HMGA1 Regulates the Expression of Replication-Dependent Histone Genes and Cell-Cycle in Breast Cancer Cells

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Abstract:

Breast cancer (BC) is the primary cause of cancer mortality in women and triple-negative breast cancer (TNBC) is the most aggressive and difficult to treat subtype. It is characterized by poor differentiation and high proliferative properties. Usually, adjuvant therapy (i.e. anthracyclines-based regimens) is recommended after surgical intervention of patients affected by TNBC.

High mobility group A1 (HMGA1) is an oncogenic factor involved in transcriptional and epigenetic regulatory mechanisms. Moreover, HMGA1 intervenes in the onset and progression of the neoplastic transformation of BC. Here, we unraveled that the replication dependent-histone (RD-HIST) gene expression is enriched in BC tissues and correlates with HMGA1 expression. Subsequently, we investigated the hypothesis of existing an HMGA1-dependent pathway promoting the histone gene expression.

We explored the role of HMGA1 in modulating the RD-HIST gene expression in TNBC cells and showed that MDA-MB-231 cells, depleted of HMGA1, express low levels of core histones. We show that HMGA1 participates in the activation of the HIST1H4H promoter and that it interacts with the nuclear protein of the ataxia-telangiectasia mutated locus (NPAT), the coordinator of the transcription of the RD-HIST genes. Further, we demonstrate that HMGA1 silencing increases the percentage of cells in the G0/G1 phase both in TNBC and epirubicin-resistant TNBC cells. Moreover, HMGA1 silencing causes an increase in epirubicin IC50 both in parental and epirubicin resistant cells thus suggesting that targeting HMGA1 could affect the efficacy of epirubicin treatment.

We concluded that HMGA1 expression could not be neglected in epirubicin treatment regimens for TNBC-HMGA1 expressing cancer and that HMGA1 could be a valuable means to predict epirubicin responsiveness in resistance BC cells.

Biography of presenting author

I studied Molecular Diagnostics at the University Federico II in Naple, Italy and I graduated as MS in 2016 discussing the thesis entitled: Evaluation of the altered expression of the long non-coding RNA "RPSAP52" in pituitary tumors. Then I joined the research group of Prof. Manfioletti at the University of Trieste at Life Science Department. I received my PhD degree in Molecular Biomedicine in 2021 discussing the thesis, already published, entitled: HMGA1 regulates the expression of Replication-Dependent Histone genes and cell-cycle in breast cancer cells. At the end of my phD I published research articles/Reviews about brest cancer. After I moved to Thelethon Institute of Genetic and Medicine (TIGEM) in Pozzuoli to join the group of Dott. Paolo Grumati, the director of Mass Spectrometry Facility at TIGEM. Recently I won a research Fellow as post-doc focusing my interest on Cell Biology e Disease Mechanisms.

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