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Identification of a synergistic relationship between paracetamol and 5-aza-2'-deoxycytidine in the treatment of head and neck squamous cell carcinoma

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Aberrant DNA methylation (5mC) is one of the key characteristics of many cancers including head and neck squamous cell carcinoma (HNSCC). Therefore, the DNA demethylating agent 5-aza-2'-deoxycytidine (DAC) has anti-cancer therapeutic potential, but is currently hindered by unwanted side effects when used at high concentrations. Here we investigated the potential use of DAC in the treatment of HNSCC and show that its efficacy is primarily dependent on the ability of DAC to demethylate DNA. In order to establish whether HNSCC cells can be sensitized to DAC, a panel of 100 generic drugs were screened in combination. None of the drugs were able to increase sensitivity to DAC in DAC-resistant HNSCC cell lines. However, interestingly it was identified that paracetamol increased DAC efficacy in the DAC-responsive HNSCC cell lines. DAC and paracetamol were established as working in synergy, allowing DAC to be used at therapeutically relevant low doses. The mechanisms underlying the DAC-paracetamol synergy are multifactorial and encompass both effects of DAC on paracetamol action (alterations in the cyclooxygenase (COX) pathway and mimicry of paracetamol overdose) as well as decreased DNA methylation by paracetamol. We propose DAC to be a potential therapeutic in a subset of HNSCC patients with its efficacy significantly increased by use of the common analgesic paracetamol. The DAC-paracetamol synergy should also be considered in cancers with an approved DAC treatment regime.

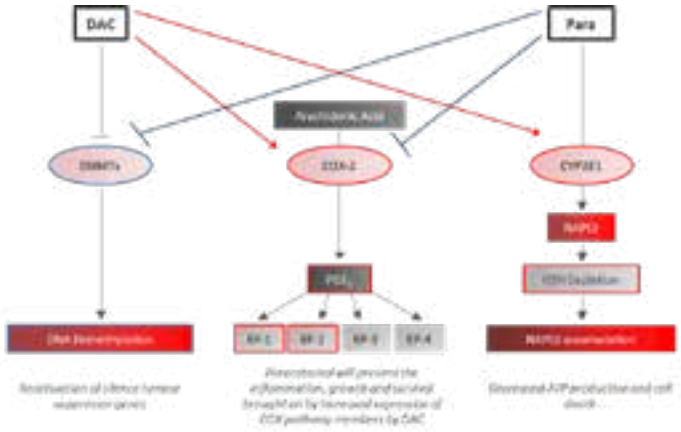

Figure 1: DAC and paracetamol work in synergy to reduce viability in HNSCC cells. Schematic showing the pathways altered by combined treatment with DAC and paracetamol in DAC responsive cell lines. Pathways described by the literature are denoted by black arrows, while the effect of DAC and paracetamol described by this study are shown in red and blue respectively.

Recent Publications

1. Tsai H C, et al. (2012) Transient low doses of DNA-demethylating agents exert durable antitumor effects on hematological and epithelial tumor cells. Cancer Cell 21(3):430-46.
2. Steinmann K, et al. (2009) Frequent promoter hypermethylation of tumor-related genes in head and neck squamous cell carcinoma. Oncology Reports 22(6):1519-1526.
3. Nervi C, E De Marinis and G Codacci-Pisanelli (2015) Epigenetic treatment of solid tumors: a review of clinical trials. Clin Epigenetics 7:127.
4. Wu Y J, et al. (2013) Acetaminophen enhances cisplatin- and paclitaxel-mediated cytotoxicity to SKOV3 human

ovarian carcinoma. Anticancer Res 33(6):2391-400.

5. Posadas I, et al. (2007) Acetaminophen potentiates staurosporine-induced death in a human neuroblastoma cell line. Br J Pharmacol 150(5):577-85.

Biography

Hannah Eadie is a final year PhD student at University of Birmingham. Her research examines the potential use of the DNA demethylating agent 5-Aza-2□-Deoxycytidine (Decitabine or DAC) in the treatment of head and neck cancer. This work has two main aims: to investigate genome wide changes in DNA methylation and hydroxymethylation in response to DAC treatment; and to determine whether the efficacy of DAC treatment can be increased through novel combination therapy.

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