Rapamycin synergizes cisplatin sensitivity in basal-like breast cancer cells through up-regulation of p73.

Abstract

Recent gene expression profiling studies have identified five breast cancer subtypes, of which the basal-like subtype is the most aggressive. Basal-like breast cancer poses serious clinical challenges as there are currently no targeted therapies available to treat it. Although there is increasing evidence that these tumors possess specific sensitivity to cisplatin, its success is often compromised due to its dose-limiting nephrotoxicity and the development of drug resistance. To overcome this limitation, our goal was to maximize the benefits associated with cisplatin therapy through drug combination strategies. Using a validated kinase inhibitor library, we showed that inhibition of the mTOR, TGFβRI, NFκB, PI3K/AKT, and MAPK pathways sensitized basal-like MDA-MB-468 cells to cisplatin treatment. Further analysis demonstrated that the combination of the mTOR inhibitor rapamycin and cisplatin generated significant drug synergism in basal-like MDA-MB-468, MDA-MB-231, and HCC1937 cells but not in luminal-like T47D or MCF-7 cells. We further showed that the synergistic effect of rapamycin plus cisplatin on basal-like breast cancer cells was mediated through the induction of p73. Depletion of endogenous p73 in basal-like cells abolished these synergistic effects. In conclusion, combination therapy with mTOR inhibitors and cisplatin may be a useful therapeutic strategy in the treatment of basal-like breast cancers.

Keyword: Basal-like breast cancer; Cisplatin; p73; Rapamycin; Synergism