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Efficient gene vector with size changeable and nucleus targeting in cancer therapy

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ABSTRACT

The nucleus is one of the most important cellular organelles, where gene encode and transcribe at that location. However, nucleus-targeting gene delivery are rare been reported. It is important to develop a high-efficiency nucleus-targeting gene vector that can deliver targeted gene into nucleus directly for destroy of cancer cells. Here, special nucleus-targeting and size changeable deliver system based on TAT-SS-PAMAM-D3 with TAT functional on the surface and disulfide linked between D2 and D3 is designed to perform highly efficient nucleus-targeting gene delivery for effective cancer cell killing in vitro. CLSM observations reveal that more TAT-SS-PAMAM-D3 are enter into the nucleus when compare to SS-PAMAM-D3. The TAT modified vector can also act as gene deliver to reach high gene transfection efficiencies, high apoptosis and low viability in HeLa cells. This TAT functionalized and disulfide linking in the carrier may become a prospective vector for cancer gene treatment and also offered a different strategy for designing a better gene delivery system.

1. Introduction

Nowadays, cancer still one of the highest mortality rate disease in the world [1]. So, it is urgent to develop an effective treatment for cancer. In many therapeutic methods, gene therapy has become a promising strategy in the past decades. For this strategy, a safe gene carrier with high efficiency plays a big part in the treatment. To that end, many different kinds of gene carrier were developed, such as poly (L-lysine) [2,3], polyethylenimine (PEI) [4], chitosan [5–10], cationic poly(amidoamine) (PAMAM) dendrimers have been designed to deliver gene into the cells and exert the therapeutic action. Different from other gene carrier, PAMAM dendrimers synthetic macromolecules own well-defined architectures, precise molecular weights, and multivalent functionalization sites [11,12]. They provide tailorable scaffolds for the development of nucleic acid carriers and have been widely used for the delivery of plasmid DNA or siRNA [13,14].

However, these gene vector are lack of the nucleus-targeting properties. For an effective therapeutic treatment, targeted gene was delivered into nucleus of the tumor cells is necessary [15]. Nucleus is regarded as one of the most important organelle for the gene encode and transcribe at that place. The main effect of the nucleus is to keep the completeness of genes by regulating its gene expression [15,16]. However, due to the limited access to into the nucleus, it becomes hardly for targeted genes to reach nucleus and exert its subsequent function.

Generally, changing dimension of the vector make them smaller than nuclear pore and the surface modification by using some nucleus-targeted molecules are considered to be the best plan for nuclear entry. However, vector smaller than nuclear pore may create another problem: only a few vector can accumulate in the tumor tissue [17]. To address that problem, an reasonable plan would be that the sizes of the vector are changeable: the sizes of the vector are big for them to infiltrated into the tumor at first but become smaller than the nuclear pore to permit the vector enter into nucleus when endocytosis in tumor cells. Based on the idea, here we demonstrate a new size changeable and nucleus localization signal (NLS) peptide modified polymer based on TAT-SS-PAMAM-D3 dendrimer that facilitates vector enter into nucleus and releases desired gene in the nucleus. The dendrimer holds a

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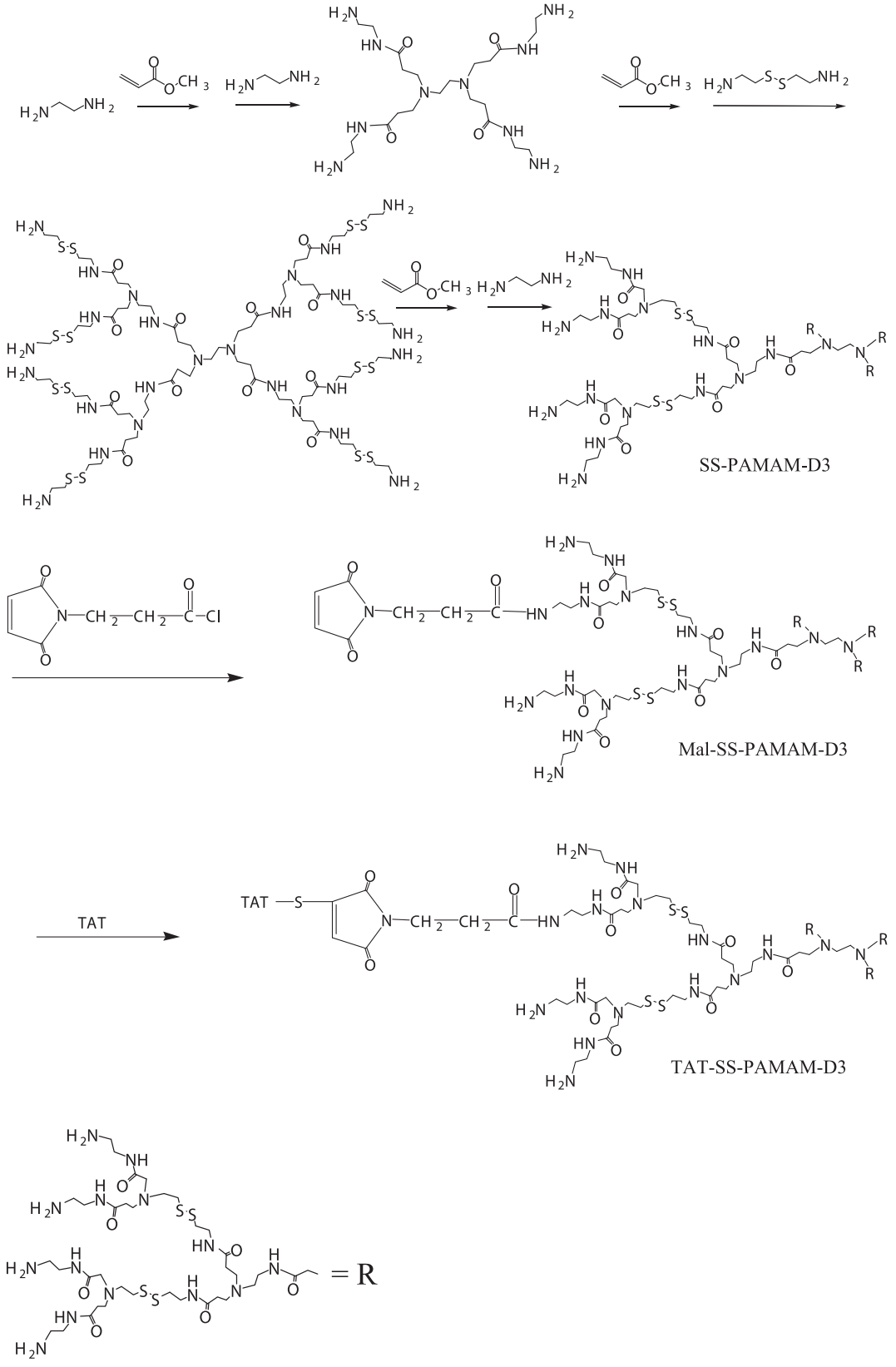

Fig. 1. Synthesis of the TAT-SS-PAMAM-D3.

definite dendritic construction, in which D2 conjugated with D3 via a disulfide bond, and the surface of the dendrimer is modified by an amidized NLS peptide transactivator of transcription (TAT). TAT is one type of cell-penetrating peptides (CPPs), besides its capacity to transfer fast into almost all living cells [18,19]. TAT also can be identified by the nucleopore complexes (NPCs) [20], and thus can actively deliver proteins [21], DNA [22,23], nanoparticles [19,24], and other goods from the cytosol into nucleus. Disulfide bonds of polymers which can