Influence of oncometabolites in the response to DNA damage

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One of the main characteristics of tumour cells is the deregulation of the energetic metabolism, caused by accumulation of metabolites from the Krebs cycle. It may be caused by punctual mutations in genes encoding Krebs cycle enzymes, such as isocitrate dehydrogenase, succinate dehydrogenase and fumarate hydratase which result in the accumulation of oncometabolites: R-2-hydroxyglutarate, succinate and fumarate, respectively. Through inhibition of histone demethylases, that contain Jumonji domain (JmjC), and TET 5-methylcytosine hydroxylase proteins, which demethylate DNA, they are able to alter chromatin structure and, therefore, to directly modify the accessibility of DNA repair systems to DNA damage. Since alteration of DNA damage repair might be very relevant when considering cancer treatments, like chemotherapy and radiotherapy, the general aim of this work is to study the impact of these molecules on DNA damage responses, after treatment with different genotoxic agents.

As a first step, PC12 cells, from a rat pheochromocytoma of the adrenal medule, were used to study the influence of succinate in the response to hydrogen peroxide induced DNA damage, using the comet assay to quantify it. Since succinate is not capable of entering cells, its methyl derivative was used in this work. PC12 cells were pre-treated with methyl-succinate concentrations in the range 1-5 mM (much lower than the corresponding IC50) for one hour, and then part of them were also treated with 200 μM H_2O_2 for 10 min. The other part were used to detect possible genotoxic effects of methyl-succinate.

The obtained data show that 1h treatment with 1 mM methylsuccinate (physiological concentration) presented not significant effect, whereas treatment with 5 mM methylsuccinate increases around a 30% the spontaneous DNA damage, but almost a 50% the DNA damage induced by H_2O_2. In both cases the increases were statistically significant. Although these are preliminary results, if confirmed, they could suggest that alteration of chromatin structure would make cells more susceptible to the effect of genotoxic agents.

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