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LIRAGLUTIDE AS A NOVEL DNA DEMETHYLATING AGENT AND ITS POTENTIAL USE IN THE ADJUVANT TREATMENT OF HIGLY INVASIVE BREAST CANCER

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Objective: The aim of this study was to evaluate the effect of the GLP-1 analogue Liraglutide, currently utilized in the treatment of diabetes mellitus, as a new DNA demethylating agent in breast cancer. **Methods:** the breast cancer cell lines MCF7, MDA-MB-231 and MDA-MB-436 were treated with Liraglutide and submitted to methylation pattern analysis, gene expression and protein translation to evaluate the treatment response over the estrogen receptor (*ESR1*) and the cell adhesion (*CDH1*) and *ADAM33* genes. *In vivo*, Ehrlich mammary adenocarcinoma tumor model was induced in mice that were subsequentially treated with Liraglutide, Paclitaxel or Liraglutide and a half dose of Paclitaxel. The relative tumor volume was measured and compared with DNA methylation and protein analysis. **Results:** Our results revealed that Liraglutide reduced cell growth and migration in breast tumor cell lines, including triple negative breast cancer (TNBC), the most aggressive type. Meanwhile, we show that the treatment with Liraglutide induced gene and protein expression of Estrogen Receptor in previously triple-negative cells, adhesion protein, such as E-cadherin and ADAM33, a recently identified molecular marker for TNBC. The DNA demethylation, and consequential increase in gene expression, occurs in a manner similar to decitabine, a known DNA-demethylating agent used in the treatment of hematological cancer. *In vivo* Liraglutide treatment significantly decreased tumor volume in animal models. The combined treatment of Liraglutide and Paclitaxel allowed a significant dose reduction of the chemotherapy without loss of efficiency. The *CDH1* and *ADAM33* genes and proteins were expressed highlighting the demethylation potential *in vivo*. **Conclusion:** This is the first report that displays the Liraglutide´s potential as a DNA-demethylating agent and to propose it as an adjuvant agent in the treatment of breast cancer, including TNBC.