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Role of oncometabolites succinate and fumarate in the response to induced DNA damage

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Genetic mutations in genes coding Krebs cycle enzymes, like succinate dehydrogenase (SDH) and fumarate hydratase (FH), cause a buildup of succinate and fumarate. These increases disrupt energy metabolism and lead to tumor development; moreover, they seem to affect chromatin structure by inhibiting histone and DNA demethylases, what, joined with their inhibition of some DNA repair proteins, contribute to DNA repair impairment that, in turn, might influence cancer therapy. To check the effects of oncometabolite accumulation on the response to different DNA-induced damages, three cell lines: PC12 (rat adrenal medulla pheochromocytoma), A2780 (ovarian carcinoma), and GM04312 (human fibroblast deficient of the nucleotide excision repair system), were treated with hydrogen peroxide or cisplatin. The DNA damage response (DDR) analysis included apoptosis, cell cycle progression, viability, clonogenic activity and genomic instability assays, and the determination of cisplatin induced DNA adducts using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). The presence of SDHB and FH proteins was determined by immunofluorescence. PC12 cells, used to check the effects of metabolites on the response to induced DNA oxidative damage, revealed firstly that the metabolites were not toxic and did not affect cell cycle progression, although they showed a slight increase in DNA damage, likely due to impaired repair of spontaneous damage. In addition, they altered apoptosis and the induced DNA damage, showing differences between the analysed oncometabolites.

A2780 and GM04312 cells were used to study the role of oncometabolites in the response to induced DNA cross-links. Results of GM04312 cells reveal an increase in DNA-adducted Pt, but only in co-treatments with cisplatin and oncometabolites. Results of A2780 cells show that oncometabolites were not toxic, but increased DNA damage, both spontaneous and induced ones, with a statistically significant positive correlation between the amount of DNA-adducted Pt and the DNA damage detected with the comet assay, also in cotreatments. This work suggests that the impact of oncometabolites on the repair of DNA strand breaks, may be extended to other types of DNA damage, like cross-links, probably related to their effect on homologous recombination repair (HRR).

Keywords:
Oncometabolites: succinate and fumarate; DNA damage response; cisplatin; hydrogen peroxide.