

The mTOR kinase directly regulates FBP1 gene expression via interaction with SWI/SNF chromatin remodeling complex in clear cell renal cell carcinoma (ccRCC).

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Introduction & Objectives: The clear cell renal cell carcinoma (ccRCC) is featured by hyperactivation of mTOR pathway and downregulation of FBP1 gene encoding a main enzyme controlling glycolysis flux. This results in metabolic switch (Warburg effect).

Materials & Methods: For study of the mTOR and SWI/SNF interdependence, and regulation of FBP1 locus the A498 cell line was used. To verify the SWI/SNF subunit protein level in ccRCC the IHC method the samples of ccRCC patients treated in Cancer Center in Warsaw were used. Co-immunoprecipitation was used to study direct interaction between SWI/SNF complex subunits and mTOR kinase. The presence of SWI/SNF, mTOR and H3K27me3 on FBP1 locus in A498 cells after everolimus treatment vs not treated cells was assessed using ChIP method. Nucleosome positions in A498 cell line on FBP1 locus were estimated using MNase-protection assay

Results: The abundance of SWI/SNF chromatin remodeling complex subunits was strongly reduced in ccRCC patient samples vs healthy kidney tissue. The direct interaction of the core SWI/SNF subunit-BAF155 with mTOR in cell nuclei was found. Interestingly, the SWI/SNF complex containing BRM ATPase bound the FBP1 locus together with mTOR. The everolimus treatment of A498 ccRCC cell line lead to the FBP1 enzyme accumulation and caused unexpected movement of SWI/SNF on FBP1 locus. Additionally, the analysis of trimethylated histone H3 on FBP1 locus indicated the strong hypermethylation of H3 in untreated cells. This observation suggests the transcriptional inhibition of FBP1 in untreated cells, which may be related to SWI/SNF and mTOR position on FBP1 locus.

Conclusions: In ccRCC, SWI/SNF together with mTOR directly regulate FBP1 gene locus negatively affecting its expression level. The everolimus treatment causes shift in SWI/SNF binding on FBP1 locus which is coordinated with FBP1 overexpression. These study demonstrate for the first time the existence of functional interdependences between nuclear fraction of TOR kinase and chromatin remodeling machinery in transcriptional control of gene expression.

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