathways are playing a role in regulating kallikrein gene expression. It has been found that approximately 30% of all breast cancers either have mutation or in the gene encoding the tumor suppressor protein phosphatase and tensin homologue deleted from chromosome 10 (PTEN). PTH is a negative regulator of AKT function, resulting in increases in cell growth and proliferation. DREAM is a novel transcription factor that regulates the expression of a number of genes involved in cell growth and proliferation. It is worth noting that PTH/PTHrP receptors have been shown to promote expression of cytokine-like proteins in breast cancer cells. We are now realizing that many signal transduction pathways are playing a role in regulating kallikrein gene expression. We conclude that specific factors were altered in a pattern parallel to kallikrein expression. We conclude that specific factors were altered in a pattern parallel to kallikrein expression.