

Obesity and chemotherapy resistance: The nanoparticle approach

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Abstract

Obesity is associated with increased breast tumor aggressiveness and decreased response to multiple modalities of therapy. Despite advances in breast cancer treatment, obese patients still show decreased chemotherapy response. The use of nanoparticles (NPs) as a drug delivery system has evolved as a promising approach to improve therapy efficacy. However, few studies have evaluated the response to chemotherapy delivered by NPs in the context of obesity. Gemcitabine is a widely used nucleoside analog that inhibits DNA synthesis. Previously, we prepared a novel gemcitabine formulation by incorporating stearoyl gemcitabine in solid-lipid NPs (GemC18-NPs). Here we demonstrate that by using a diet-induced obesity mouse model of breast cancer, the antiproliferative effects of gemcitabine are decreased in the context of obesity. We further show that conventional mechanisms of acquired resistance are induced during obesity and that the GemC18-NPs are able to overcome the obesity-induced resistance to gemcitabine. However, the tumor growth inhibition ratio (T/C %) of GemC18-NPs in the context of obesity was lower (56%) than in control mice (82%). Further in vitro studies supported protumorigenic and pro metastatic effect of adipocyte-conditioned media. These studies demonstrate the role of obesity-driven Akt/mTOR activation in promoting tumor growth and invasiveness while decreasing tumor response to standard chemotherapy. Our findings also suggest that delivering a chemotherapeutic drug with NPs can potentially overcome chemotherapy resistance in obese patients, and suggest that to improve patient outcome, combination therapy targeting multiple signaling pathways may be necessary to disrupt the obesity-cancer link.

Biography

Rebecca De Angel, Ph.D., is a Molecular Nutrition Scientist focused on oncology, energy balance, and drug delivery since 2005, with strong background in public health, project management. She received her Ph.D. from The University of Texas at Austin and an MPH in epidemiology from Loma Linda University. Her post-doctoral Research was completed at the Dell Pediatric Research Institute in Austin, TX