Applying protein tyrosine phosphatase inhibitors in cancer therapeutics

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Abstract

The protein tyrosine phosphatase (PTP) gene family encodes for 107 genes in the human genome. This remarkable diversity is reflected in the function of these enzymes in important regulatory axes ranging from growth factor and cytokine signaling, to cell-cell interaction, cytoskeletal regulation and cell specification. Not surprisingly, the past 30 years of PTP studies have led to the identification of broad numbers of disease contexts where members of this family were found to be either mutated or inappropriately expressed, including cancer, metabolic, neurological and immune diseases.

Their diverse functions have also provided exciting opportunities to employ modulators of these enzymes to treat several diseases. Unfortunately, they remain largely impervious to targeting in clinical applications due to similarity of the catalytic domain, presence of charged residues, poor inhibitor uptake and other issues.

In this presentation, I will review several approaches that we have undertaken to target specific PTP enzymes in disease. Among those that I will discuss are our efforts to comprehend the roles and additive effects of two small intracellular PTPs, PTP1B and TC-PTP, and the therapeutic relevance of targeting these in prostate and pancreatic cancers, particularly through our new immunotherapy platform.

A second major interest of the laboratory has been to examine the oncogenic mechanisms of the trio of PTP4A enzymes, with a focus on our recent finding of their modulatory activity on the CNNM magnesium sensors. This represents a novel paradigm in cellular metabolism that places the PTP4A/CNNM protein complexes at the center of oncometabolism, infectious disease, and normal mammalian physiology.

Our overarching conclusion on PTP function is that protein tyrosine phosphatases act as finely tuned sensors of signaling output. Their stoichiometry is key to maintaining homeostasis. Therefore, their study and targeting must reflect this dosage effect since such functions are often poorly exposed in gene knock-out disease models, yet they are likely to open novel approaches in translational applications.