The role of succinate and fumarate in the response to cisplatin induced DNA damage

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When the genes encoding Krebs cycle enzymes succinate dehydrogenase (SDH) and fumarate hydratase (FH) are mutated, cells accumulate succinate and fumarate, respectively. This increase in metabolites results in dysregulation of energy metabolism, but also in the development of a tumor phenotype, because these oncometabolites inhibit α-ketoglutarate dependent dioxygenases (α-KGDD), like histone and DNA demethylases. Moreover, this inhibition modifies chromatin structure and, consequently, DNA repair activities, and thus might influence cancer treatments such as chemotherapy and radiotherapy.

To study the role of the oncometabolites succinate and fumarate in the response to DNA damage induced by a 3h treatment with 20 μM cisplatin, we worked with ovarian carcinoma A2780 cells, sensitive to cisplatin, and with GM04312 human fibroblasts, mutant for the XPA gene and deficient in the nucleotide excision repair (NER) system. We used succinate and methyl-succinate, to check a possible effect of succinate receptor. To analyze this DNA damage response (DDR), we analysed apoptosis, cell cycle progression, viability, clonogenic activity and genomic instability (using the comet assay); cisplatin-induced DNA adducts were determined with Inductively Coupled Plasma Mass Spectrometry (ICP-MS) as DNA-bound platinum. Furthermore, the presence of SDHB and FH proteins was determined by immunofluorescence in both cell lines, and in a third one, SDHB knockout, from a kidney cancer tumor (RCC4).

In A2780 cells, the results show that the oncometabolites, under the conditions and concentrations tested, did not induce relevant mortality, did not modify cell cycle progression or apoptosis, and did not influence clonogenic activity, except in the case of methyl-succinate, but cisplatin did. The % of tail DNA (used as a measure of DNA damage) shows that fumarate and succinate, regardless of concentration, generated DNA damage.

In GM04312 cells, both in pretreatments and co-treatments with these metabolites, the percentage of cisplatin-induced % of tail DNA increased with the highest oncometabolite concentrations. Moreover, these concentrations also increased the cisplatin DNA adducts, suggesting that oncometabolite accumulation prevents the repair of these DNA damage.