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- Review -

Development of PLGA Nanoparticles for Astrocyte-specific Delivery of Gene Therapy: A Review

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Recently, as nanotechnology has been introduced and used in various fields, the development of new drugs has been accelerating. Nanoparticles have maintained blood drug concentration for extended periods of time with a single administration of the drug. The drug can then be selectively released only at the pathological site, thereby reducing side effects to other non-pathological sites. In addition, nanoparticles can be modified for selective target sites delivery for other specific diseases, with polymers being widely used in the manufacture of these nanoparticles. Poly (D,L-lactic-*co*-glycolic acid) (PLGA) is one of the most extensively developed biodegradable polymers. PLGA is widely used in drug delivery for a variety of applications. It has also been approved by the FDA as a drug delivery system and is widely applied in controlled release formulations, such as in gene therapy treatments. PLGA nanoparticles have been developed as delivery systems with high efficiency to specific cell types by using passive and active targeting methods. After the development of a drug delivery system using PLGA nanoparticles, the drug is selectively delivered to the target site, and the effective blood concentration for extended periods of time is optimized according to the disease. In this review paper, we focus on ways to improve cell-specific treatment outcomes by examining the development of astrocyte selective nanoparticles based on PLGA nanomaterials for gene therapy.

Key words : Astrocyte, gene therapy, nanoparticle, PLGA (Poly (D,L-lactic-*co*-glycolic acid))

Introduction

A drug delivery system selectively delivers a drug to a target site and optimizes the effective blood concentration for extended periods of time according to the diseas [38], thereby maximizing the therapeutic efficacy and effect and minimizing the side effects of the drug [1, 32]. By controlling the release and absorption of drugs and targeting and delivering drugs to a specific site in the body [1, 31], it is possible to retain the required amount of drug in the target site for a specified period of time. Furthermore, recent studies have focused on drug delivery systems using chemical polymers [3, 44]. The development of high molecular weight polymers that slow the release of the drug so that the drug can be effective for an extended period of time has therefore emerged as an important topic [40].

Nanoparticles are solid spherical structures of approximately 100 nm, which are prepared from natural or synthetic polymers. A wide variety of drugs, such as hydrophilic or hydrophobic small drugs, vaccines, and biological macromolecules, can be delivered using nanoparticles. Nanoparticles also facilitate targeted administration to specific organs or cells, as well as controlled drug delivery. Nanoparticles are broadly divided into different categories depending on their morphologies, sizes, and physical and chemical properties [17]. Nanoparticles can be carbon-based, ceramic, metal, semiconductor, polymeric, or lipid-based. Polymeric nanoparticles have been the most extensively studied for drug delivery [20, 27]. In addition to small drug molecules, they can also be used to deliver genes and proteins. Polymeric nanoparticles can penetrate through cell membranes, have serum stability, and can be easily manufactured. Furthermore, the surface of nanoparticles can be modified for various medical applications [24, 25].

Poly (lactic-*co*-glycolic acid) (PLGA) is one of the most successfully used biodegradable polymers because its hydrolysis leads to metabolite monomers, lactic acid and glycolic

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acid [23](Fig. 1). Because these two monomers are endogenous and easily metabolized by the body via the Krebs cycle, minimal systemic toxicity is associated with the use of PLGA for drug delivery or biomaterial applications. PLGA has been approved by the USA Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for drug delivery systems in humans. These polymers are commercially available with different molecular weights and copolymer compositions. The degradation time can vary from several months to several years, depending on the molecular weight and copolymer ratios. Forms of PLGA are usually identified by the monomer ratios used. For example, PLGA 50:50 is a copolymer whose composition is 50% lactic acid and 50% glycolic acid. PLGA nanoparticles are internalized in cells partly through fluid phase pinocytosis and also through clathrin-mediated endocytosis [7]. However, the nanoparticles rapidly escape internalization into lysosomes and enter the cytoplasm within 10 min of incubation [30]. This is facilitated by the interaction of nanoparticles with vesicular membranes leading to transient and localized destabilization of the membrane, resulting in the escape of nanoparticles into the cytosol.

Astrocytes are the largest and most prevalent type of glial cell in the central nervous system (CNS). Astrocytes contribute to the formation of the blood brain barrier (BBB), participate in the maintenance of extracellular ionic and chemical homeostasis, are involved in the response to injury, affect neuronal development and plasticity, and are critical for neuronal homeostasis [2]. Astrocytes also regulate the contents of the synaptic cleft and synaptic transmission as part of the tripartite synapse, control CNS metabolism, and maintain BBB integrity. Impairment of these functions through a disturbance in astrocyte integrity is likely to impact multiple aspects of brain physiology [29, 41]. Notably, astrocytes also can undergo a functional decline. Therefore, given that the primary and most important role of astrocytes in the brain is to maintain neuronal health [19, 35, 46], enhancing the efficiency of drug delivery in astrocytes is an important objective for treating brain diseases.

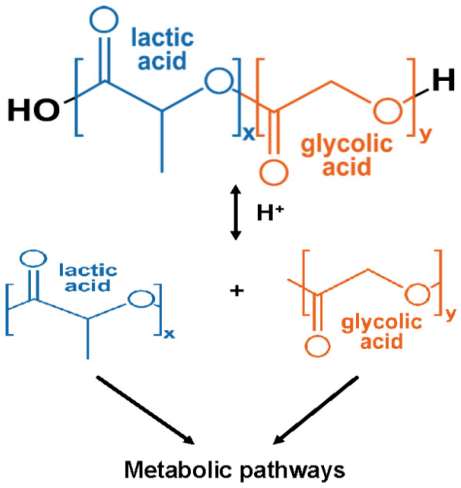

Fig. 1. Chemical structure and hydrolysis of PLGA nanoparticles.

Currently, delivery systems for the CNS using PLGA nanoparticles rarely are specific for astrocytes (Fig. 2). Other glial cells, such as microglia, have more than 50% cellular uptake capacity, followed by neuron cells. We will therefore describe efforts to overcome these problems. In this review, we will first discuss how PLGA-based nanoparticles can be engineered to target only specific cells and then how PLGA-based nanoparticles can work by targeting only astrocytes to deliver drugs. Finally, we will describe the potential development of these nanoparticles

In vivo delivery mechanisms of PLGA nanoparticles in nanomedicine

The delivery mechanism of PLGA nanoparticles is divided into two main categories; the first is passive targeting by the Enhanced Permeation and Retention (EPR) effect [15, 16]. Passive targeting using the EPR effect controls the size of the nanoparticle so that it minimally penetrates into normal cells but penetrates with high efficiency into the desired tissue. Nanoparticles smaller than 2 nm can easily pass through the voids in blood vessels, substances smaller than

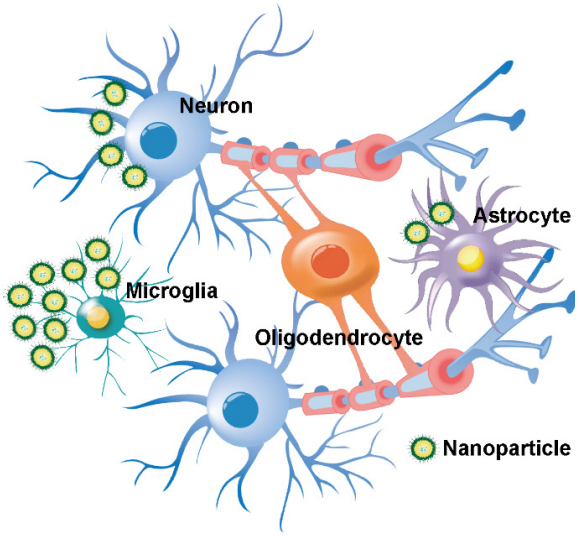

Fig. 2. Schematic diagram of the cellular uptake of PLGA nanoparticles by type of cells in brain.

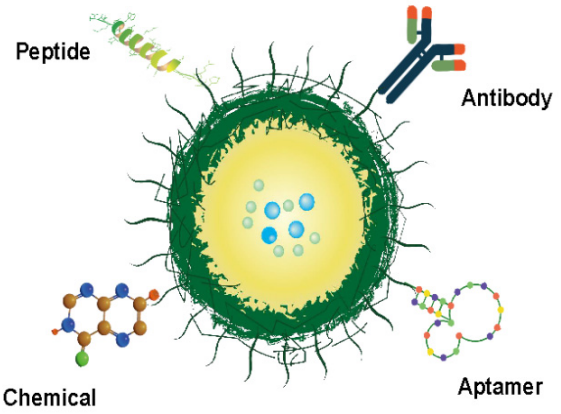

Fig. 3. Schematic representation of PLGA nanoparticles for active targeting.

10 nm can be easily excreted through the kidneys, and nanoparticles with sizes between 100-150 nm tend to accumulate in the liver [22]. Therefore, it has been determined that the optimal size of nanoparticles is 10-100 nm.

Alternatively, a nanoparticle can be passively targeted due to its charge (Fig. 3). The epidermal cells of blood vessels have many negatively charged components, so negatively charged nanoparticles tend to be repelled. Moreover, because brain tissue is protected by the BBB, targeting is limited by the size and surface characteristics of the nanoparticles, which has been the subject of extensive research. Passive targeting does not involve selective labeling of a specific target substance but instead involves a process in which the target tissue is labeled due to a difference in the biological and physical environments.

The second delivery mechanism is active targeting, in which targeting ligands are grafted at the surface of the PLGA nanoparticle [5]. The targeting ligand may be a peptide or an antibody that binds to a specific receptor, or developed more recently, it can be in the form of an aptamer or a compound [45]. The surface of nanoparticles can also be modified in order to graft, coat, or conjugate with specific targeting moieties. For example, KB cells rapidly take up folic acid-coated PLGA nanoparticles, suggesting that they are mainly taken up by folate receptor-mediated endocytosis [18]. As another example, in glioblastoma multiformes, it was shown that PLGA nanoparticles functionalized with OX26 monoclonal antibodies against the transferrin receptor more than doubled the drug delivery [36]. Recently, aptamer-labeled paclitaxel using PLGA nanoparticles has been reported to increase drug targeting to cancer cells [4].

Gene therapy and PLGA nanoparticle-based delivery systems

Gene-based therapy has become increasingly popular in the nanomedicine field. In past years, several studies have reported evidence of promising PLGA-based vector systems loaded with plasmid or siRNA therapeutics directed against disease-associated targets [39, 42]. This is possible because of advances in genetics and bioengineering, which enable manipulation of vectors for the delivery of genes or the introduction of gene editors including synthetic RNAi, miRNA, and long non-coding RNA, in addition to plasmid or CRISPR/Cas9 for silencing, enhancing, or editing of genes [10, 21]. Gene therapy, which can control gene expression, has had a major impact on diseases caused by specific gene mutations. This therapy has shown great potential for precision medicine because it can treat the disease at its origin. However, its potential still exists mainly in the laboratory, and its application is still far from being fully developed as a therapeutic agent.

Astrocyte-targeted PLGA nanoparticles for gene therapy

Astrocytes, the star-shaped glial cells in the brain, contribute to formation of the BBB, and participate in the maintenance of extracellular ionic and chemical homeostasis. During homeostasis, astrocytes regulate neurotransmission and synaptic activity by sequestering potassium and neurotransmitters, including glutamate. Furthermore, astrocytes secrete several neurotrophic and neuroinflammatory mediators. Thus, astrocyte-targeted gene therapy could be used to upregulate neurotrophic factor expression and/or silencing of toxic mediators. Although astrocytes play an important role in neuroprotection in the brain, efficient delivery of drugs to these cells is difficult. This is due to the intracranial delivery barrier called the BBB, which decreases delivery efficiency and hinders the development of drug delivery systems targeting astrocytes.

Peptide-conjugated PLGA nanoparticles for targeting astrocytes can be combined with an anti-Somatostatin receptor 2 (SSTR2) peptide. Furthermore, anti-SSTR2 peptide modified nanoparticles could be a promising nanocarrier for glioma neovasculature endothelial cells and glioma cells for dual targeting [6] The method of binding compounds to the surface of PLGA nanoparticles is another delivery system specific to astrocytes. Normal PLGA nanoparticles do not localize to the nucleus; however, the addition of arginine-modi-

Table 1. Active targeting of PLGA nanoparticles to astrocytes

	Type	Component	Reference
1	Peptide	Anti-SSTR2	[34]
2	Chemical	Glutathione, Arginine, Transferrin	[27], [35], [37], [38]
3	Aptamer	AS1411	[29], [36]
4	Antibody	Transferrin R (TfR)	[28]

fied polymers significantly improved nuclear localization of plasimd and successfully achieved gene expression in primary human astrocytes [34]. Glutathione (GSH)-coated PLGA nanoparticles can also permeate the BBB. GSH-coated docetaxel nanoparticles were significantly better at killing glioma cancer cells than docetaxel alone. Aptamers are a class of therapeutic oligonucleotides that bind to cell surface receptors with high affinity and specificity. This property of aptamers has been exploited develop targeted drug carriers that can deliver a variety of cargo into cells. According to a recent report, the efficiency of intracellular influx of aptamer-conjugated PLGA nanoparticles into astrocytes was greatly improved [4, 14] compared to PLGA nanoparticles alone. Antibodies can also be used to target nanoparticles to specific cells types. For example, PLGA nanoparticles functionalized with Transferrin R monoclonal antibody-encapsulated temozolomide increased the delivery efficiency of the drug into glioma cells.

Discussion

Nanoparticles enable effective treatment by selective target site delivery to a specific disease site, while minimizing side effects that may occur in normal organs, tissues, and cells [9]. To achieve this, it is important to appropriately modify and control the characteristics of the nanomaterial polymer.

The development of nanotechnology has led to remarkable developments in drug delivery and bioimaging, and as a result, diagnosis, treatment, and methods of monitoring the progress of the treatment process have been improved, and customized treatments based to the patient's diagnosis have now become a possibility. It is not possible to accurately predict how effective medical advances will be in the future by understanding the properties of materials and applying them to medicine in the nanotechnology field; however, it is clear that nanomaterials will play a decisive role in more accurate diagnoses and quality treatments in the near future.

Due to the enormous diversity of nanomaterials, their potential toxicity and environmental impact is not completely understood. Therefore, studies on the stability of these materials are also being conducted at the same time. As described in this review, control of drug delivery, targeting of nanoparticles, and development of cell-specific nanoparticles have developed at a rapid pace, but there are still only a few drugs that can be directly used in clinical practice. Design and targeting strategies for nanoparticles will need to be more diverse and depend on the differences in diseases, degree of development, and location of the lesion. Successful clinical use of nano-pharmaceuticals for therapeutic and diagnostic purpose will then be possible.

PLGA-based nanoparticles present many advantages for drug delivery [11, 43, 47]. They can protect drugs from degradation and enhance their stability. Moreover, due to their size, nanoparticles can penetrate specific tissues via receptors overexpressed by target cells or in the BBB. This allows specific delivery of drugs, proteins, peptides, or nucleic acids to their target tissues. PLGA-based nanoparticles can increase the efficacy of treatments because of the sustained release of the therapeutic agent from stable nanoparticles. They can improve pharmacokinetic and pharmacodynamics profiles. Another major advantage of PLGA over other polymers is that PLGA has been approved by the FDA and EMA in various drug delivery systems, so PLGA-based nanoparticles are in a good position for use in clinical trials. However, these systems also present some disadvantages, such as a low drug loading capacity, high cost of production, and difficulty in scaling-up production. One of the most significant challenges limiting the use of drug-loaded PLGA-based nanoparticles in clinical trials is the low drug loading efficiency.

The aggregation of PLGA nanoparticles during the solvent evaporation processes is also a notable problem, regardless of the specific method used. To prevent PLGA-nanoparticle aggregation, polymer stabilizers are often used to coat the nanoparticle surfaces, including the use of polyvinyl alcohol, polyvinyl pyrrolidone, Tween 80, and human serum

albumin [43]. However, these stabilizers are difficult to remove even with thorough washing protocols, and some are toxic to the BBB. In an effort to avoid this problem, a new washing method is needed, and the agglomerates must be released in a size and shape suitable for drug delivery in the body.

The brain is one of the most vital and sensitive organs in the body, which, to perform its functions in an appropriate way, needs nutrients and gases. Due to its pivotal role and functions, it is protected in many ways, including by the skull, outer skin, three layers of meninges, and the BBB. The BBB is a layer of endothelial cells associated with pericytes and astrocytes, which acts to separate blood from parenchymal cells, thus preventing penetration of drugs into the CNS. It therefore protects the brain from overexposure to substances such as potassium, glycine, and glutamate, which, in high levels such as those found in pathological conditions, are neurotoxic [26, 28]. The BBB is the major barrier for drug delivery to the brain [33, 37]. The failure of therapies administered via the intravenous or oral route is often due to their inability to cross/penetrate the brain parenchyma or BBB. Therefore, it is necessary to increase the efficiency of PLGA nanoparticles crossing through the BBB when developing new products. However, improving the delivery efficiency of nanoparticles is a different problem than developing nanoparticles to target specific cells.

In most cases, a single strategy does not achieve the goals of both improving delivery across the BBB and targeting astrocytes for treatment of CNS diseases. To provide successful therapies, different strategies are needed, such as the formulation and construction of multifunctionally-engineered PLGA nanoparticles.

In this review, possible applications for the use of PLGA-based nanoparticles targeting astrocytes have been described. These examples illustrate the promise of using nanoparticles for novel treatments. PLGA nanoparticles are a non-viral, biocompatible, and effective delivery system for targeting gene therapy to the human brain, specifically astrocytes. This approach may provide a powerful tool for delivering therapeutic genes not only to the brain, but also to other difficult to target cell types.

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The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : 별아교세포 선택적 유전자 치료전달을 위한 PLGA 나노입자 개발

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최근에는 나노기술이 다양한 분야에 도입되고 활용되면서 신약개발이 가속화되고 있다. 나노입자는 약물의 단일 투여로 장기간 동안 혈중 약물 농도를 유지하고, 병리학적 부위에만 선택적으로 방출되는 장점이 있어 비병리 주위에 대한 부작용을 줄일 수 있다. Poly (D,L-lactic-*co*-glycolic acid) (PLGA)는 가장 광범위하게 개발된 생분해성 고분자 중 하나이다. PLGA는 다양한 응용분야의 약물전달에 널리 사용된다. 또한 FAD에 의해 약물전달 시스템으로 승인되었으며, 유전자 치료제와 같은 제어방출제형에 널리 적용된다. PLGA 나노입자는 수동 및 능동 표적화 방법을 사용하여 특정 세포 유형에 고효율의 전달 시스템으로 개발되었다. 이러한 PLGA 나노입자를 이용한 약물전달체 개발 후 표적 부위에 선택적으로 약물을 전달하고 질병에 따라 장기간 유효 혈중 농도를 최적화한다. 이 리뷰논문에서 우리는 유전자 치료를 위한 PLGA 나노 물질을 기반으로 하는 성상 세포 선택적 나노입자의 개발을 조사하여 세포 특이적으로 치료결과를 향상시키는 방법에 중점을 두고자 한다.