Gene Delivery through Combinatorial Chemistry

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Introduction

The human effort for maintaining a healthy body that could function effectively in complete harmony with human’s environment, has brought a lighting up to the innovative therapeutic approaches [1]. Meanwhile, the battle with various genetic diseases has witnessed tremendous advances, therefore, scientists learned to profit from neoteric features of nanotechnologies for controlled and targeted tracking of the proteins and gene to cells. Transfection of DNA, RNA, and oligonucleotides into an individual cell type for the selective inhibition or expression of genes for therapeutic purposes have revolutionized the entire process of gene delivery [2].

Nowadays, the synergy of materials domain with combinatorial chemistry is leading to new functionalized and conjugated materials for treating diseases [3,4]. Combinatorial chemistry uses chemical synthesis methods that make it possible to prepare a large library of scaffolds in a single process [5]. In this regard, one of the emerging fields is the utilization of multicomponent reactions (MCRs) for the functionalization and synthesis of novel gene carriers. In the MCRs, three or more starting materials are combined in a one-pot vessel and caused to the production of skeletal diverse compounds [6]. Hence, most of the MCRs caused to pseudopeptide or heterocyclic scaffolds there.
are valuable pathways for functionalization of materials for medicinal approaches [7].

Since pseudopeptide structures showed admirable efficiency for binding to the protein and genes [8] one of the emerging investigations in this field is the construction of pseudopeptide-functionalized macroradical molecule of calix[n]arenes for protein binding. Calix[n]arenes are a class of macrocyclic molecules which have been widely used in modern technologies such as fluorescent probes, [9] catalyst [10] and use as protein-binding agents [11]. Since the modification of the hydrophobic core of calix[4]arene with diverse functional groups could improve their binding affinity toward proteins, Zadmard group accomplished Meldrum’s acid-based MCR for the synthesis of diverse acridine-calix[4]arene, calix[4]arene-hexamamide derivatives with the binding ability toward Calf Thymus DNA (CT-DNA), [12] β-Lactoglobulin (BLG) [13] and lysozyme, respectively [14].

In another work, Graphene Oxide (GO), one of the promising materials for the advanced gene delivery, [15-17] was utilized as an acid part and Ethidium Bromide (EtBr) as an amine part of the Ugi Four-Component Reaction (4CR), important kind of MCRs carried out through the reaction of an acid, aldehyde, amine and isocyanide, for the synthesis of a novel nonviral stable Amphiphilic Graphene-EtBr (AG-EtBr) gene carrier for high efficient Plasmid DNA (pDNA) transfection into mammalian through the water [18]. The results confirmed the higher capacity of AG-EtBr nanocarrier to interact with pDNA in comparison with GO with no visible sign of DNA fragmentation. Interestingly, the advantages of AG-EtBr in cell transfection are more dramatic (3-fold higher) than Lipofectamine 2000 as a commercial nonviral vector which confirmed by fluorescence microscopy (Figure 1) [18]. Likewise, the MCR approach has been utilized for the covalent attachment of cell-adhesion proteins on the surface of nanographene in water at ambient temperature [19]. The peptide-graphene biomaterial synthesized through Ugi-4CR showed excellent biocompatibility and accelerated the proliferation of Human Mesenchymal Stem Cells (hMSCs) at a better rate regarding the tissue plate due to the presence of RGD on the graphene surface.

Zha et al., benefited from the MCR strategy for effective achieving of the endosomal escape particularly for intracellular gene transport via the Passerini Three-Component Reaction (P-3CR) between acid, aldehyde and isocyanide, followed by RAFT technique through the integration of alkyl and imidazolyl moieties. The synthesized endosomal escape polymers were introduced into poly (2-dimethylaminoethyl methacrylate) (PDMAEMA) as the gene delivery vectors and the results confirmed the enhancement in hemolytic activity at endosomal pH. ALSO, the plasmid DNA (pDNA)-loaded polyplexes showed efficient endosomal escape compared with PDMAEMA, ultimately achieving dramatically increased gene transfection efficacy (Figure 2) [20].

Additionally, a small library of cationic polymers as important non-viral carriers for gene therapy were also synthesized through P-3CR. In vitro transfection efficacies of the polymers were tested using Hela human epithelial carcinoma cell line and results demonstrated that a high amino density and high hydrophobicity with aromatic rings were essential for a polymer to have efficient gene transfection [21]. Despite tremendous advances of MCR-functionalized materials and their widespread utilization in a plethora of applications, it seems that there is still room for investigation of their efficiency in protein and gene delivery that require further researches. Although the approach of integrating the combinatorial chemistry for materials functionalization is relatively new, it is firmly believed that the application of MCRs-functionalized gene carriers will continue to grow steadily. Besides, this protocol has the ability to conjugate useful biomolecules such as nucleic acids and antibodies on the surface of diverse materials that makes them great candidates for controlled delivery of the biomolecules to cells.

References
3. Triggle DJ, Taylor JB. Comprehensive Medicinal Chemistry II; Elsevier. 2006; 8.


