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Autor(en) des Beitrags: Tresilwised, N; Pithayanukul, P; Mykhaylyk, O; Holm, PS; Holzmüller, R; Anton, M; Thalhammer, S; Adigüzel, D; Döblinger, M; Plank, C

Titel des Beitrags: Boosting oncolytic adenovirus potency with magnetic nanoparticles and magnetic force.

Abstract: Oncolytic adenoviruses rank among the most promising innovative agents in cancer therapy. We examined the potential of boosting the efficacy of the oncolytic adenovirus dl520 by associating it with magnetic nanoparticles and magnetic-field-guided infection in multidrug-resistant (MDR) cancer cells in vitro and upon intratumoral injection in vivo. The virus was complexed by self-assembly with core-shell nanoparticles having a magnetite core of about 10 nm and stabilized by a shell containing 68 mass % lithium 3-[2-(perfluoroalkyl)ethylthio]propionate) and 32 mass % 25 kDa branched polyethylenimine. Optimized virus binding, sufficiently stable in 50% fetal calf serum, was found at nanoparticle-to-virus ratios of 5 fg of Fe per physical virus particle (VP) and above. As estimated from magnetophoretic mobility measurements, 3,600 to 4,500 magnetite nanocrystallites were associated per virus particle. Ultrastructural analysis by electron and atomic force microscopy showed structurally intact viruses surrounded by magnetic particles that occasionally bridged several virus particles. Viral uptake into cells at a given virus dose was enhanced 10-fold compared to nonmagnetic virus when infections were carried out under the influence of a magnetic field. Increased virus internalization resulted in a 10-fold enhancement of the oncolytic potency.
in terms of the dose required for killing 50% of the target cells (IC(50) value) and an enhancement of 4 orders of magnitude in virus progeny formation at equal input virus doses compared to nonmagnetic viruses. Furthermore, the full oncolytic effect developed within two days postinfection compared with six days in a nonmagnetic virus as a reference. Plotting target cell viability versus internalized virus particles for magnetic and nonmagnetic virus showed that the inherent oncolytic productivity of the virus remained unchanged upon association with magnetic nanoparticles. Hence, we conclude that the mechanism of boosting the oncolytic effect by magnetic force is mainly due to the improved internalization of magnetic virus complexes resulting in potentiated virus progeny formation. Upon intratumoral injection and application of a gradient magnetic field in a murine xenograft model, magnetic virus complexes exhibited a stronger oncolytic effect than adenovirus alone. We propose that this approach would be useful during in vivo administration to tumor-feeding blood vessels to boost the efficacy of the primary infection cycle within the tumor. For systemic application, further modification of magnetic adenovirus complexes for shielding and retargeting of the whole magnetic virus complex entity is needed.