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Opposing effects of inhibitors of Aurora-A and EGFR in autosomal-dominant polycystic kidney disease

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Abstract

© 2015 Nikonova, Deneka, Eckman, Kopp, Hensley, Egleston and Golemis. Aurora-A kinase (AURKA) overexpression in numerous tumors induces aneuploidy, in part because of cytokinetic defects. Alisertib and other small-molecule inhibitors targeting AURKA are effective in some patients as monotherapies or combination therapies. Epidermal growth factor receptor (EGFR) pro-proliferative signaling activity is commonly elevated in cancer, and the EGFR inhibitor erlotinib is commonly used as a standard of care agent for cancer. An erlotinib/alisertib combination therapy is currently under assessment in clinical trials, following pre-clinical studies that indicated synergy of these drugs in cancer. We were interested in further exploring the activity of this drug combination. Beyond well-established functions for AURKA in mitotic progression, additional non-mitotic AURKA functions include control of ciliary stability and calcium signaling. Interestingly, alisertib exacerbates the disease phenotype in mouse models for autosomal-dominant polycystic kidney disease (ADPKD), a common inherited syndrome induced by aberrant signaling from PKD1 and PKD2, cilia-localized proteins that have calcium channel activity. EGFR is also more active in ADPKD, making erlotinib also of potential interest in this disease setting. In this study, we have explored the interaction of alisertib and erlotinib in an ADPKD model. These experiments indicated erlotinib-restrained cystogenesis, opposing alisertib action. Erlotinib also interacted with alisertib to regulate proliferative signaling proteins, albeit in a complicated manner. Results suggest a nuanced role of AURKA signaling in different pathogenic conditions and inform the clinical use of AURKA inhibitors in cancer patients with comorbidities.

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Keywords

Aurora-A kinase, EGFR, Mouse models, PKD1, Renal cyst, SRC