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5-Aza-2'-Deoxycytidine Induces Alterations in Murine Spermatogenesis and Pregnancy Outcome

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Because of the ability of cytidine analogues, such as 5-aza-2'-deoxycytidine, to incorporate into DNA and lead to decreases in DNA methylation, there has recently been renewed interest in using these drugs in anticancer therapy. To determine the effects of paternal 5-aza-2'-deoxycytidine treatment on spermatogenesis and progeny outcome in the mouse and whether effects are modulated by decreased levels of the predominant DNA methyltransferase, DNMT1, adult *Dnmt1*$^{+/+}$ and *Dnmt1*-deficient (*Dnmt1*$^{c/+}$) male mice were treated with 5-aza-2'-deoxycytidine for 7 weeks, which resulted in dose-dependent decreases in testicular weight, an increase in histological abnormalities, and a decline in sperm counts, with no apparent effect on androgen status. Testes of *Dnmt1*$^{c/+}$ mice, however, were less severely affected by 5-aza-2'-deoxycytidine than were those of wild-type mice. The exposure of *Dnmt1*$^{+/+}$ male mice to even low doses of 5-aza-2'-deoxycytidine followed by mating elicited significantly reduced pregnancy rates and elevated preimplantation loss in females. *Dnmt1* deficiency, however, protected against such drug-induced decreases in pregnancy rate but not preimplantation loss. Altered DNA methylation or DNMT1 activity may explain such adverse effects, because treatment resulted in dose-dependent decreases in the global methylation of sperm DNA. Thus, in the mouse, paternal administration of 5-aza-2'-deoxycytidine interferes with normal male germ cell development and results in reduced fertility, whereas lowering DNMT1 levels appears to partially protect the seminiferous epithelium from deleterious drug effects.

Key words: DNA methylation, 5-azacytidine, DNMT, DNMT1, mouse, fertility, DNA methyltransferase 1

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