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Tumor growth inhibition through targeting liposomally bound curcumin to tumor vasculature

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Abstract.

Increasing number of Phase I/II clinical studies have demonstrated clinical potential of curcumin for treatment of various types of human cancers. Despite significant anti-tumor efficacies and bio-safety profiles of curcumin, poor systemic bioavailability is retarding its clinical success. Efforts are now being directed toward developing stable formulations of curcumin using various drug delivery systems. To this end, herein we report on the development of a new tumor vasculature targeting liposomal formulation of curcumin containing a lipopeptide with RGDK-head group and two stearyl tails, di-oleyolphosphatidylcholine (DOPC) and cholesterol. We show that essentially water insoluble curcumin can be solubilized in fairly high concentrations (~500 μg/mL) in such formulation. Findings in the Annexin V/Propidium iodide (PI) binding based flow cytometric assays showed significant apoptosis inducing properties of the present curcumin formulation in both endothelial (HUVEC) and tumor (B16F10) cells. Using syngeneic mouse tumor model, we show that growth of solid melanoma tumor can be inhibited by targeting such liposomal formulation of curcumin to tumor vasculature. Results in immunohistochemical staining of the tumor cryosections are consistent with tumor growth inhibition being mediated by apoptosis of tumor endothelial cells. Findings in both in vitro and in vivo mechanistic studies are consistent with the supposition that the presently described liposomal formulation of curcumin inhibits tumor growth by blocking VEGF-induced STAT3 phosphorylation in tumor endothelium. To the best of our knowledge, this is the first report on inhibiting tumor growth through targeting liposomal formulation of curcumin to tumor vasculatures.

Key Words. Curcumin formulations, tumor vasculature targeting, tumor growth inhibition, liposomal drug delivery, RGDK-lipopeptides.

1. Introduction

Curcumin (diferuloylmethane), the dietary polyphenol constituent of the perennial herb *Curcuma longa* (popularly known as turmeric), possesses wide range of bioactivities including anti-oxidant, anti-inflammatory, anti-cancer, anti-angiogenic and anti-microbial [1]. In particular,