Assessment of Critical DNA Damage Responsible for the Cytotoxicity of Anticancer Drugs

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Anticancer drugs can concurrently generate three detrimental DNA lesions including DNA double-strand breaks (DSBs), DNA-protein cross-links (DPCs), and interstrand cross-links (ICLs) to varying degrees, and these lesions may differentially contribute to the toxicity of the drugs. However, no systematic studies have been performed about how much individual DSB, DPC, and ICL lesions contribute to cell killing upon treatment with anticancer drugs. Keeping this in mind, we treated HeLa cells with the equitoxic doses (LD20) of anticancer drugs and analyzed the induction of DSBs and DPCs. The association of ICLs with drug toxicity was assessed by the unique sensitivity of Chinese hamster ovary cells deficient in the xeroderma pigmentosum complementation group F gene. The results show that DNA lesions intimately associated with drug cytotoxicity vary significantly when HeLa cells are treated at the physiologically relevant doses. The critical cytotoxic DNA lesions are DSBs and DPCs for topoisomerase inhibitors (camptothecin and etoposide), DPCs for a DNA cytosine methyltransferase inhibitor (2'-deoxy -5-azacytidine), DPCs and ICLs for platinum drugs (cisplatin and oxaliplatin). Interestingly, cytotoxic DNA lesions are different for melphalan and mitomycin C although both are bifunctional alkylating agents. DSBs, DPCs, and ICLs are all associated with the cytotoxicity of melphalan, whereas ICLs alone are associated with the cytotoxicity of mitomycin C. Overall, our results provide a critical role of DPCs in anticancer drugs toxicity and raise the impact of DPC as a target for cancer therapies.

Keywords:

Anticancer drugs, DNA damage, DNA-protein cross-links, DNA repair

Recent Publications:

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Biography:

Mahmoud Ibrahim Shoulkamy, PhD. Joined School of Medicine, Shenzhen University, China in 2019 as an Associate Research Scientist in Genome Stability & Disease Prevention lab. He also works as Associate Professor in Minia University, Egypt. He did his Ph.D. in Molecular and Cell Biology (DNA repair) at Hiroshima University in 2013, where he studying the induction and repair of DNA damage induced by various DNA damaging agents. He went on to do his post-doctoral work in Gene Chemistry lab, Hiroshima University, where he got 3 years special appointed Assistant Professor. His current work investigates the molecular mechanisms and signaling pathways of gastric cancer.

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