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Structure and substrate selectivity of PvuRts1I

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5-hydroxymethylation is a mysterious modification of cytosine discovered decades before, with its functional roles awaiting elucidation in eukaryotes. Cumulative evidence demonstrates that 5-hydroxymethylcytosine is an epigenetic marker serves critical roles in multiple biological processes. Moreover, the profile of 5-hydroxymethylcytosine is changed under disease conditions such as cancer. Several methods including AbaSI-coupled sequencing have been developed to decipher hydroxymethylome at single-base resolution. However, the technical hurdles of AbaSI-coupled sequencing derived from the enzymatic property of AbaSI, a member belonging to PvuRts1I family endonuclease, may impede the application of this method. PvuRts1I is a modification dependent endonuclease with high selectivity to 5-hydroxymethylcytosine over 5-methylcytosine and cytosine. To improve the substrate selectivity of PvuRts1I family member, we solved the crystal structure of PvuRts1I. One nuclease domain and one SRA-like domain are located at the N- and C-terminal half of the structure, respectively. In comparison with other SRA domain structures, the SRA-like domain of PvuRts1I has been proposed to be the 5-hmC recognition module. Several mutants of PvuRts1I with enzymatic activity to 5-hydroxymethylcytosine only have been generated based on structural analysis, providing perfect candidates for dissection of hydroxymethylome from methylome.

Keywords: 5-hydroxymethylcytosine, endonuclease, substrate selectivity