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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

Radka Fahey

GlycoScience Group, the National Institute for Bioprocessing, Research and Training (NIBRT), Dublin, Ireland and UCD School of Medicine, College of Health and Agricultural Science (CHAS), University College Dublin (UCD), Dublin, Ireland

Abstract

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.

Keywords: Glycosylation, Biochemistry

Biochemists are interested, for example, in mechanisms of brain function, cellular multiplication and differentiation, communication within and between cells and organs, and the chemical bases of inheritance and disease. The biochemist seeks to determine how specific molecules such as proteins, nucleic acids, lipids, vitamins, and hormones function in such processes. Particular emphasis is placed on the regulation of chemical reactions in living cells.

Biochemistry is both life science and a chemical science - it explores the chemistry of living organisms and the molecular basis for the changes occurring in living cells. It uses the methods of chemistry,

"Biochemistry has become the foundation for understanding all biological processes. It has provided explanations for the causes of many diseases in humans, animals and plants."

physics, molecular biology, and immunology to study the structure and behaviour of the complex molecules found in biological material and the ways these molecules interact to form cells, tissues, and whole organisms.

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