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A dual-targeting delivery system based on multi-walled carbon nanotube (MWNT) for anti-angiogenic therapy in lung cancer

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Lung cancer has grown into malignant tumor with highest morbidity and mortality in the world, yet the horrific data is persistently rising. Anti-angiogenesis therapy, compared with traditional therapy, gradually emerges as a great potential treatment strategy for this representative vessels dependence lesion. Previous studies indicated that angiotensin II plays a significant role in lung cancer angiogenesis through angiotensin II type 1 receptor (AT_1R) and angiotensin II type 2 receptor (AT_2R), which enlightened us to develop a treatment strategy that regulate both of the receptors for synergistic treatment. For this purpose, MWNT was employed as backbone with super penetrability and modest complexation ability. Candesartan (CD), ARBs which specifically block AT_1R and AT_2 gene which express AT_2R were chosen as therapeutic agents. In this study, iRGD tumor penetrating peptide was connected to PEI 1.8k further linked to MWNT skeleton, accompanying with CD conjugated to MWNT mediated by cystamine (SS) linkage arms. Finally, the constructed conjugate was self-assembled with AT_2 gene to form iRGD-PEI-MWNT-SS-CD/pAT_2 delivery system. The highly stable dispersion iRGD-PEI-MWNT-SS-CD/pAT_2 complexes in physiological pH, possessing desirable size distribution, moderate positive charge and uniform morphology, exhibited excellent drug loading ability with smart release. Introducing the two ligands, iRGD and CD, specifically recognizing overexpression receptors in lung cancer highly improved the receptor-mediated endocytosis and gene transfection, endowed the vector superior targeting ability to tumor tissues which was far surpassed non- or mono-targeting ones. Additionally, effective co-delivery of CD and AT_2 gene remarkably decreased VEGF expression, playing a synergistic inhibition to angiogenesis *in vitro* and *in vivo*. A549 bearing nude mice treated with iRGD-PEI-MWNT-SS-CD/pAT_2 complexes showed significant tumor growth inhibition compared with mono- or mixed-delivery system. The work described here demonstrated that our created iRGD-PEI-MWNT-SS-CD/pAT_2 delivery system accurately targeting to lung cancer tissue effectively inhibited tumor growth which is a promising strategy for anti-angiogenic therapy in lung cancer, laying the foundation of MWNT based co-delivery system.

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