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Identification and characterization of key epigenetic regulators ("epidrivers") of breast cancer onset, progression and phenotypes

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Epigenetic regulator genes (ERGs) are a group of over 400 genes which regulate gene expression by DNA methylation, histone modification and chromatin remodeling. ERGs play a crucial role in the establishment and maintenance of cell identity and genome integrity in health and disease. Indeed, ERGs are found to be commonly altered in cancer. This was further confirmed and extended by our pan-cancer genome, transcriptome and methylome analyses of ERGs'deregulations showing high rates of deregulations in specific ERGs within and across cancer types, including breast cancer (BC).
BC is the most frequent cancer type in women and represents most of the cancer-related deaths in this group. BC is a heterogeneous disease, categorized into four molecular subtypes according to the expression of estrogen, progesterone and HER2 receptors. The subtypes vary greatly in gene expression patterns, prognostic, phenotypes and response to treatments. Epigenetic deregulations play major roles in BC, with differential methylation patterns and histone modifications figuring as some of the known alterations contributing to this disease. Thus, we hypothesize that ERGs could act as drivers (epidrivers) of BC onset and progression, contributing to its molecular subtypes and their associated phenotypes.
To identify epidrivers of BC, we performed an in silico curation of ERGs'alterations in the BC subtypes using TCGA datasets and in vitro pooled loss-of-function genome editing screens targeting all ERGs. Our studies identified putative epidriver candidates that are currently under validation, and their role in cancer cell plasticity and different phenotypes is being assessed by an in depth functional and molecular characterization using non-tumorigenic breast and BC cell lines and patient-derived organoids.
Our study will advance the knowledge of mechanisms of BC and unravel novel epigenetics-based "Achilles heels"of BC which may be exploited to the development of targeted therapeutic approaches.

Keywords: epigenetics, breast cancer, CRISPR editing

Primary authors: GOMES DA SILVA ARAUJO, Mariana (IARC); HALABURKOVA, Andrea (IARC); SALLE, Aurelie (IARC); CUENIN, Cyrille (IARC); CAHAIS, Vincent (IARC); Dr GHANTOUS, Akram; KHOUEIRY, Rita (IARC); HERCEG, Zdenko (IARC)

Presenter: GOMES DA SILVA ARAUJO, Mariana (IARC)

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