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Nanomedicine & Nanotechnology Open Access
ISSN: 2574-187X

Benefits of Branched Polymeric Nanoparticles for Enhanced Targeted Drug Delivery

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Mini Review
Volume 5 Issue 3
Received Date: June 30, 2020
Published Date: August 27, 2020
DOI: 10.23880/nnoa-16000187

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Keywords: Drug Delivery; Nanoparticles; Polymeric; Active Targeting; Branched; Multi-Functional

Abbreviations: EPR: Enhanced Permeability And Retention; PAMAM: Polyamidoamine.

Introduction

By taking advantage of the benefits of the fields of biomaterials and nanotechnology, drug delivery has made tremendous advances. Implied in the name, drug delivery aims to more effectively and safely deliver drugs and other therapeutic agents to specific sites of action in the body and with a desired temporal profile [1,2]. Delivering drugs should ideally be done in a temporally controlled and/or spatially targeted manner, which has been an ever-present challenge, especially in an effort to avoid the side effects of systemic drug administration and overcome various issues posed by many drugs. These issues include poor drug solubility, low bioavailability, decreased absorption in the body, and off-target toxicity [3]. Nanoparticles are by far the most common type of drug delivery vehicles in research used to overcome the drug delivery challenges mentioned. Simply based on the ability to customize their size, physicochemical properties, and the ability to take advantage of other phenomena that may be at work such as the enhanced permeability and retention (EPR) effect in tumor environments, for example, some nanoparticles are able to be passively taken up by cells or permeate into tumor tissues [4-6]. Increasing the number of particles that reach the target site and achieve cellular uptake can be done through active targeting approaches that generally involve attaching a targeting moiety or ligand with high cell affinity and cell specificity to the nanoparticle surface to help guide more particles to the intended treatment site[7-9]. Creating a targeted drug delivery system simultaneously increases the efficacy of the nanoparticle delivered as well as that of the loaded drug and decreases drug side effects.

While numerous targeted nanoparticle systems have been developed in the literature, a recent article has highlighted the fact that a surprisingly low number, a median of 0.7%, of nanoparticles delivered *in vivo* actually reach the tumor or targeted site [10]. This overwhelmingly low efficacy of targeted nanoparticle systems evaluated for the past 10 years has a number of consequences that have ultimately limited their clinical application. To address this problem, a number of strategies can be employed, including identifying better receptor-ligand interactions and developing chemistries that enhance nanoparticle homing and internalization. From a biomaterials standpoint, one of the most promising strategies is to utilize branched polymer chemistries. This tactic and its benefits will be briefly discussed here.

Branched Polymers for Targeted Drug Delivery

Several factors influence how well a targeted nanoparticle drug delivery system works in the body including the size of the particles, surface charge, and targeting ligand type. One factor that should be emphasized when developing

a targeted nanoparticle system is the ligand density of the particle surface. Utilizing a linear polymer generally allows for low nanoparticle functionalization, especially where the functional groups for conjugation are the ends groups. However, a branched polymer chemistry that allows for increased ligand density or concentration has been found to show increased cell binding and targeting [11]. These branched chemistries should be more broadly considered in developing an effective nanoparticle system.

Biomaterial scientists often think of dendrimers when contemplating how to fabricate a branched nanoparticle system. Dendrimers are three-dimensional, highly-branched, well-organized macromolecules that originate from a single inner core that radially branches outwards [8,12]. Dendrimers are able to produce numerous branches as the molecule generation is increased and they can therefore be highly functionalized with targeting ligands. However, the toxicity of dendrimers has been widely discussed in the literature, including the well-known polyamidoamine (PAMAM) dendrimer, as the concentration and the generation number are increased. This unfortunately limits their use in drug delivery and nanomedicine applications. Instead, extraordinary branched nanoparticles from chemistries such as amphiphilic co-polymers with graft, star, or other sophisticated branched architectures have been developed and found to decrease toxicity compared to dendrimers [13-15,17,18]. They have also been found to show improved efficacy compared to their linear or nonbranched counterparts. These branched or sometimes hyper-branched polymers mimic dendrimers in their structure and tend to have properties that make them more ideal as biomaterials for drug delivery. Namely, the ability to control the degree of branching, produce more elaborate or specific structures, dictate the surface charge, and have simpler and more reproducible synthesis procedures all stand out as the benefits of using a branched polymer chemistry approach over the use of dendrimers for creating improved targeted nanoparticles [16,17]. The ability to load the desired drugs into a polymer shell with more control over the release kinetics is an additional benefit of a branched polymer used to form nanoparticles with respect to not only enhancing targeting but also controlling the drug transfer and release. Dendrimers often dump the drugs loaded into the molecules' branches and lack the ability to show sustained, long-term drug release [19,20].

Outside of the scope of simply enhancing targeted drug delivery through the benefits mentioned, these polymers can be used to create more elaborate multi-functional nanoparticle platforms. In this way, particles can be used to simultaneously facilitate drug delivery and imaging/detection [14,21,22]. The control in the branching structure and functionalization can also allow for simultaneous receptor targeting and inhibition, for example, to better treat certain disease states with a dual-function branched nanoparticle system. The homogenous structure of dendrimers would make such an application quite difficult if not impossible.

Conclusion

When developing a targeted nanoparticle drug delivery system, there is much to be considered from the polymer and its properties (e.g. molecular weight) to the ideal nanoparticle size, the targeting moiety that should be utilized, mode of delivery, ideal surface charge, and type of drug that should be delivered. By continuing to develop novel branched polymeric chemistries, which can take on a wide range of structures, and attaching appropriate and specific targeting ligands, better targeting and uptake results can be achieved in drug delivery. With improved targeted nanoparticle strategies based on increased ligand presentation and spatial control of the attached ligands, effective strategies can more readily move from the research bench into the clinic. The versatility and creativity of polymeric branched chemistries and their formulated nanoparticles continues to allow for these enhanced drug targeting solutions.

Acknowledgments

The training of Yasmine Doleyres that enabled the writing of this review paper was supported by the following funding sources awarded to Dr. Peter X. Ma: (1) ATGC, Inc. and the National Institute of Health (NIH) grant R42 TR001711 and (2) National Heart, Lung, and Blood Institute (NHLBI)/NIH R01 HL139735 grant. Support was also provided for Yasmine Doleyres by the National Institute for Dental and Craniofacial Research (NIDCR) for the Tissue Engineering and Regeneration (TEAM) Training Grant (DE00007057) and the Rackham Graduate School at the University of Michigan for the Rackham Merit Fellowship (2012-2014, 2016-2017).

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