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FoxO1 may play a role in SREBP1 interaction with DNA

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Motivation and Aim: Sterol regulatory element-binding proteins (SREBPs) are a class of transcription factors that regulate lipid metabolism by controlling the synthesis of cholesterol, fatty acids, triglycerides, and phospholipids. The forkhead box-O1 (FoxO1) plays a key role in gluconeogenesis and glycogenolysis by insulin signaling, adipogenesis, cell cycle, proliferation, apoptosis, autophagy, stress resistance, DNA repair, tumor inhibition, and other cellular activities. Both transcription factors are insulin inducible and their mutual inhibition in Hepatoblastoma, leading to the increase of intracellular fatty acid metabolism ultimately facilitated the development of Hepatoblastoma. The aim of our study was to evaluate the mutual role of SREBP1 and FoxO1 in the regulation of mouse gene expression.

Methods and Algorithms: We have developed the Argo_CEL system [this issue], which makes it possible to *de novo* identify significant mutually correlated pairs of IUPAC motifs corresponding to potential composite elements in a set of regulatory regions of genes. It was used to analyze the [–100; 100] sequences relative to the peak maxima of ChIP-Seq experiments with the transcription factor SREBP1 from [1]. The resulting motifs were annotated using the Tomtom system against the Jaspar and Hocomoco databases. Then, the correlation of the mutual presence of the most significant motifs corresponding to the SREBP1 (CSCCRCCS) and FoxO1 (TYRTTDWY) binding sites in the sequences of the ChIP-Seq peaks localized in the core promoter regions and in the intergenic regions was evaluated.

Results: From the results of the analysis presented in the table, it can be seen that for the CSCCRCCS (SREBP1) and TYRTTDWY (FoxO1) motifs, a high anti-correlation is observed in almost all orientations in the promoter region, which sharply decreases in intergenic regions. Based on this observation, it can be assumed that, in the absence of a strong motif for binding site of the transcription factor SREBP1, the interaction of this transcription factor with DNA is mediated by the presence of accompanying binding sites for partner transcription factors, such as FoxO1. Using the DAVID system, we performed a functional annotation of genes in the regulatory [–2000; 500] regions of which the ChIP-Seq SREBP1 peaks were localized, in which there were motifs corresponding to the FoxO1 binding sites, but there were no motifs corresponding to the SREBP1 binding sites. It turned out that such genes were significantly ($p < 0.05$) characterized by GO terms “cell cycle” and “cell cycle process”.

Table 1. Changes in the correlations of the mutual arrangement of non-overlapping motifs found in ChIP-Seq peaks of SREBP1 in different regions of DNA relative to the closest start of transcription. The red arrows mark the CSCCRCCS motif in all orientations; the blue arrows mark the TYRTTDWY motif. Cells with significant correlations are marked with color ($p < 0.05$)

Mutual motifs orientation and arrangement		Regions of DNA relative to the closest start of transcription			
		-500 +500	-2000 +500	-5000 +500	-5000000 -50000
CSCCRCCS	TYRTTDWY	-0.0679311	-0.0788838	-0.0680081	-0.0301905
RWHAAYRA	SGGYGGSG	-0.0629877	-0.0621974	-0.0612617	-0.0285889
TYRTTDWY	CSCCRCCS	-0.0944169	-0.100894	-0.0878829	-0.0301905
SGGYGGSG	RWHAAYRA	-0.0477108	-0.0483002	-0.0496487	-0.0285889
CSCCRCCS	RWHAAYRA	-0.0823771	-0.0827146	-0.0761681	-0.000118922
TYRTTDWY	SGGYGGSG	-0.0713339	-0.0770609	-0.0687663	0.00486136
RWHAAYRA	CSCCRCCS	-0.0823771	-0.0827146	-0.0761681	-0.000118922
SGGYGGSG	TYRTTDWY	-0.0971916	-0.0993576	-0.0885172	-0.0320027

Conclusion: Our analysis showed that in the sequences of the ChIP-Seq peaks of experiments with antibodies to SREBP1, context motifs that best correspond to the binding sites of SREBP1 and FoxO1 significantly avoid coexistence. Furthermore, in cell cycle genes, the binding of SREBP1 to its binding site may be mediated by the presence of FoxO1.

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References

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