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Crosstalk between ERK, AKT, and cell survival

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It is historically well known that signaling by the PI3K-AKT and MEK1/2-ERK1/2 pathways in a cell type-dependent fashion can collaborate to maintain cell viability.[1-3] Signaling pathways can also crosstalk with each other wherein one pathway can signal to either enhance or suppress signaling by another.[4] Signaling by the ERK1/2 pathway can also stimulate release of growth factors which can feed back onto tumor cells to re-energize signaling pathways.[5] The studies described by Toulany et al. add to this knowledge base by examining the relationship between PI3K-AKT and MEK1/2-ERK1/2 pathway signaling, EGF receptor signaling, K-RAS function, and tumor cell survival.[6]

Initial studies comparing lung and head and neck tumor cells demonstrated that the total level of K-RAS activity in tumor cells rather than its mutational status correlated with clonogenic plating efficiency/survival. Studies using the EGF receptor inhibitor erlotinib demonstrated in head and neck tumor cells with elevated EGF receptor expression that they used this receptor to cause high levels of wild-type K-RAS activity and thus colony plating efficiency; in cells expressing a mutant activated K-RAS or with low EGF receptor expression inhibitors of the EGF receptor had no effect on plating efficiency. Downstream of K-RAS the PI3K/mTOR pathway was judged to play a greater role than the ERK1/2 pathway in regulating colony formation, though in cells expressing mutant active K-RAS the ability of a PI3K/mTOR inhibitor to cause a sustained ~24 h reduction in phospho-AKT levels was not complete.

Based on the possibility that crosstalk could be occurring between the PI3K and ERK1/2 pathways, the authors then examined at later time points (24 h) the role of ERK1/2 in mediating sustained AKT phosphorylation in the face of a PI3K/mTOR inhibitor. Inhibition of MEK1/2 or knockdown of ERK2 blocked sustained AKT activity in cells treated with a PI3K/mTOR inhibitor. In colony formation assays inhibition of MEK1/2 synergized with inhibition of PI3K/mTOR signaling to kill tumor cells. Thus in cells with constitutive K-RAS activity, short-term inhibition of PI3K/mTOR suppresses AKT activity that rebounds by 24 h; the rebound being due to ERK1/2 pathway signaling.

The present studies do not further explore how/why this form of crosstalk signaling occurs, though enhanced paracrine ligand signaling through the EGF receptor was ruled out. It is possible that modulation of PTEN function by MEK1 activity or signaling by H-RAS (that preferentially binds PI3K) may play roles in this process.[7] Further studies will thus be required to define this new pathway by which ERK regulates AKT.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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