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Tissue-specific and de novo promoter methylation of the mouse glucose transporter 2

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The expression of GLUT2 is reduced in neoplastic hepatic lesions and in most hepatoma cell lines. Here we examined the involvement of epigenetic modifications in the regulation of GLUT2. Four CpGs in the GLUT2 promoter were undermethylated in GLUT2-expressing tissues, including liver. In isolated hepatocytes, GLUT2 expression declined and the promoter was methylated de novo, albeit with a delay. This de novo methylation occurred with a similar time-course in hepatocytes cultured in a high-glucose medium that induced GLUT2 expression, suggesting that de novo methylation can be induced independently of GLUT2 expression. GLUT2 was reactivated in hepatocytes following exposure to the methylation inhibitor 5-aza-2'-deoxycytidine (AzaC) and to the histone deacetylase inhibitor trichostatin A, but only after the methylation had occurred. In p53-deficient mouse liver, the CpGs were methylated de novo; the GLUT2 expression declined. The GLUT2 promoter was hypermethylated in Hepa1c1c7 cells, but expression could be rescued by AzaC. We propose that DNA methylation has an important role in the regulation of GLUT2.

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