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EDITORIAL

An Epigenetic Switch Between Differentiation and Proliferation in Hepatoblastoma

CCAAT enhancer binding protein α (C/EBPα) is a widely expressed basic leucine zipper transcription factor that plays diverse roles including the regulation of differentiation and cell-cycle progression. Studies in C/EBPα-null mice and zebrafish have shown that it promotes liver development and key metabolic functions while inhibiting hepatocyte proliferation.[1,2] A large body of work by Timchenko et al has shown that C/EBPα function is critically regulated by its phosphorylation at serine 190 (correlating to S193 in mice), which has effects on gene expression, metabolism, proliferation, and carcinogenesis in the liver. These effects are modulated, at least in part, by differential association of C/EBPα with other regulatory proteins including histone deacetylase 1 (HDAC1). In mice, dephosphorylation of S193 (or a phosphorylation-resistant S193A mutant) is associated with the development of liver cancer in chemical carcinogenesis and genetic models.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Rivas et al[3] examine the potential role of C/EBPα, HDAC1, and the transcription factor Sp5 in the epigenetic regulation of human hepatoblastoma. This is the most common pediatric liver tumor and is characterized histologically by varying features of dedifferentiation. Although children with localized disease often can be managed with resection, those with metastatic or recurrent disease face a worse prognosis.[4,5] Notably, relatively few oncogenic mutations have been identified in hepatoblastoma (most commonly affecting the WNT/β-catenin and NFE2L2/NRF2 pathways),[4,5] suggesting that epigenetic regulation may play an important role in the development, histologic appearance, and aggressiveness of this malignancy.

The authors used banked hepatoblastoma tissue obtained immediately after surgery and focused on those expressing high levels of C/EBPα and Sp5. Notably, C/EBPα in these tumors was highly dephosphorylated at S190, consistent with their findings in mouse models. They evaluated the expression of protein phosphatase 2A (PP2A), a multiprotein complex that has been shown to dephosphorylate C/EBPα, and found that it overexpressed and was bound to C/EBPα in the tumors. Dephosphorylated C/EBPα and HDAC1 formed complexes in both human hepatoblastoma and mouse tumors from transgenic mice carrying the S193A mutant. In addition, Sp5 expression was increased in human hepatoblastoma and formed complexes with HDAC1. Chromatin immunoprecipitation studies of hepatoblastoma specimens found that binding of C/EBPα and Sp5 to known target genes was associated with increased binding of HDAC1 as well as decreased histone acetylation. In the case of Sp5, they showed these findings on the promoter of the p21 cell-cycle inhibitory protein, which showed decreased expression. Similarly, the expression of corresponding C/EBPα-regulated metabolic proteins was decreased, suggesting that this epigenetic mechanism contributes to hepatocyte dedifferentiation in hepatoblastoma.

In human hepatoblastoma cell lines, pharmacologic inhibition of PP2A led to increased S190 phosphorylation of C/EBPα, markedly decreased abundance of C/EBPα–HDAC1 complexes, and increased C/EBPα–p300 complexes, which are known to activate gene expression in hepatocytes. This was associated with increased expression of metabolic proteins reflective of differentiation as well as decreased cell-cycle protein expression and proliferation. Inhibition of HDAC1 had similar effects, further suggesting that regulation of histone modifications plays a role in both differentiation and proliferation of these cells. These findings suggest that drug treatments directed toward the PP2A and HDAC1 enzymes may warrant further evaluation in this cancer.

A major strength of this study was the use of a substantial number of human hepatoblastoma specimens, which is significant given the rarity of this tumor, to address specific mechanistic hypotheses derived from extensive prior research by this group. The findings highlight the importance of epigenetic and post-translational modifications in hepatoblastoma, which are critical to understanding both tumor biology and potential treatment strategies.

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Conflicts of interest
The author discloses no conflicts.


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