Poster #26
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Title of Research: Genetic Factors and Molecular Mechanisms that Mediate HER2-Positive Breast Cancer
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Introduction/Purpose:
TFAP2C and mouse homolog TCFAP2C are transcription factors that play a critical role in mammary gland development and in maintaining the luminal breast cancer phenotype. Interestingly, several human HER2-positive breast cancer cell lines display genetic dependency on TFAP2C. However, the role of TFAP2C in carcinogenesis and progression in Neu-activated breast cancer remains unknown.

Experimental Design:
Mice expressing MMTV-Neu with and without mammary gland conditional knockout (KO) of Tcfap2c were generated. The time until palpable tumor formation was measured in mice harboring the Neu oncogene with and without Tcfap2c. Immunohistochemistry was used to characterize tumors. Paired cell lines from an animal expressing activated Neu with with differential expression of Tcfap2c were established by infecting the cells with Adenovirus-Cre (Ad-Cre) or Adenovirus-Empty (Ad-Empty). Proliferation was assessed by MTT. ChIP-seq and RT-PCR were used to elucidate TCFAP2C targets.

Results:
Mice with homozygous conditional deletion of Tcfap2c demonstrated a significant delay in tumor formation compared to littermate controls that retained Tcfap2c expression ($p<0.004$). Immunohistochemistry of the tumors demonstrated a luminal phenotype; cytokeratin 8 (CK8), a luminal marker, was more strongly expressed compared to cytokeratin 5 (CK5), a basal marker, in tumors from both control ($p<0.0005$) and KO animals ($p<0.0005$). Cleaved caspase-3 (CC3) showed that apoptosis was increased in tumors from KO compared to control animals ($p<0.0008$). Ki-67 showed that proliferation was decreased in KO compared to control ($p<0.009$). MTT demonstrated that loss of Tcfap2c expression resulted in a 30% decrease in proliferation rate ($p<0.006$). Athymic mice that were xenografted with the paired cell lines (Ad-Cre and Ad-Empty) demonstrated that KO of Tcfap2c resulted in a significant delay in tumors reaching a 2 cm threshold ($p<0.003$). We identified Erbb3 and Egfr as two TCFAP2C target genes by ChIP-seq. KO of Tcfap2c resulted in a 3-fold and 12-fold reduction in Erbb3 and Egfr expression, respectively ($p<0.05$).

Conclusions:
Tcfap2c appears to positively regulate known oncogenes such as Erbb3 and Egfr. Taken together, these findings indicate that Tcfap2c plays a critical role in oncogenesis and progression of HER2-positive mammary cancer. Additional investigation into how EGFR contributes to ERBB2-positive breast cancer may provide improved personalized clinical management strategies.