THE EFFECTS OF CISPLATIN TREATMENT ON NORMAL COLORECTAL EPITHELIAL CELLS

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Whole-genome sequencing of normal colonic crypts from cisplatin-treated testicular cancer survivors shows each cisplatin cycle adds 617 single base substitutions per crypt, equivalent to nearly 16 years of normal aging, but residual platinum detected years later is not mutagenic.

KEY POINTS

- Each cisplatin cycle adds an estimated 617 single base substitutions (95% CI 316-910) and 19 indels (95% CI 0.86-38) per colonic crypt, compared to 34 single base substitutions and 3 indels accumulated per year during normal aging.
- The excess mutations were predominantly attributed to platinum-associated mutational signatures SBS31 and SBS35.
- A single cisplatin cycle produces a mutation burden equivalent to nearly 16 years of age-associated mutation accumulation in unexposed individuals.
- Platinum-associated signatures SBS31 and SBS35 were abundant before late coalescence events but absent after, indicating that residual cisplatin detected in plasma and urine many years after treatment is not mutagenic.
- No evidence was found of cisplatin causing a precancerous field effect or increasing clonal spread in normal colonic epithelium.
- A novel indel mutational signature, IDA-N1, suspected to be cisplatin-related, was identified.

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