

Abstract

Therapeutic Potential of Black Pepper Compound for BRAF Resistant Melanoma [†]

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Abstract: Malignant melanoma is significant problem for Caucasian population in the western countries. Mutations in BRAF gene in 60% of patients is responsible for developing resistance to BRAF inhibitors. Our results delineated the mechanism of resistance and identified a suitable drug combination to overcome the resistance. Treatment of BRAF mutant melanoma cells with vemurafenib or dabrafenib (BRAF inhibitors) alone or in combination with trametinib (MEK1/2 inhibitor) resulted in induced expression of Mcl-1. Melanoma cells resistant to BRAF inhibitors exhibited substantial expression of Mcl-1 as compared to sensitive cell lines. Silencing of Mcl-1 using siRNA completely sensitized resistant cells to growth suppression and induction of apoptosis by BRAF inhibitors. Piperlongumine, an active component of black pepper substantially suppressed the growth of vemurafenib resistant melanoma cells by inducing apoptosis and inhibiting Mcl-1 expression. Vemurafenib resistant A375 xenografts showed substantial tumor growth inhibition in mice when treated with a combination of vemurafenib and Mcl-1 inhibitor or siRNA. Oral administration of piperlongumine also suppressed the growth vemurafenib resistant tumor xenografts in athymic nude mice. Immunohistochemistry and western blot analyses confirmed enhanced expression of Mcl-1 and activation of ERK1/2 in vemurafenib-resistant tumors whereas level of Mcl-1 or p-ERK1/2 was reduced in the tumors of mice treated with either of the combination or piperlongumine. Biopsied tumors from the patients treated with or resistant to BRAF inhibitors revealed overexpression of Mcl-1. These results suggest that the combination of BRAF inhibitors with Mcl-1 inhibitor such as piperlongumine may have therapeutic advantage to melanoma patients with acquired resistance to BRAF inhibitors alone or in combination with MEK1/2 inhibitors.

Keywords: melanoma; BRAF mutation; BRAF inhibitors; MEK1/2 inhibitors; piperlongumine; Mcl-1; trametinib; A375



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