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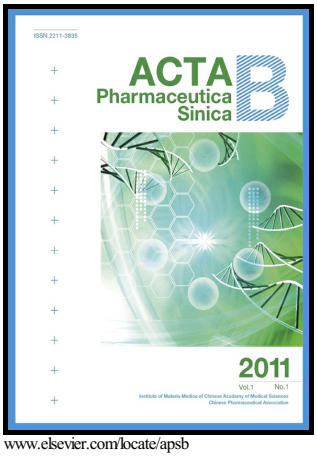

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Original article

Efficacy of inverso isomer of CendR peptide on tumor tissue penetration

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Abstract The dense extracellular matrix and high interstitial fluid pressure of tumor tissues prevent the ability of anti-tumor agents to penetrate deep into the tumor parenchyma for treatment effects. C-end rule (CendR) peptides can enhance the permeability of tumor blood vessels and tumor tissues *via* binding to neuropilin-1 (NRP-1), thus aiding in drug delivery. In this study, we selected one of the CendR peptides (sequence RGERPPR) as the parent L-peptide and substituted D-amino acids for the L-amino acids to synthesize its inverso peptide $_{D}$(RGERPPR). We investigated the NRP-1 binding activity and tumor-penetrating ability of $_{D}$(RGERPPR). We found that the binding affinity of $_{D}$(RGERPPR) with NRP-1 and the cellular uptake was significantly higher than that of RGERPPR. Evans Blue tests revealed that $_{D}$(RGERPPR) exhibited improved tumor-penetrating ability in C6, U87 and A549 tumor-bearing nude mice. Using nude mice bearing A549 xenograft tumors as a model, we found that the rate of tumor growth in the group co-administered with $_{D}$(RGERPPR) and gemcitabine (Gem) was significantly lower than the gemcitabine-treated group with a tumor suppression rate (TSR%) of 55.4%. Together, our results demonstrate that $_{D}$(RGERPPR) is a potential tumor-penetrating peptide.

KEY WORDS Inverso isomer; CendR peptide; NRP-1; Tumor penetration; gemcitabine

1. Introduction

Tumor tissues exhibit specific pathological features, including large amounts of random vasculature with high permeability, the absence of lymphatic drainage, a dense extracellular matrix, high interstitial fluid pressure, and an acidic and anoxic environment in the center of the tumor that is caused by poor elimination of metabolites owing to insufficient blood supply[1-8]. Because of the dense extracellular matrix and high interstitial fluid pressure, antitumor agents are unable to reach deep into the tumor parenchyma, leading to retention of drugs around the tumor blood vessels. This