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Overcoming resistance to BRAF therapy in melanoma

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Melanoma harboring BRAF mutations frequently develop resistance to BRAF inhibitors, limiting the impact of treatment. The most prevalent mechanisms of acquired resistance appear to reactivate MAPK pathway. Furthermore, relatively little is known about the determinants of de novo resistance. We identified a mechanism of resistance and subsequently a suitable drug combination to overcome the resistance. Single treatment of BRAF mutant melanoma cell lines with BRAF inhibitors such as vemurafenib or dabrafenib (BRAF inhibitors) alone or in combination with trametinib resulted in overexpression of Mcl-1. Overexpression of Mcl-1 in melanoma cells completely blocked BRAF and MEK1/2 inhibitor-mediated inhibition of cell survival and apoptosis. Melanoma cells resistant to BRAF inhibitors showed massive expression of Mcl-1 as compared to respective sensitive cell lines. Silencing of Mcl-1 completely sensitized resistant melanoma cells to growth suppression and induction of apoptosis by BRAF inhibitors. Vemurafenib resistant A375 xenografts implanted in mice showed significant tumor growth inhibition when treated with a combination of vemurafenib and Mcl-1 inhibitor or siRNA. Immunohistochemistry and western blot analyses demonstrated enhanced expression of Mcl-1 and activation of ERK1/2 in vemurafenib-resistant tumors whereas level of Mcl-1 or p-ERK1/2 was diminished in the tumors of mice treated with either of the combination. Tumors obtained from the patients treated with or resistant to BRAF inhibitors demonstrated overexpression of Mcl-1. These results suggest that the combination of BRAF inhibitors with Mcl-1 inhibitor may have therapeutic advantage to melanoma patients with acquired resistance to BRAF inhibitors alone or in combination with MEK1/2 inhibitors.

Biography

Sanjay K Srivastava is a Professor of Biomedical Sciences and Associate Dean for Sciences at Texas Tech University Health Sciences Center, Amarillo, Texas, USA. His research funded by NIH has been published in more than 120 papers and has several books and patents. He is in the Editorial Board of several journals. His laboratory is focused on finding novel drugs to reduce drug resistance and enhance the therapy of difficult-to-treat cancers. His group recently identified the mechanism of the failure of two recently FDA-approved drugs for the treatment of malignant melanoma, a type of skin cancer affecting the Caucasian population when exposed to sunlight. His research has demonstrated that combination of Mcl-1 inhibitors with traditional chemo drugs like vemurafenib or dabrafenib, significantly suppresses melanoma tumor growth by overcoming resistance. After in silico screening of a library, his group identified several potent inhibitors of Mcl-1 and now aggressively working on developing those inhibitors as drugs for combination therapy for melanoma treatment.

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