A comprehensive survey of the mutagenic impact of common cancer cytotoxics

Background: Genomic mutations caused by cytotoxic agents used in cancer chemotherapy may cause secondary malignancies as well as contribute to the evolution of treatment-resistant tumour cells. The stable diploid genome of the chicken DT40 lymphoblast cell line, an established DNA repair model system, is well suited to accurately assay genomic mutations. Results: We use whole genome sequencing of multiple DT40 clones to determine the mutagenic effect of eight common cytotoxics used for the treatment of millions of patients worldwide. We determine the spontaneous mutagenesis rate at 2.3 x 10^-10 per base per cell division and find that cisplatin, cyclophosphamide and etoposide induce extra base substitutions with distinct spectra. After four cycles of exposure, cisplatin induces 0.8 mutations per Mb, equivalent to the median mutational burden in common leukaemias. Cisplatin-induced mutations, including short insertions and deletions, are mainly located at sites of putative intrastrand crosslinks. We find two of the newly defined cisplatin-specific mutation types as causes of the reversion of BRCA2 mutations in emerging cisplatin-resistant tumours or cell clones. Gemcitabine, 5-fluorouracil, hydroxyurea, doxorubicin and paclitaxel have no measurable mutagenic effect. The cisplatin-induced mutation spectrum shows good correlation with cancer mutation signatures attributed to smoking and other sources of guanine-directed base damage. Conclusion: This study provides support for the use of cell line mutagenesis assays to validate or predict the mutagenic effect of environmental and iatrogenic exposures. Our results suggest genetic reversion due to cisplatin-induced mutations as a distinct mechanism for developing resistance.

General information
Publication status: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Hungarian Academy of Sciences, UCL Cancer Institute, Eötvös Loránd University
Number of pages: 1
Publication date: 2016
Peer-reviewed: Yes

Publication information
Journal: Genome Biology
Volume: 17
Article number: 99
ISSN (Print): 1474-7596
Ratings:
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 11.12 SJR 11.203 SNIP 2.88
Web of Science (2016): Impact factor 11.908
Web of Science (2016): Indexed yes
Original language: English
Keywords: Whole genome sequencing, Mutagenesis, Cisplatin, Cyclophosphamide, Etoposide, Cytotoxics, Cancer chemotherapy, Chemotherapy resistance, BRCA2, Spontaneous mutagenesis, DT40
Electronic versions:
DOIs:
10.1186/s13059-016-0963-7

Bibliographical note
© 2016 Szikriszt et al. Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Source: FindIt
Source ID: 2304095264
Research output: Contribution to journal › Journal article – Annual report year: 2016 › Research › peer-review