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Spermiogenic Germ Cell Phase–Specific DNA Damage Following Cyclophosphamide Exposure

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The production of genetically competent spermatozoa is essential for normal embryo development. The chemotherapeutic drug cyclophosphamide creates cross-links and DNA strand breaks in many cell types, including germ cells. This study assessed the phase specificity of the susceptibility of spermiogenic germ cells to genetic damage induced by cyclophosphamide. Adult male rats were given cyclophosphamide using one of four schedules: 1) high dose/acute— day 1, 100 mg/kg; 2) low dose/subchronic, 4 days—days 1–4, 6.0 mg/kg/d; 3) high dose/subchronic, 4 days—day 1, 100 mg/kg, and days 2–4, 50 mg/kg/d; and 4) low dose/chronic—daily, 6.0 mg/kg/d for 14–28 days. To capture cauda epididymal spermatozoa exposed to cyclophosphamide during late, mid-, and early spermiogenesis, animals were sacrificed on days 14, 21, and 28, respectively. Spermatozoa were analyzed for DNA strand breaks using the comet assay. No dramatic increases in damage were seen after high-dose/acute exposure to cyclophosphamide. Subchronic exposure showed a dose-related increase in DNA damage; maximal damage, as demonstrated by comet tail parameters, was seen after 21 days, reflecting an increased susceptibility of step 9–14 spermatids. Low-dose chronic exposure to cyclophosphamide induced DNA damage, which reached a plateau by day 21. The magnitude of damage at all time points after low-dose chronic exposure was much greater than that following low-dose exposure for 4 days, indicating an accumulation of damage over time. Thus, the DNA damage induced by cyclophosphamide is germ cell phase–specific. The most damaging effects of cyclophosphamide occurred during a key point of sperm chromatin remodeling (histone hyperacetylation and transition protein deposition). We speculate that strand breaks disrupt chromatin remodeling, hence affecting chromatin structure and embryo development.

Key words: Sperm, comet assay, chromatin remodeling, susceptibility, toxicology

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