Current therapies for breast cancer and other epithelial tumours are in many cases not effective because of intrinsic or acquired resistance, and tumours often relapse, leading to metastatic disease.

Research in the Transformation and Metastasis Group aims to identify novel therapeutic targets for cancer prevention and treatment, and to elucidate resistance mechanisms to drugs currently available. Tumours exploit and manipulate for their benefit the same mechanisms that work correctly in healthy tissue. Thus, we first aim to understand normal development and identify the key events that lead to tumour initiation, progression and metastasis to avoid and combat them. We work with primary cell cultures (including 3D cultures), genetically modified mouse models, patient derived xenografts and clinical samples.

The main contributions of the Group are within the field of mammary gland biology and breast cancer. Our goal is to translate our basic research findings into relevant clinical results.

“Using a collection of patient-derived breast cancer xenografts and multi-OMIC approaches, we have identified mechanisms of chemoresistance and propose novel strategies to guide the use of the right chemotherapy.”
Amplification of chromosome 12p in triple negative breast cancer is associated with emergent docetaxel resistance and carboplatin sensitivity

Taxanes are standard therapy in clinical practice for metastatic breast cancer, however, primary or acquired chemoresistance are a common cause of mortality. Breast cancer patient-derived xenografts (PDXs) are powerful tools for the study of cancer biology and drug treatment response. Specific DNA methylation patterns have been associated to different breast cancer subtypes, but their association with chemoresistance remains unstudied. Aiming to elucidate docetaxel resistance mechanisms, we performed genome-wide DNA methylation in breast cancer PDX models, including luminal and triple-negative breast cancer (TNBC) models sensitive to docetaxel, their matched models after emergence of chemoresistance, and residual disease after short-term docetaxel treatment. We found that DNA methylation profiles from breast cancer PDX models maintain the subtype-specific methylation pattern of clinical samples. Two main DNA methylation clusters were found in TNBC PDX and remained stable during the emergence of docetaxel resistance; however, some genes/pathways were differentially methylated according to docetaxel response. A DNA methylation signature of resistance able to segregate TNBC based on chemoresistance was identified. Transcriptomic profiling of selected sensitive/resistant pairs and integrative analysis with methylation data demonstrated correlation between some differentially methylated and expressed genes in docetaxel-resistant TNBC PDX models. Multiple gene expression changes were found after the emergence of docetaxel resistance in TNBC. DNA methylation and transcriptional changes identified in docetaxel-sensitive and -resistant TNBC PDX models or residual disease may have predictive value for chemotherapy response in TNBC. IMPLICATIONS: Subtype-specific DNA methylation patterns are maintained in breast cancer PDX models. While no global methylation changes were found, we uncovered differently DNA methylated and expressed genes/pathways associated with the emergence of docetaxel resistance in TNBC. FIGURE 2.

The altered transcriptome and DNA methylation profiles of docetaxel resistance in breast cancer PDX models

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