Rational design of bacteriophages as a platform for cancer therapy

Tânia Mendes

MIT Portugal Bioengineering Systems, Centre of Biological Engineering, University of Minho
taniamendes@ceb.uminho.pt

Background: MSc in Biological Engineering/ School of Engineering, Department of Biological Engineering, University of Minho / Portugal
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Supervisors: Lígia Rodrigues[1]; Leon Kluskens[1]
[1]Centre of Biological Engineering, University of Minho

OBJECTIVES

The aim of this work is to engineer a bacteriophage-based platform to specifically target, invade and control cancer.

WORK PLAN

Firstly, a targeted drug-carrying bacteriophage will be constructed. Genetic manipulation to endow phages with cancer-specificity-conferring ligands, as well as chemical conjugation to load the targeted phages with cytotoxic drugs will be performed. Secondly, novel ligand peptides will be screened and selected to inhibit cell proliferation and induce cell death when coupled with drug-carrying phages. Phage display and iPhage technology to screen surface- and internalizing-peptide libraries will be applied. Thirdly, a phage-based gene therapy approach will be developed to regulate cancer proliferation and metastasis. Specifically, phages will carry zinc finger nucleases specific for mammalian target of rapamycin (mTOR) and ribosomal S6 kinase (RSK) pathways. Fourthly, the effect of temperature will be studied to induce modifications of portal and protein capsid conformation on phages, triggering nanoparticle disassembly and cargo delivery. Finally, the mechanisms underlying internalization and trafficking of engineered phages will be elucidated.

RESULTS

Using molecular biology tools a filamentous phage, M13KE, was engineered to display a target-specific (231 peptide) and cell-penetrating peptides (Penetratin and TAT-HIV) in the pIII minor capsid protein in order to promote specific internalization, thereby facilitating the direct delivery of the drug. Engineered phages were conjugated with doxorubicin, an anti-carcinogenic drug, and incubated with breast cancer (MDA-MB-231) and breast epithelium (MCF-10-2A) cell lines to evaluate internalization of phage particles and cytotoxicity. Up to now, there are good indicators that drug-carrying phages equipped with specific peptides for cancer cells can be specifically internalized promoting cell death.

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