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Activation of AMPK-TSC axis is involved in cryptotanshinone inhibition of mTOR signaling in cancer cells

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Abstract : Cryptotanshinone (CPT), a fat-soluble tanshinone from Salvia miltiorrhiza Bunge, has been demonstrated to inhibit mTOR pathway, resulting in inhibition of cancer cell proliferation. However, the molecular mechanism how CPT acts on mTOR is unknown. Here, cancer cells expressing rapamycin-resistant mutant mTOR are also sensitive to CPT, while phosphorylation of AMPK and TSC2 was activated, suggesting that CPT inhibition of mTOR maybe due to activating upstream of mTOR, AMPK, but not directly binding to and inhibiting mTOR. Further results indicated that Compound C, inhibitor of AMPK, could partially reversed CPT inhibition effect on cancer cells, and dominant-negative AMPK in cancer cells conferred resistance to CPT inhibition of 4EBP1 and phosphorylation of S6K1, as well as sh-AMPK. Furthermore, compared with MEF cells with AMPK positive, MEF cells with AMPK knock out are less sensitive to CPT by the findings that 4E-BP1 and phosphorylation of S6K1 express comparatively much. Furthermore, downexpression of TSC2 slightly recovered expression of 4EBP1 and phosphorylation of S6K1, while co-immunoprecipitation of TSC2 did not affect expression of TSC1 by CPT. Collectively, the above-mentioned results suggest that CPT inhibited mTOR pathway mostly was due to activation of AMPK-TSC2 pathway rather than specific inhibition of mTOR and then induction of subsequent lethal cellular effect.

Keywords : cryptotanshinone, AMPK, TSC2, mTOR, cancer cells
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