

Abstract

RAS-driven malignancies such as melanoma, pancreatic, colorectal and pancreatic cancer are the epitome of recalcitrant diseases driven by pharmacologically intractable RAS oncoproteins. Downstream of RAS oncoproteins, the RAF→MEK→ERK MAP kinase signaling pathway plays a central role in RAS-driven tumorigenesis. However, paradoxically, inhibition of RAF→MEK→ERK signaling with FDA-approved, potent pharmacological inhibitors has provided no clinical benefit to patients with these diseases. We have recently demonstrated that inhibition of KRAS→RAF→MEK→ERK signaling elicits autophagy, a process of cellular recycling that can protect cancer cells from the cytotoxic effects of KRAS pathway inhibition. Mechanistically, inhibition of MEK1/2 leads to activation of the LKB1→AMPK→ULK1 signaling axis, a pathway that is a key regulator of autophagy initiation. Furthermore, combined inhibition of MEK1/2 plus autophagy displays synergistic anti-proliferative effects against PDA cell lines in vitro and promotes regression of xenografted patient-derived PDA tumors in mice. Moreover, treatment of a patient with advanced, treatment refractory KRAS(G12R)-driven pancreatic cancer with the combination of trametinib plus hydroxychloroquine resulted in a partial, but nonetheless striking disease response. These data suggest that this combination therapy may represent a novel strategy to target RAS-driven cancers.