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Exercise preconditioning alters colon tissue to withstand DNA damage and epigenetic changes during carcinogenesis

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Exercise reduces colorectal cancer risk, but its protective mechanisms in early carcinogenesis remain unclear. Male C57BL/6 mice (n=10/group) underwent 6-week progressive swimming (30 to 60 min/day, 5 d/week, 0 to 2% body weight load) initiated either before (preconditioning) or concurrent with (during) Azoxymethane (AOM) exposure (10 mg/kg/week i.p. x 6w). Aberrant foci and mucin-depleted lesions were assessed post-chronic AOM exposure. Acute responses to AOM(8/24 h) were analyzed post-final injection via γH2AX quantification, pyrosequencing (Mgmt CpGs), and qPCR. We demonstrate that 6 weeks of swimming exercise before, but not during, carcinogen exposure reduced premalignant mucin-depleted foci incidence ($P = 0.03$). Mechanistically, exercise preconditioning remodeled colon tissue to resist genotoxic stress, yielding 4-fold lower AOM-induced DNA double-strand breaks (γH2AX foci, $P < 0.05$) and accelerated normalization of DNA repair responses (Mgmt expression returned to baseline by 24h vs. sustained elevation in non-exercised controls, $P = 0.002$). Exercise also induced colon-specific epigenetic reprogramming, including hypermethylation of the Mgmt promoter (27% increase, $P = 0.0043$) and suppression of the mutagenic deaminase Apobec3 (3-fold lower, $P < 0.0001$). Notably, these molecular changes occurred without altering global LINE-1 methylation or body composition, suggesting targeted tissue adaptation rather than systemic effects. Our findings reveal that exercise preconditioning (not concurrently) reprograms colon biology to enhance genomic stability following carcinogen attack. Exercise-induced tissue-specific reduction of Apobec3, a recognized driver of mutation patterns in human cancers, identifies a novel preventative strategy that may have implications beyond colorectal cancer. These results provide a mechanistic foundation for the observed clinical benefits of lifelong exercise in cancer prevention, and highlight the importance of timing in protective interventions.

Keywords

Colon Carcinogenesis
Exercise
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Preconditioning

Conflict of Interest & Ethical Approval

yes

Abstract submitters declaration

yes

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