Inhibition of tumor cell invasion and ErbB2/PI3K signaling pathways by the glutathione disulfide-mimetic NOV-002

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Abstract

NOV-002, a glutathione disulfide-mimetic, is in advanced clinical development for the treatment of solid malignancies. In the current study, NOV-002 was evaluated for its effects on tumor cell invasion and proliferation in xenograft models and cell cultures. The results indicated that NOV-002 interferes with the redox state of the tumor environment, inducing apoptosis of cancer cells and inhibiting their invasion. Further, NOV-002 was shown to suppress the activation of a well-characterized, redox sensitive ErbB2/PI3K signaling pathway. These data suggest that NOV-002 may affect pathways which are specific for invasion. In vitro NOV-002 (the highest concentration tested in the invasion and migration assays) was not toxic to any of the tumor cell lines studied even after 72 hours of culture using MTT viability assay. These effects were shown to involve the suppression of downstream (Akt and RhoA) signaling proteins. Analysis demonstrated that NOV-002 induced the expression of the ErbB2/PI3K signaling pathway in a dose-dependent manner and decreased cell migration and migration of tumor cells without affecting the total amount of phosphorylated (active) forms of signaling proteins ErbB2 and PI3k, known to regulate tumor cell invasion in A549 and Colo205 cells, without affecting the total amount of these proteins. In conclusion, NOV-002 is a novel drug candidate for the treatment of human solid tumors.

Figure 1 NOV-002 is Not Toxic to Cancer Cell Lines

MTT assay was performed 72 hours after the addition of 1 mM (final concentration) of NOV-002 in cancer cells. No toxicity of NOV-002 on these cells was observed.

Figure 2 NOV-002 Suppresses Tumor Cell Migration

NOV-002 suppressed the migration of HCT15 and Colo205 in a dose-dependent manner. Migration assay was performed on these cell lines following the addition of NOV-002.

Figure 3 NOV-002 Suppresses Tumor Cell Invasiveness

NOV-002 suppressed the invasion of HCT116, HCT15, Colo205, MDA-MB-435 and AS49 in a dose-dependent manner. Invasion assay was performed on these cell lines following the addition of NOV-002.

Figure 4 NOV-002 Suppresses ErbB2/PI3K Pathway Activity

NOV-002 reduces the expression of phosphorylated ErbB2 and PI3K whereas has no effect on the total protein expression of these two molecules.

Figure 4 NOV-002 Reduces Akt and RhoA Expression

NOV-002 reduces the expression of active form of Akt and RhoA whereas has no effect on the total protein expression of these two molecules.

Conclusions

- NOV-002 is not toxic to cancer cell lines.
- NOV-002 specifically interferes with invasion process of cancer cell lines.
- NOV-002 suppresses the ErbB2/PI3K pathway.
- NOV-002 reduces the expression of active Akt and RhoA.