J Cancer Sci Ther 2016, 8:11(Suppl)
http://dx.doi.org/10.4172/1948-5956.C1.091

Emerging nano-pharmaceuticals and cancer therapy

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Treatment of a human disease in the genetic level either providing a cell with a functional gene or a nucleic acid sequence to precisely silence a harmful gene is a powerful approach to revolutionize the clinical medicine. Despite existence of both genetically engineered viral vectors and synthetically designed lipid- or polymer-based nano-carriers, an ideal delivery system in terms of safety and efficacy is still lacking. We have recently developed a highly efficient gene delivery device based on carbonate apatite nano-crystals having high affinity for siRNA or drugs (through electrostatic interactions) but fast dissolution kinetics for effective release of the payloads during vesicular acidification. Moreover, for cell-specific and more efficient transgene delivery, we successfully assembled a desirable cell-recognizable protein and a highly hydrophilic protein onto the crystal surfaces, thereby creating dual surface properties, one facilitating cell-specific delivery and the other blocking non-specific interactions. A delicate control on manipulation of particle diameter additionally helps us passively to target the nanoparticles to the tumor via EPR effect. As a result, intravenous delivery of nanoparticles-associated siRNAs targeting growth factor receptors and anti-apoptotic genes resulted in significant reduction in tumor regression in a syngeneic mouse model of breast cancer and remarkably sensitized the tumor to the chemotherapy drugs, thus shedding light on their potential applications in treating cancer in human patients.

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Dopamine receptor-1 in breast cancer: Expression, signaling and therapeutic targeting

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Dopamine (DA) is a catecholamine which binds to five G-protein-coupled membrane receptors. We discovered overexpression of DA type-1 receptors (D1R) in breast cancer, thereby identifying these receptors as novel therapeutic targets in this disease. Strong to moderate immunoreactive D1R expression was found in 30% of 751 primary breast carcinomas and this expression was associated with larger tumors, higher tumor grades, node metastasis and shorter patient survival. Unexpectedly, DA and D1R agonists were found to signal through the cGMP/protein kinase G (PKG) pathway. Several selective activators of this pathway suppressed cell viability, inhibited invasion and induced apoptosis in multiple breast cancer cell lines. Fenoldopam, a peripheral D1R agonist which does not penetrate the brain, dramatically suppressed tumor growth in two mouse models with D1R-expressing xenograft by increasing both necrosis and apoptosis. D1R-expressing primary tumors and metastases in mice were detected by fluorescence imaging. In conclusion, D1R overexpression is associated with advanced breast cancer and poor prognosis. Activation of the D1R/cGMP/PKG pathway induces apoptosis in vitro and causes tumor shrinkage in vivo. Fenoldopam, which is FDA-approved to treat renal hypertension, could be repurposed as a novel therapeutic agent for patients with D1R-expressing tumors.

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