Histone Methyl Transferase DOT1L Affects Tamoxifen Actions Through its Interaction with ERα in MCF7 Breast Cancer Cell Line

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Estrogens play an essential role in the development and progression of Breast Cancers (BC), mainly of the hormone-responsive ones, representing around 70% of total. In this BC subgroup, estrogens effects are mediated by Estrogen Receptor α (ERα), a ligand-activated transcription factor that is therefore targeted by anti-estrogen based therapies. To understand the molecular mechanisms underlying ERα action is momentous to identify new target candidates in order to develop new possible BC therapies. By applying functional proteomics aimed at the identification of ERα interactome under anti-estrogen treatments we identified the histone methyltransferase DOT1L as a molecular partner of ERα in MCF7 breast cancer cell line treated with Tamoxifen stimulus. DOT1L is an enzyme that catalyzes mono-, di- and tri-methylation of H3K79, known for its involvement in the pathogenesis of Mixed Lineage Leukemia.

Starting from this data, we investigated the possible role of DOT1L in mediating Tamoxifen action, considering its interaction with ERα. To this aim, we firstly validated the interaction by co-immunoprecipitation experiments and Proximity Ligation Assay. Then, we used shRNAs to silence DOT1L expression in MCF7 cells treated or not with Tamoxifen and performed a gene expression profiling with Illumina platform to assess the effect of DOT1L silencing on ERα/Tamoxifen-driven gene expression.

Functional analysis of genes whose expression was affected by DOT1L silencing revealed its impact on several cellular processes, demonstrating that DOT1L is able to alter Tamoxifen-mediated signal transduction in breast cancer cells.

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