HIF1A-EP300-BRG1 functional crosstalk on the chromatin defines transcription of ABC transporters in paclitaxel resistant breast and lung cancers

ShT-04.3-1

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Paclitaxel is a first-line drug for the treatment of advanced non-small cell lung cancers and metastatic breast cancers. However, the development of resistance to paclitaxel leads to treatment failure and tumor recurrence. One of the mechanisms of paclitaxel resistance is overexpression of ABC transporters, which may actively efflux anticancer drugs from the cell or trap these drugs in intracellular organelles. Analysis of TCGA Pan-Cancer dataset suggests the link between transcription of SMARCA4, which encodes chromatin remodeling complex SWI/SNF subunit BRG1, and ABC transporters. Using ChIP-Seq, RNA-Seq, co-immunoprecipitation, confocal microscopy, and other molecular biology methods we provide evidence on the occurrence and functional role of BRG1 at the promoters of ABC transporters, which are overexpressed in breast and lung cancer resistant phenotypes. Motif spacing analysis of BRG1 enriched regions indicate that BRG1 co-occurs on the chromatin on paclitaxel resistant cells with HIF1A, ISL1, MAF and ZNF76 transcription factors, but their functional impact on ABC overexpression revealed HIF1 as primary, effective BRG1 co-factor. TCGA Pan-Cancer data from drug untreated tumors suggest the existence of strong ABC gene co-repression between BRG1 and HIF, where the deficiency of both proteins boosts transcription of inter alia ABCC3, which remains repressed in paclitaxel resistant cells. Subsequently, we identify EP300 as co-activator of HIF1A. Transient silencing of either of these three factors considerably declined abundance of ABC proteins, which are overexpressed and enriched in lysosomes of paclitaxel-resistant cells, and intralysosomal accumulation of anticancer drugs. Our study provides first experimental evidence on the formation of BRG1-EP300-HIF1 functional complex at the promoters of ABC genes, which confer intralysosomal drug sequestration and, hence, paclitaxel resistance in breast and lung cancer cells.

Grant: LIDER/22/0122/L-10/18/NCBR/2019.