Drugging the undruggable: exploiting PTP1B as a therapeutic target

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Abstract

The protein tyrosine phosphatases (PTPs) are important regulators of signal transduction. These cysteine-dependent phosphatases hydrolyze phosphoester bonds in proteins and non-protein substrates. Overall, the objective of the lab is to characterize the structure, regulation and function of PTPs, to define their role in critical tyrosine phosphorylation-dependent signaling events under normal and pathophysiological conditions, and to identify novel therapeutic targets and strategies based upon the PTPs themselves, or from components of the signaling pathways they regulate.

PTP1B plays a well-established role in down-regulating insulin and leptin signaling and is a validated therapeutic target for diabetes and obesity. Furthermore, PTP1B is a positive regulator of signaling by the HER2 oncoprotein tyrosine kinase, such that inhibition of the phosphatase also abrogates breast tumorigenesis and metastasis. Several potent, specific, reversible small molecule inhibitors of PTP1B have been developed, but they target the conserved, highly charged active site and exhibit poor oral bioavailability, which limits their drug development potential. This led industry to dismiss the members of the PTP family as “undruggable”.

In contrast, I will illustrate how a detailed understanding of the structure, regulation and function of PTP1B, which has been generated in an academic setting, has revealed new approaches to the development of small molecule drug candidates that target this enzyme. For example, we are exploiting a physiological mechanism of regulation of PTP function by reversible oxidation and inactivation that is induced following stimulation of cells, such as with insulin or leptin. Our data illustrate that stabilization of the oxidized, inactive form of PTP1B with appropriate therapeutic molecules may offer a novel paradigm for phosphatase drug development. Furthermore, we have identified small molecule

inhibitors that target a unique allosteric site in the regulatory, C-terminal segment of PTP1B. In addition to stimulating insulin signaling, we have demonstrated that such allosteric PTP1B inhibitors antagonize HER2 function, including abrogation of tumor metastasis in the NDL2 transgenic mouse model of HER2-positive breast cancer. This new approach to cancer therapy is currently the subject of a clinical trial. Finally, the application of such inhibitors is revealing new functions of PTP1B and suggesting new indications in which inhibition of PTP1B may be of therapeutic benefit, such as for treatment of the autism spectrum disorder Rett syndrome.