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Mevalonate pathway blockage enhances the efficacy of mTOR inhibitors with the activation of retinoblastoma protein in renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) is the most common malignancy of kidney and remains largely intractable once it recurs after resection. mTOR inhibitors have been one of the mainstays used against recurrent RCC; however, there has been a major problem of the resistance to mTOR inhibitors, and thus new combination treatments with mTOR inhibitors are required. We here retrospectively showed that regular use of antilipidemic drug statins could provide a longer progression free survival (PFS) in RCC patients prescribed with an mTOR inhibitor everolimus than without statins (median PFS, 7.5 months vs. 3.2 months, respectively; hazard ratio, 0.52; 95% CI, 0.22-1.11). In order to give a rationale for this finding, we used RCC cell lines and showed the combinatorial effects of an mTOR inhibitor with statins induced a robust activation of retinoblastoma protein, whose mechanisms were involved in statins-mediated hindrance of KRAS or Rac1 protein prenylation. Finally, statins treatment also enhanced the efficacy of an mTOR inhibitor in RCC xenograft models. Thus, we provide molecular and (pre)clinical data showing that statins use could be a drug repositioning for RCC patients to enhance the efficacy of mTOR inhibitors.