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Drug Discovery of Novel Targeted Therapeutics for Metastatic Breast Cancer

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Drug Discovery of Novel Targeted Therapeutics for Metastatic Breast Cancer*

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Abstract

Metastatic disease is the primary cause of breast cancer mortality, due to the lack of effective therapy. The Rho GTPase Rac is integral for the promotion of cancer cell migration/invasion, proliferation, and survival. Since metastatic breast cancers often overexpress or exhibit high Rac activity, inhibition of Rac is a viable strategy against metastatic cancer. Recently, we characterized EHop-016, a small molecule that inhibits Rac activity of metastatic breast cancer cells more efficiently than previously available Rac inhibitors (IC_{50} of 1μM). EHop-016 inhibits the activity of the Rac downstream effector p21 activated kinase and cell migration of metastatic breast cancer cells.

We also reported that EHop-016 at ? 25mg/kg body weight significantly reduced tumor growth and metastasis in mice. However, our recent pharmacokinetic study of EHop-016 in a mouse model demonstrated that the bioavailability of Ehop-016 needs to be improved for pharmacological development. The hypothesis is that improvement of the EHop-016 structure will provide probes with increased potency against Rac and, therefore, increased bioavailability.

Several Ehop-016 derivatives have been tested for their effects on breast cancer cell viability using the MTT assay. We found one compound, HV-107, which at concentrations ?1μM inhibits the viability of metastatic breast cancer cell lines MDA-MB-231 and MDA-MB-435 by 45%. The effects of HV-107 on the inhibition of Rac activation were tested by pulldown assays. At 250nM, HV-107 inhibits Rac activation by 55% in MDA-MB-231 and MDA-MB-435 cells. Taken together, our findings suggest HV-107 has potential as an anti-metastatic agent and should, therefore, be further characterized.

KEYWORDS: Metastatic disease; Breast cancer; Rho GTPase Rac

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Metastatic disease is the primary cause of breast cancer mortality, due to the lack of effective therapy. The Rho GTPase Rac is integral for the promotion of cancer cell migration/invasion, proliferation, and survival. Since metastatic breast cancers often overexpress or exhibit high Rac activity, inhibition of Rac is a viable strategy against metastatic cancer. Recently, we characterized EHop-016, a small molecule that inhibits Rac activity of metastatic breast cancer cells more efficiently than previously available Rac inhibitors (IC_{50} of 1µM). EHop-016 inhibits the activity of the Rac downstream effector p21 activated kinase and cell migration of metastatic breast cancer cells.

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