Specific modulators of protein phosphatase-1 and their application in heart failure

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Protein serine/threonine-specific phosphatases have in the past been considered to be housekeeping enzymes, undruggable, and challenging to study due to their multiple roles and the conservation of the catalytic subunits. However, this view is currently changing. Of these, protein phosphatase-1 (PP1) is an important ubiquitous phosphatase that is estimated to remove phosphate groups from about a third of all phosphorylated serines and threonines in eukaryotic cells, counteracting more than a hundred kinases. PP1 catalytic subunit (PP1c) has broad substrate specificity but is restrained in vivo by numerous PP1c-interacting proteins that impart high substrate specificity to it and function for example as activity-modulating or localization-determining factors. These so-called PP1-holoenzymes play roles in many different diseases such as cancer, diabetes, and cardiovascular diseases. The lack of selective modulators of PP1 has in the past been a limiting factor in its research. We have addressed this challenge by designing peptides that target PP1c and disrupt its protein–protein interactions with regulatory proteins, leading to the release of free, active PP1c inside cells. I will report on the probe development and describe their application to study and target PP1 activity in the pathomechanism of heart failure.