BREAST CANCER

Characterizing the genetic heterogeneity of murine breast cancer models

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Tumor heterogeneity among patients with breast cancer complicates diagnosis and challenges therapy. Although breast cancer has been classified into subtypes on the basis of biomarkers such as hormone receptors and human epidermal growth factor receptor 2 (HER-2) to help clinicians select the most efficient therapy for each cancer subtype, differences in treatment response remain. Efforts are therefore underway to further understand tumor heterogeneity and design personalized therapies.

In the past decade, large multiplatform studies have provided key insights into the genomic heterogeneity of human breast cancer. To translate these findings into new treatments, investigators use model systems, including genetically engineered mouse models (GEMMs). However it remains unknown whether the genomic landscape of mouse models mirrors human disease. A new study reveals that the genome of GEMMs shows similar alterations to those observed in the genome of patients with breast cancer. These findings support the use of mouse models in breast cancer research to understand tumor heterogeneity in patients.

The genomes of two highly used mouse models of breast cancer—MMTV-Neu and MMTV-PyMT transgenic mice—were analysed and compared to human genomic data. Whole-genome sequencing revealed large differences in the genomic landscape of the two models, notably in copy number variants (CNV). In MMTV-Neu tumors, a CNV including collagen type 1 alpha 1 (*Col1a*) and chondroadherin (*Chad*) was associated with dramatic differences in collagen content and metastatic potential. A similar COL1A/CHAD amplification was found in breast cancer patients, occurring more frequently in HER2+ tumors than in other subtypes. Then, the investigators knock-downed COL1A1 and CHAD in the Her2 amplified, COL1A/CHAD amplified human BT-474 breast cancer cell line. Histological and functional assays revealed that knock-down cells had reduced collagen production, decreased ability to migrate in vitro, and lower metastatic potential in vivo compared with control BT-474 cells, confirming the role COL1A/CHAD amplification in tumor phenotype.
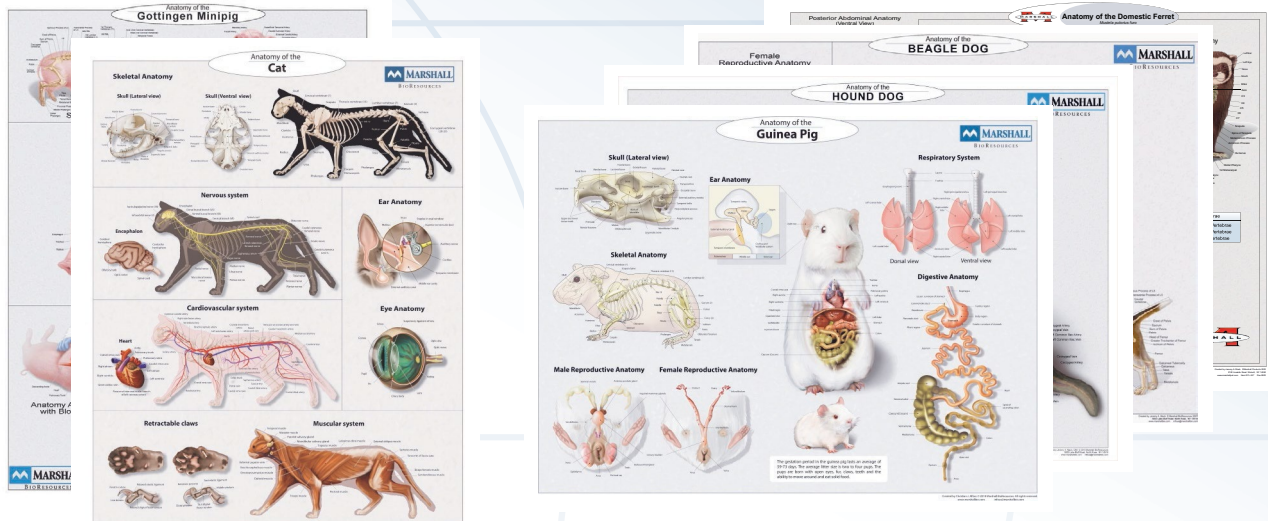
The investigators also looked into the mutational landscape of the two mouse models. In PyMT tumors, they identified a highly conserved mutation in the gene coding the protein tyrosine phosphatase receptor (*Ptprh*) resulting in elevated EGFR activity and erlotinib sensitivity.

In the discussion of the study, the investigators conclude: "Taken together, this manuscript provides a resource for investigators to determine how well the subtype of cancer they examine is represented by MMTV-Neu and MMTV-PyMT mouse model systems."

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