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Role of Glycine *N*-Methyltransferase in the Regulation of T-Cell Responses in Experimental Autoimmune Encephalomyelitis

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Glycine *N*-methyltransferase (GNMT) is known for its function as a tumor suppressor gene. Since 100% of female *Gnmt*$^{-/-}$ mice developed hepatocellular carcinoma, we hypothesized that *Gnmt*$^{-/-}$ mice may have defective immune surveillance. In this study, we examined the immune modulation of GNMT in T-cell responses using experimental autoimmune encephalomyelitis (EAE). The results showed that EAE severity was reduced significantly in *Gnmt*$^{-/-}$ mice. Pathological examination of the spinal cords revealed that *Gnmt*$^{-/-}$ mice had significantly lower levels of mononuclear cell infiltration and demyelination than the wild-type mice. In addition, quantitative real-time PCR showed that expression levels of proinflammatory cytokines, including interferon (IFN)-γ and interleukin (IL)-17A, were much lower in the spinal cord of *Gnmt*$^{-/-}$ than in that of wild-type mice. Accordingly, myelin oligodendrocyte glycoprotein (MOG)-specific T-cell proliferation and induction of T-helper (Th)1 and Th17 cells were markedly suppressed in $MOG_{35–55}$-induced *Gnmt*$^{-/-}$ mice. Moreover, the number of regulatory T (Treg) cells was increased significantly in these mice. When the T-cell receptor was stimulated, the proliferative capacity and the activation status of mTOR-associated downstream signaling were decreased significantly in *Gnmt*$^{-/-}$ $CD4^+$ T cells via an IL-2- and CD25-independent manner. Moreover, GNMT deficiency enhanced the differentiation of Treg cells without affecting the differentiation of Th1 and Th17 cells. Furthermore, the severity of EAE in mice adoptive transferred with GNMT-deficient $CD4^+$ T cells was much milder than in those with wild-type $CD4^+$ T cells. In summary, our findings suggest that GNMT is involved in the pathogenesis of EAE and plays a crucial role in the regulation of $CD4^+$ T-cell functions.

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INTRODUCTION

Glycine *N*-methyltransferase (GNMT, EC 2.1.1.20) regulates the ratio of *S*-adenosylmethionine (SAM) to *S*-adenosylhomocysteine (SAH) and serves as a folate-binding protein (1,2). GNMT binds environmental carcinogens and prevents the DNA adduct formation and cytotoxicity induced by these carcinogens (3,4). Recently, we reported that GNMT was involved in the mammalian target of rapamycin (mTOR) signal transduction pathway and in intracellular cholesterol trafficking by interacting with DEP domain-containing mTOR-interacting protein (DEPTOR) and Neimann-Pick type C2 (NPC2) proteins, respectively (5,6). Moreover, expression of GNMT was downregulated in human hepatocellular carcinoma (HCC), and 50% male and 100% female *Gnmt* knockout (*Gnmt*$^{-/-}$) mice spontaneously devel-

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