J Cancer Sci Ther 2018, Volume 10
DOI: 10.4172/1948-5956-C10-151

Robust inhibition of lung cancer stem-like cell growth and tumorigenicity by triptonide via selectively attenuating Sonic Hedgehog-*Gli1* signaling pathway

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Lung cancer is a leading lethal disease with the 5-year survival rate of the cancer patients only 16%. Inadequate potent anti-lung cancer drugs, particularly for suppression of lung cancer stem cells, appear to be a bottleneck in the treatment of the disease; hence, the effective anti-lung cancer drug is highly desired. In this study, we aim to explore new compound against lung cancer. Using human H1299 and A549 lung carcinoma cell lines as a model to screen and test the anti-lung cancerous compounds, we found that triptonide, a bioactive small molecule purified from the herb *Tripterygium wilfordii* Hook caused a marked suppression of cell proliferation and colony formation of lung cancer cells at very low concentrations of 5-10nM. More interestingly, triptonide robustly inhibited the lung cancer cell formation of tumorspheres, and reduced the stemness and tumorigenicity of the sphere-forming cells, suggesting that triptonide is a new inhibitor of cancer stem-like cells. In vivo tumor xenograft assay in mice showed that administration of triptonide at the dose of 5mg/Kg markedly inhibited the tumor growth with low toxicity. Molecular mechanistic studies revealed that triptonide significantly decreased expression of the glioma-associated oncogene 1 (*Gli1*) at both mRNA and protein levels through repressing *Gli1* gene promoter activity. Additionally, triptonide reduced the levels of cancer stem cell key signaling protein sonic hedgehog (Shh), but increased the amount of Ptch1 which is a protein binding to the smoothened protein (SMO) to diminish the Shh signal transduction, resulting in inhibiting an Shh-*Gli1* signaling pathway in lung cancer cells. Together, our findings show that triptonide effectively inhibits lung cancer stem-like cell growth, stemness, and tumorigenicity, and support the notion that triptonide is a new inhibitor of cancer stem-like cells and Shh-*Gli1* signaling inhibitor, and is a novel anti-lung cancer drug candidate for further developing effective lung cancer therapeutics.

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