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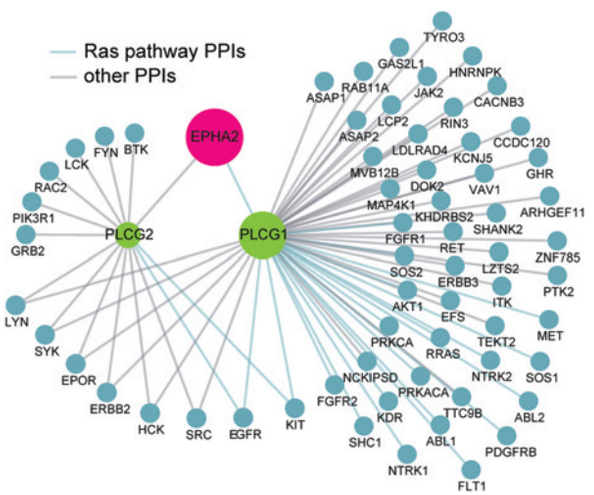
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

EphA2 Interacts with PLCγ1 in Lung Cancer



Song *et al.* | Page 1735

Altered receptor tyrosine kinase (RTK) activity has long been recognized as a key source of pro-mitotic and pro-survival signals that support the proliferation of cancer cells. The RTK EphA2 is particularly known to be overexpressed and to contribute to tumorigenic signaling in lung cancer. However, the downstream signaling pathways that transduce EphA2 signaling into biological outcomes are not well understood. Here, Song and colleagues identify phospholipase Cγ1 (PLCγ1) Y783 as a key phosphorylation substrate and crucial signaling mediator downstream of EphA2. Perturbations of EphA2 and PLCγ1 expression and/or activity revealed that this axis was necessary for tumor proliferation in multiple models. Taken together, the data provide a foundation for developing interventions that target EphA2-PLCγ1 signaling for therapeutic benefit.

Stromal Regulation of Breast Cancer Invasion

Hanley *et al.* | Page 1615

Heterotypic interactions between the tumor cells and the stromal compartment play a key role in guiding the development of tumor development and metastasis. Here, Hanley and colleagues report a dynamic regulatory feedback loop between breast cancer cells and their cognate stroma. By culturing breast cancer organoids alongside autologous fibroblasts, the authors observed an increase in keratin-14 (KRT14) expression in tumor cells. KRT14 expression marked a transcriptomic profile with basal epithelial characteristics and a propensity toward metastasis, regardless of whether the organoids were originally luminal- or basal-type. Importantly, conditioned medium from fibroblasts did not induce KRT14 expression: instead, it was found that TGF-β signaling from cancer cells to fibroblasts was necessary to induce NOX4 expression, which in turn induced KRT14 expression and alteration of the organoids' molecular phenotype. Taken together, the data elucidate a novel mechanism by which fibroblasts can influence tumor biology and progression.

RNF8 Promotes EMT in Lung Cancer

Kuang *et al.* | Page 1638

Despite significant progress in recent decades, lung cancer remains the leading cause of cancer mortality and there is an ongoing clinical need to identify novel therapeutic targets. Ring finger protein 8 (RNF8), an E3 ubiquitin ligase with roles in DNA repair and spermatogenesis, was recently reported to contribute to breast cancer progression and metastasis. In this study, Kuang and colleagues identify RNF8 as a potential therapeutic target in lung cancer by virtue of a novel tumorigenic mechanism. RNF8 expression had significant bearing on cell motility, similar to its known role in breast cancer. Distinct from these earlier findings, however, RNF8 activity in lung cancer was found to be mediated through stabilization of the pro-metastatic transcription factor Slug. Specifically, RNF8 mediated Slug stabilization through ubiquitination of lysine residue 63, thus promoting PI3K/Akt signaling and epithelial–mesenchymal transition in lung cancer cells. Overall, the study provides new mechanistic insights into the role of RNF8 in cancer and nominate it as a potential therapeutic target to inhibit metastatic spread.

RCC2 Promotes Esophageal Tumor Growth through Sox2

Calderon-Aparicio *et al.* | Page 1660

Esophageal cancer is a common and deadly malignancy whose incidence is increasing worldwide. In this study, Calderon-Aparicio and colleagues identify regulator of chromosome condensation 2 (RCC2) as a novel oncogene in esophageal cancer. Whereas RCC2 normally functions as a regulator of Aurora kinase B activity to mediate mitosis, the authors report that increased RCC2 expression in the esophagus served to activate the expression and activity of the oncogenic transcription factor Sox2. The RCC2-Sox2 network was shown to be crucial for the proliferation and migration of esophageal cancer cells *in vitro*. RCC2-Sox2 was also shown to be overexpressed *in vivo*, specifically in the esophageal basal cell layer, and was necessary for both the genesis and progression of esophageal cancer in mice. These data mechanistically demonstrate a novel role for RCC2 in esophageal cancer, which may be a candidate for the development of targeted interventions.

Molecular Cancer Research

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