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Therapeutic delivery vehicle development by combinatorial post-modification

Polymers are widely used in the construction of nanocarriers for therapeutic delivery because of their precisely controllable structure and low toxicity. Combinatorially modified polymers usually have a portion of similar structures, while other specific structures determine the therapeutic delivery efficiency. It is necessary to build a polymer library for delivery vehicle screening that the idea was first suggested by Langer and coworkers. They successfully synthesized a polymer library of poly(*β*-amino ester)s by polymerization of different monomers, what's more, they systematically studied structure-property-function relationships in gene delivery systems. These results prove that the construction of polymer library is a promising direction. We would like to emphasize that the process of constructing a polymer library could be a combinatorial post-modification of reactive polymers (Fig. 1), other than the polymerization of different monomers, because the backbone structure of the post-modified polymers is concentrated, and the specificity is distinguished. In this way, small molecules can be grafted onto the polymer skeletons to produce the polymer library. Structurally comparable small molecules should be chosen, which is significant for the construction of combinatorially post-modified polymer library. Different nanocarriers combine different therapeutics to select the best combination. Different therapeutic delivery systems work together to treat disease for better outcomes. These advantages make the combinatorially post-modified polymers more useful in the field of therapeutic delivery.

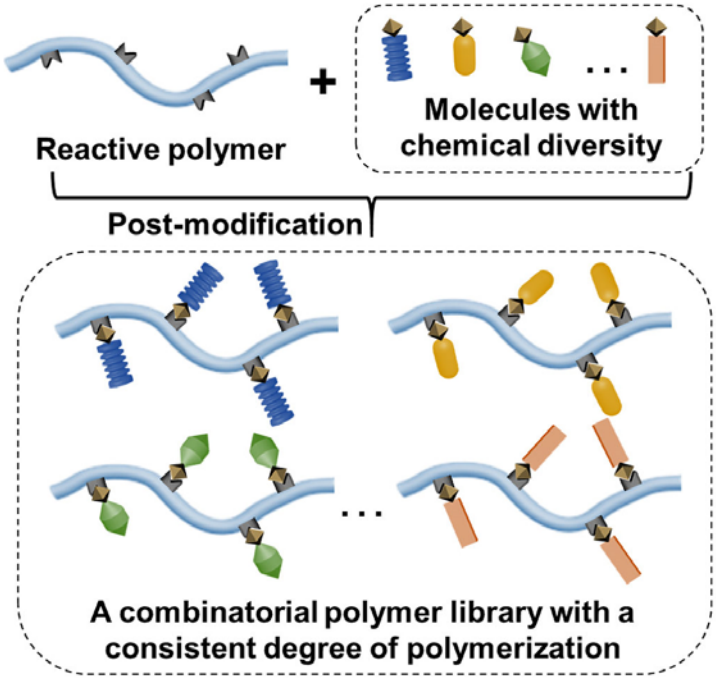

Fig. 1. Schematic illustration of combinatorial polymer libraries synthesized by post-modification of reactive polymers for the optimization of therapeutic delivery polymers.

In this contribution we discuss the application of several post-modified polymer libraries composed of reactive polymers and corresponding small molecule libraries in the field of therapeutic delivery. 1) *N*-Hydroxysuccinimide-functionalized polyacrylates. Poly(*N*-methacryloxysuccinimide) can react with primary or secondary aliphatic or cycloaliphatic amines. The screening of combinatorial polymer libraries synthesized by modifying poly(*N*-methacryloxysuccinimide) with cationic and hydrophobic pendant amines got the best gene delivery efficiency in 2009. 2) Azlactone-functionalized polymers. Poly(2-vinyl-4,4-dimethylazlactone) can efficiently react with primary amines in the absence of a catalyst to obtain a polymer library. The optimal vector was obtained by comparing the gene delivery efficiency and the structure-property-function relationships were analyzed by Lynn and coworkers in 2012. 3) Hydrazide-functionalized polymers. Acyl hydrazide functional groups of polymers can react with an aldehyde group to form acyl hydrazones. For example, the functional polymers synthesized by modifying poly(acryloyl hydrazide) with positively charged and hydrophobic aldehydes could efficiently deliver small interfering RNA. This work demonstrated that different species and proportions of hydrophobic aldehydes led to different delivery efficiency. 4) Natural polysaccharides and derivatives. In terms of using a combinatorial polymer library approach for delivery vehicle optimization, Amiji and coworkers demonstrated that hyaluronic acid modified with polyamines and lipids through an amidation reaction was useful for the construction of a library of functional polymers. 5) Oligo(amino acid)s-based platforms. Wang et al. reported that linear-dendritic polymers synthesized from poly(ethylene glycol) and oligolysine had a good protein encapsulation ability. They used a synergistic effect based on multivalent electrostatic and hydrophobic interactions to encapsulate the therapeutic proteins to obtain nanoparticles with small size and high encapsulation efficiency.

According to our statistics, the interactions between therapeutic payloads and nanocarriers are mainly electrostatic and hydrophobic interactions. On the basis of these principles, we can optimize the post-modified polymeric nanocarrier by *in situ* packaging and computational assistance. In summary, the combinatorially post-modified polymers as therapeutic delivery vehicles not only provide an efficient platform but also show a very promising side in the field of therapeutic delivery.

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