

Deciphering the combinatorial DNA-binding code of the CCAAT-binding complex and the iron-regulatory basic region leucine zipper (bZIP) transcription factor HapX.

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Abstract

The heterotrimeric CCAAT-binding complex (CBC) is evolutionary conserved in eukaryotic organisms including fungi, plants and mammals. The CBC consists of three subunits, which are named in the filamentous fungus *Aspergillus nidulans* HapB, HapC and HapE. HapX, a fourth CBC subunit was identified exclusively in fungi, except of *Saccharomyces cerevisiae* and closely related *Saccharomycotina* species. The CBC:HapX complex acts as the master regulator of iron homeostasis. HapX belongs to the class of basic region leucine zipper (bZIP) transcription factors. We demonstrated that the CBC and HapX bind cooperatively to bipartite DNA motifs with a general HapX:CBC:DNA 2:1:1 stoichiometry in a class of genes that are repressed by HapX:CBC in *A. nidulans* during iron limitation. This combinatorial binding mode requires protein-protein interaction between the N-terminal domain of HapE and the N-terminal CBC-binding domain of HapX as well as sequence-specific DNA-binding of both the CBC and HapX. Initial binding of the

CBC to CCAAT boxes is mandatory for DNA recognition of HapX. HapX specifically targets the minimal motif 5'-GAT-3', which is located in a distance of 11 to 12 base pairs downstream of the respective CCAAT box. Single nucleotide substitutions at the 5'- and 3'-end of the GAT motif as well as different spacing between the CBC and HapX DNA-binding sites revealed a remarkable promiscuous DNA-recognition mode of HapX. This flexible DNA-binding code may have evolved as a mechanism for fine-tuning the transcriptional activity of CBC:HapX at distinct target promoters.

Involved units

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