

Role of Ad4-Binding Protein/Steroidogenic Factor 1 in regulating NADPH production in adrenocortical Y-1 cells

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(副腎皮質由来 Y-1 細胞での NADPH 産生における Ad4-Binding Protein/Steroidogenic Factor の役割り)

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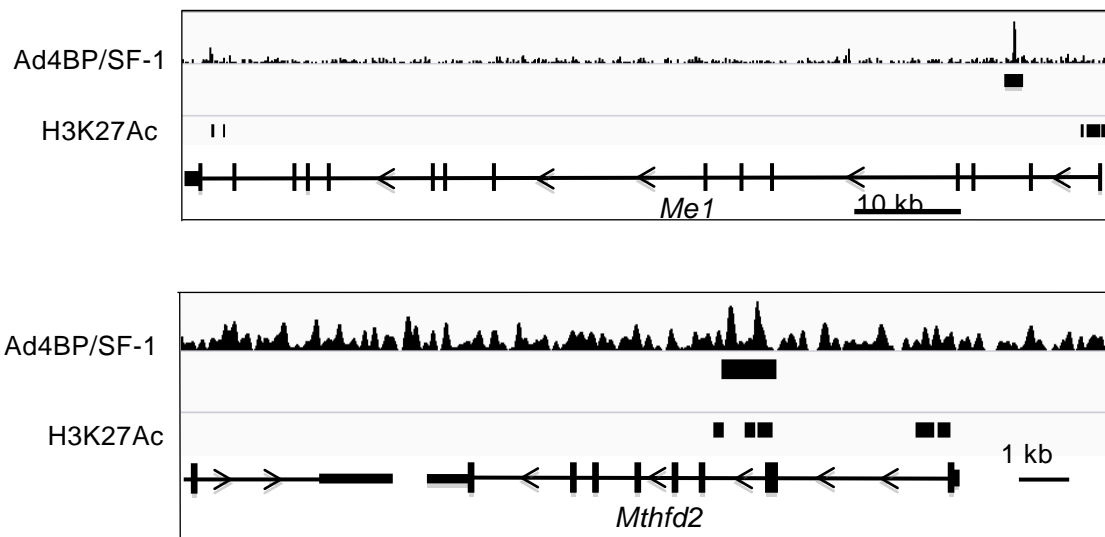
論 文 内 容 の 要 旨

Ad4BP/SF-1 (Ad4-binding protein/steroidogenic factor 1), a member of the nuclear receptor superfamily, is expressed in steroidogenic cells and regulates all steroidogenic gene expression. We recently employed mRNA and chromatin immunoprecipitation sequencing to demonstrate that Ad4BP/SF-1 directly regulates the expression of nearly all glycolytic genes. The pentose phosphate pathway contributes to the production of nicotinamide adenine dinucleotide phosphate (NADPH). Although the expression of pentose phosphate pathway genes and intracellular NADPH were decreased by Ad4BP/SF-1 knockdown, these genes were not the direct targets of Ad4BP/SF-1. This study therefore investigates whether Ad4BP/SF-1 directly regulates genes implicated in NADPH production. Examination of previously published data sets of mRNA sequence (mRNA-seq) and chromatin immunoprecipitation sequence (ChIP-seq) strongly suggested a possibility that other NADPH-producing genes, such as *malic enzyme 1 (Me1)* and *methylenetetrahydrofolate dehydrogenase 2 (Mthfd2)*, are the direct targets of Ad4BP/SF-1. Reporter gene assays and determination of intracellular NADPH concentration supported the notion that Ad4BP/SF-1 regulates NADPH production by regulating these genes. NADPH is required for macromolecule synthesis of compounds such as steroids, and for detoxification of reactive

oxygen species. When synthesizing steroid hormones, steroidogenic cells consume NADPH through enzymatic reactions mediated by steroidogenic P450s. NADPH is also consumed through elimination of reactive oxygen species produced as the byproducts of the P450 reaction. Overall, Ad4BP/SF-1 potentially maintains the intracellular NADPH level through cooperative regulation of genes involved in the biological processes for consumption and supply.

Key words: steroidogenesis, Ad4BP/SF-1 (NR5A1), NADPH, *Me1*, *Mthfd2*

ChIP-seq



Luciferase assay

