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5-AZA-dC induces epigenetic changes associated with modified glycosylation of secreted glycoproteins and increased EMT and migration in chemo-sensitive cancer cells

Glycosylation, one of the most fundamental post-translational modifications, is altered in cancer and is subject in part, to epigenetic regulation. As there are many epigenetic-targeted therapies currently in clinical trials for the treatment of a variety of cancers, it is important to understand the impact epi-therapeutics have on glycosylation. Ovarian and triple negative breast cancer cells were treated with the DNA methyltransferase inhibitor, 5-AZA-2-deoxycytidine (5-AZA-dC). Branching and sialylation were increased on secreted N-glycans from chemosensitive/non-metastatic cells following treatment with 5-AZA-dC. These changes correlated with increased mRNA expression levels in *MGAT5* and *ST3GAL4* transcripts in ovarian cancer cell lines. Using siRNA transient knock down of GATA2 and GATA3 transcription factors, we show that these regulate the glycosyltransferases ST3GAL4 and MGAT5, respectively. 5-AZA-dC-treated cells displayed an increase in migration, with a greater effect seen in chemo-sensitive cell lines. Western blots showed an increase in apoptotic and senescence (p21) markers in all 5-AZAdC-treated cells. The alterations seen in N-glycans from secreted glycoproteins in 5-AZA-dC-treated breast and ovarian cancer cells were similar to the N-glycans previously known to potentiate tumour cell survival. Moreover, increased expression of ST3GAL4 was associated with poor recurrence free survival in ovarian and lymph node positive TNBC patients. While the FDA has approved epi-therapeutics for some cancer treatments, their global effect is still not fully understood. This study gives insight into the effects that epigenetic alterations have on cancer cell glycosylation and how this potentially impacts on the overall fate of those chemo-sensitive and chemo-resistant ovarian and breast cancer cells.

Biography

Dr Radka Fahey (Saldova) completed her PhD in Chemistry, specialization Glycobiology, at Institute of Chemical Technology in Prague, Czech Republic (2007). Radka has joined GlycoScience group under Prof PM Rudd supervision (2005) in Oxford University, UK and moved with the group to NIBRT, Ireland (2006), where Radka became independent investigator at 2014. Radka became adjunct research fellow at UCD in 2017 and CÚRAM investigator in 2018. Her research interests include glycobiomarker discovery, regulation and role of glycosylation in cancer and inflammatory diseases using multidisciplinary approach, and the development of high-throughput technologies for glycoanalysis. Radka has published 74 peer-reviewed publications (https://orcid.org/0000-0001-5085-5080).