Type 2 Transglutaminase inhibition deregulates MIR210HG lncRNA expression impacting hypoxia-related genes in triple-negative breast cancer cell line

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Type 2 Transglutaminase (TG2) is a ubiquitously expressed protein involved in several physiological and pathological processes, strongly associated with cancer. Among these several roles attributed to TG2, its involvement as a gene expression modulator has also been described, through serotonylation of histones [Previously published in: Farrelly LA et al. (2019) Nature 567, 535-539], as well as the cross-linking of transcription factors [Previously published in: Farrelly LA et al. (2019) Nature 567, 535-539].

This study aimed to inhibit TG2 using the AA9 inhibitor, followed by a bulk RNA-sequencing, to highlight alterations in lncRNA and canonical gene expression of MDA-MB-436 triple-negative breast cancer (TNBC) cells. MIR210HG (log2FC= -1.56) has been identified as significantly down-regulated upon treatment of 24 hours. MIR210HG is an antisense long non-coding RNA (lncRNA) that has been associated with several types of cancers, particularly with TNBC, in which it enhances the Warburg's effect [Previously published in: Du Y et al. (2020) Front Oncol 10:580176]. The down-regulation of MIR210HG, which acts as a miRNA sponge to the miR-1226-3p, allows the latter to target HIF-1α, leading to the down-regulation of genes encoding for glycolytic enzyme in MDA-MB-436 cells. We assessed their expression along with other key hypoxia-related markers, under the control of HIF-1α such as the metabolic enzymes ALDOA, ENO, LDHA, ACOT, PGAM1, and TPI1, angiogenesis-related genes like VEGF and ADM, the cyclin-dependent kinase inhibitor CDKN2A, or structural protein such as P4HA1 and TUBB. All the mentioned markers resulted down-regulated by AA9. These data agrees with the effects on cancer metabolism already demonstrated, correlating with decreasing cell motility and reduced oncogenicity of cancer cells. In this context, we underline the relevance of our results, highlighting the role of TG2 in the regulation of ncRNAs expression, which has never been investigated so far.