Abstract:
Pancreatic cancer is one of the most lethal of human malignancies known to date and shows relative insensitivity towards most of the clinically available therapy regimens. 3,5-bis(2-fluorobenzylidene)-4-piperidone (EF24), a novel synthetic curcumin analog, has shown promising in vitro therapeutic efficacy in various human cancer cells, but insufficient water solubility and systemic bioavailability limit its clinical application. Here, we describe nano-encapsulation of EF24 into pegylated liposomes (Lipo-EF24) and evaluation of these particles in preclinical in vitro and in vivo model systems of pancreatic cancer. Transmission electron microscopy and size distribution studies by dynamic light scattering confirmed intact spherical morphology of the formed liposomes with an average diameter of less than 150 nm. In vitro, treatment with Lipo-EF24 induced growth inhibition and apoptosis in MIAPaCa and Pa03C pancreatic cancer cells as assessed by using cell viability and proliferation assays, replating and soft agar clonogenicity assays as well as western blot analyses. Lipo-EF24 potently suppressed NF-kappaB nuclear translocation by inhibiting phosphorylation and subsequent degradation of its inhibitor I-kappa-B-alpha. In vivo, synergistic
tumor growth inhibition was observed in MIAPaCa xenografts when Lipo-EF24 was given in combination with the standard-of-care cytotoxic agent gemcitabine. In line with in vitro observations, western blot analysis revealed decreased phosphorylation of I-kappa-B-alpha in excised Lipo-EF24-treated xenograft tumor tissues. Due to its promising therapeutic efficacy and favorable toxicity profile Lipo-EF24 might be a promising starting point for development of future combinatorial therapeutic regimens against pancreatic cancer.