Selective killing of cancer cells by ACA-28, a small molecule inducing ERK-dependent apoptosis: ~ A novel cancer therapy to stimulate oncogenic ERK signaling~

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<Background> The extracellular-signal-regulated-kinase (ERK) signaling pathway is essential for cell proliferation and is frequently deregulated and hyperactivated in approximately, one-third of all human cancers such as melanoma. Melanoma remains incurable despite the use of conventional chemotherapy as well as molecular targeted therapy, consequently development of new therapeutic agents for melanoma is highly desirable.

<Methods> Here, we performed a chemical genetic screen to identify compounds targeting the ERK hyperactivation and identified ACA-28, a synthetic derivative of 1'-Acetoxychavicol Acetate (ACA), which is a natural ginger compound. We demonstrated that ACA-28 effectively inhibited the growth of three types of melanoma cancer cells wherein ERK MAPK signaling is hyperactivated due to mutations in the upstream activating regulators. We investigated the mechanisms of action of ACA-28 to selectively kill cancer cells.

<Results> ACA-28 strongly inhibited the growth of melanoma cells than did the parental compound ACA. Importantly, the growth of normal human epidermal melanocytes (NHEM) was less affected by ACA-28 at the same 50% inhibitory concentration. In addition, ACA-28 specifically induced apoptosis in NIH/3T3 cells which were oncogenically transformed with HER2/ErbB2, but not in the parental NIH/3T3 cells. Surprisingly, ACA-28 further stimulated ERK phosphorylation in melanoma cells as well as NIH/3T3 cells oncogenically transformed with HER2/ErbB2, wherein ERK is hyperactivated. Consistently, the ACA-28-induced apoptosis in melanoma and HER2-transformed cells was abrogated when ERK activation was blocked with a specific MEK inhibitor U0126.

<Conclusions> ERK hyperactivation is a pre-requisite for ACA-28-mediated cancer cell killing. To our knowledge, this is the first demonstration that a small molecule compound can selectively kill cancer cells by inducing ERK-dependent apoptosis. ACA-28 may be effective in various cancer cells wherein ERK signaling is hyper-activated. Our data propose a novel cancer therapy to stimulate oncogenic ERK signaling and induce ERK-dependent apoptosis.