

A Protein That Prolongs the Action of cAMP-Dependent Protein Kinases Is Overexpressed in Papillary Thyroid Cancer

Cantara S, et al.

ANALYSIS AND COMMENTARY ● ● ● ● ●

The transcription factor CREB is a major substrate for free PKA catalytic subunits. When the free catalytic subunits phosphorylate CREB, it binds to the promoters of genes with CREB binding sites and increases their expression. *Praja2* is such a gene. The substantial overexpression of *praja2* presumably would provoke a cell to counter with some physiological homeostatic responses, however. In future studies, it will be important to determine the status of other factors known to affect PKA activity, such as other anchoring proteins, phosphodiesterases and heat-stable protein inhibitors, as well as the status of other proteins that *praja2* binds and ubiquitinates, such as ELK and MAGE-D1. In other tissues, the level of *praja2* expression changes in response to various stimuli, including neural differentiation, contact inhibition, hypothermia, experimental colitis, and estrogen replacement. Thus, it is quite possible that the overex-

pression of *praja2* seen in PTC reflects a homeostatic response to changes that occur as papillary cancer develops. Nonetheless, it is still possible that *praja2* does play a role in the development of PTCs, whereas this would not seem to be the case in the development of anaplastic cancer or benign adenomas. Such a role would presumably be more prominent in RET/PTC1 and BRAFV600E papillary tumors than in RET/PTC3 tumors, although the numbers of some variants studied were small.

Even if the level of *praja2* should turn out to display so much physiological variability that it cannot be used for the diagnosis of PTC, its ability to regulate PKA activity may well prove important clinically for understanding anomalies in the regulation of normal thyroid function.

— Stephen W. Spaulding, MD

Reference

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