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Phage Capsid for Efficient Delivery of Cytotoxic Drugs

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Abstract : The boom of nanomedicine in recent years has led to the development of numerous new nanomaterials that can be used as nanocarriers in the drug delivery. These nanocarriers can either be synthetic or natural-based. The disadvantage of many synthetic nanocarriers is their toxicity in patient's body. Protein cages that can naturally be found in human body do not exhibit such disadvantage. However, the release of cargo from some protein cages in target cells can be problematic. As a special type of protein cages can serve the capsid of many viruses, including phage. Phages infect bacterial cells; therefore they are not harmful to human cells. The targeting of phage particles to cancer cells can be solved by producing of empty phage capsids during which the targeting moieties (e.g. peptides) can be cloned into genes of phage capsid to decorate its surface. Moreover, the produced capsids do not contain viral nucleic acid and are therefore not infectious to beneficial bacteria in the patient's body. The protein cage composed of viral capsid is larger than other frequently used apoferritin cage but its size is still small enough to benefit from passive targeting by Enhanced Permeability and Retention effect. In this work, bacteriophage λ was used, both whole and its empty capsid for delivery of different cytotoxic drugs (cisplatin, carboplatin, oxaliplatin, etoposide and doxorubicin). Large quantities of phage λ were obtained from phage λ-producing strain of E. coli cultivated in medium with 0.2 % maltose. After killing of E. coli with chloroform and its removal by centrifugation, the phage was concentrated by ultracentrifugation at 130 000 g and 4 °C for 3 h. The encapsulation of the drugs was performed by infusion method and four different concentrations of the drugs were encapsulated (200; 100; 50; 25 μg/ml). Free molecules of drugs were removed by dialysis. The encapsulation was verified using spectrophotometric and electrochemical methods. The amount of encapsulated drug linearly increased with the amount of applied drug (determination coefficient R2=0.8013). 76% of applied drug was encapsulated in phage λ particles (concentration of 10 μg/ml), even with the highest applied concentration of drugs, 200 μg/ml. Only 1% of encapsulated drug was detected in phage DNA. Similar results were obtained with encapsulation in phage empty capsid. Therefore, it can be concluded that the encapsulation of drugs into phage particles is efficient and mostly occurs by interaction of drugs with protein capsid.

Keywords : cytostatics, drug delivery, nanocarriers, phage capsid
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