Expanding the Substrate Specificity of Macro Domain toward 3”-isomer of O-Acetyl-ADP-ribose

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Abstract

O-acetyl-ADP-ribose (*O*AADPR) is a signaling molecule identified from the conserved sirtuin reaction in *Saccharomyces cerevisiae*, involved in the important cellular functions of gene silencing, redox regulation, and aging. Here, we performed biochemical and structural characterization of the yeast Poa1p macro domain in detail, uncovering a novel deacetylase activity favoring 3″- and 1″- isomer of *O*-acetyl-ADP-ribose. The unique active-site residues of Poa1p contributing to the distinct substrate specificity thus shed light on the divergent branch of a POA1-like subclass. Moreover, disruption of Poa1p expression in yeast showed striking sensitivity to transcriptional stress, which implies a physiological role in response to nucleotide depletion. These finding provide biochemical and structural insights into a newly 3″-*O*-acetyl-ADP-ribose deacetylase, which playing the critical role in cellular nucleotide metabolism for intracellular signaling and the regulatory process.

Keywords - macro domain; Poa1p; 3″-O-acetyl-ADP-ribose; deacetylase; crystal structure