A General Strategy to Overcome Resistance to Targeted Anticancer Therapies

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Inhibition of mutated oncogenic kinases such as BRAF and EGFR in melanoma and non-small cell lung cancer respectively, has been widely recognized as a success story for targeted anticancer therapies. Rapid and often dramatic reduction in tumor burden have been reported mere weeks after the initiation of therapy. However, the durability of such antitumor responses is often short-lived, due to the emergence of resistance.

In this talk, we report that addition of a procaspase-3 activating compound (PAC-1) to targeted anticancer therapies, such as inhibitors of mutant BRAF (vemurafenib), enhances apoptotic cell death via procaspase-3 activation. Enhanced caspase-3 activity in cells treated with this combination also led to the sustained inhibition of downstream kinase signaling. As a result of increased apoptotic cell death and sustained pathway inhibition, the combination of PAC-1 with vemurafenib overcomes acquired vemurafenib resistance.