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Quantitative Study of Effects of Free Cationic Chains on Gene Transfection in Different Intracellular Stages

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Abstract: Previously, we revealed that in the application of using cationic polymer chains, polyethylenimine (PEI), to condense anionic plasmid DNA chains (pDNA) to form the DNA/polymer polyplexes, after all the pDNAs are complexed with PEI, further added PEIs exist individual chains and free in the solution mixture. It is those uncomplexed polycation chains that dramatically promote the gene transfection. In the current study, we studied how those free cationic chains with different lengths and topologies affect the intracellular trafficking of the polyplexes, the translocation of pDNA through the nuclear membrane, the transcription of pDNA to mRNA and the translocation of mRNA from nucleus to cytosol in HepG2 cells by using a combination of the three-dimensional confocal microscope and TaqMan real-time PCR. We found that free branched PEI chains with a molar mass of 25,000 g/mol and a total concentration of 1.8×10^{-6} g/mL promote the overall gene transfection efficiency by a factor of ~500 times. Our results quantitatively reveal that free chains help little in the cellular uptake, but clearly reduce the lysosomal entrapment of those internalized polyplexes (2–3 folds); assist the translocation of pDNA through nuclear membrane after it is released from the polyplexes in the cytosol (~5 folds); enhance the pDNA-to-mRNA transcription efficiency (~4 folds); and facilitate the nucleus-to-cytosol translocation of mRNA (7–8 folds). The total enhancement of those steps agrees well with the overall efficiency, demonstrating, *for the first time*, how free cationic polymer chains quantitatively promote the gene transfection in each step in the intracellular space.

Keywords: Gene delivery; Polyethylenimine; Plasmid quantification; Intracellular trafficking; Nuclear entry; Post-nuclear delivery events.

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