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Review article

The principles and applications of avidin-based nanoparticles in drug delivery and diagnosis

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A R T I C L E I N F O

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A B S T R A C T

Avidin-biotin interaction is one of the strongest non-covalent interactions in the nature. Avidin and its analogues have therefore been extensively utilized as probes and affinity matrices for a wide variety of applications in biochemical assays, diagnosis, affinity purification, and drug delivery. Recently, there has been a growing interest in exploring this non-covalent interaction in nanoscale drug delivery systems for pharmaceutical agents, including small molecules, proteins, vaccines, monoclonal antibodies, and nucleic acids. Particularly, the ease of fabrication without losing the chemical and biological properties of the coupled moieties makes the avidin-biotin system a versatile platform for nanotechnology. In addition, avidin-based nanoparticles have been investigated as diagnostic systems for various tumors and surface antigens. In this review, we will highlight the various fabrication principles and biomedical applications of avidin-based nanoparticles in drug delivery and diagnosis. The structures and biochemical properties of avidin, biotin and their respective analogues will also be discussed.

Contents

1. Introduction

Nanotechnology holds the greatest potential and promise for biomedical research. Significant progress has been achieved in nanotechnology across a wide spectrum of fields from applied physics to

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biotechnology to medicine. Naturally occurring interactions are the crux for such innovations and have been explored for various nanoscale applications to achieve uncountable scientific goals. As one of the strongest non-covalent interactions in the nature, the avidin-biotin interaction has been utilized in nanoscale drug delivery systems for pharmaceutical agents, including small molecules, proteins, vaccines, monoclonal antibodies, and nucleic acids (Fig. 1).

Avidin is a basic tetrameric glycoprotein composed of four identical subunits, each binds to biotin with high specificity and affinity ($K_d \sim 10^{-15}$ M). Avidin is originally derived from the eggs of aves, reptiles and amphibians. Avidin-biotin interaction is considered one of the most specific and stable non-covalent interactions, which is about 10^3 to 10^6 times higher than an antigen-antibody interaction [1]. Several genetically and chemically engineered avidin and its analogues have been studied to improve the functional and structural characteristics of avidins [2]. The biggest advantage of this system is its high affinity interaction, which is robust and stable against manipulation, proteolytic enzymes, temperature, pH, harsh organic reagents, and other denaturing reagents [3–6]. Therefore, the avidin-biotin interaction serves as a great tool in the biomedical and nanotechnological applications. On the other hand, biotin-based conjugates are easy to synthesize and have less impact on the activity of the biomolecules.

Compared to other covalent and non-covalent interactions, the avidin-biotin system provides enormous advantages such as amplification of weak signals, efficient operation, robust stability. Therefore, avidin has been a very versatile modality in the field of biotechnology, especially biochemical assays and affinity purification, over four decades. Tremendous efforts have also been converged to utilize the inherent properties of avidin in biotechnology medicines, and some of them have been evaluated in clinical studies. Recently, the avidin-biotin technology underwent a renaissance in nanoscale drug delivery and diagnostics. Targeting ligands or imaging agents can be easily coupled to nanocarriers via the avidin-biotin linkage. For example, PMA hydrogel capsule functionalized with biotin forms a stable nanocomplex with avidin-coupled antibodies and improved its cellular uptake in cancer cells [7]. Liposomes modified with biotinylated polyethylene glycol can attract a layer of neutravidin on the surface to resist nonspecific binding to serum proteins, thus leading to prolonged circulation time [8]. Microbubbles coupled with RGD peptide via avidin-biotin linkage were developed for the detection of Hep-2 related tumor angiogenesis [9]. Neutravidin conjugated superparamagnetic iron oxide nanoparticle has also been explored as an imaging agent for rhodopsin degeneration [10]. More recently, the avidin-based nanotechnology has found its applications in tissue engineering and cellular regeneration [11,12]. In one such study, an avidin-biotin system was used to improve osteoblast-like cell adhesion to a highly porous calcium phosphate glass scaffold for bone tissue engineering [12].

The aim of this review is to highlight the unprecedented advantages of avidin and its analogues in nanotechnology. We will critically evaluate a wide variety of applications that have been recently explored for drug delivery and diagnosis. It is our hope that this review will serve as a one-stop reference for investigators who are interested in exploring the avidin-based nanotechnology in their fields.

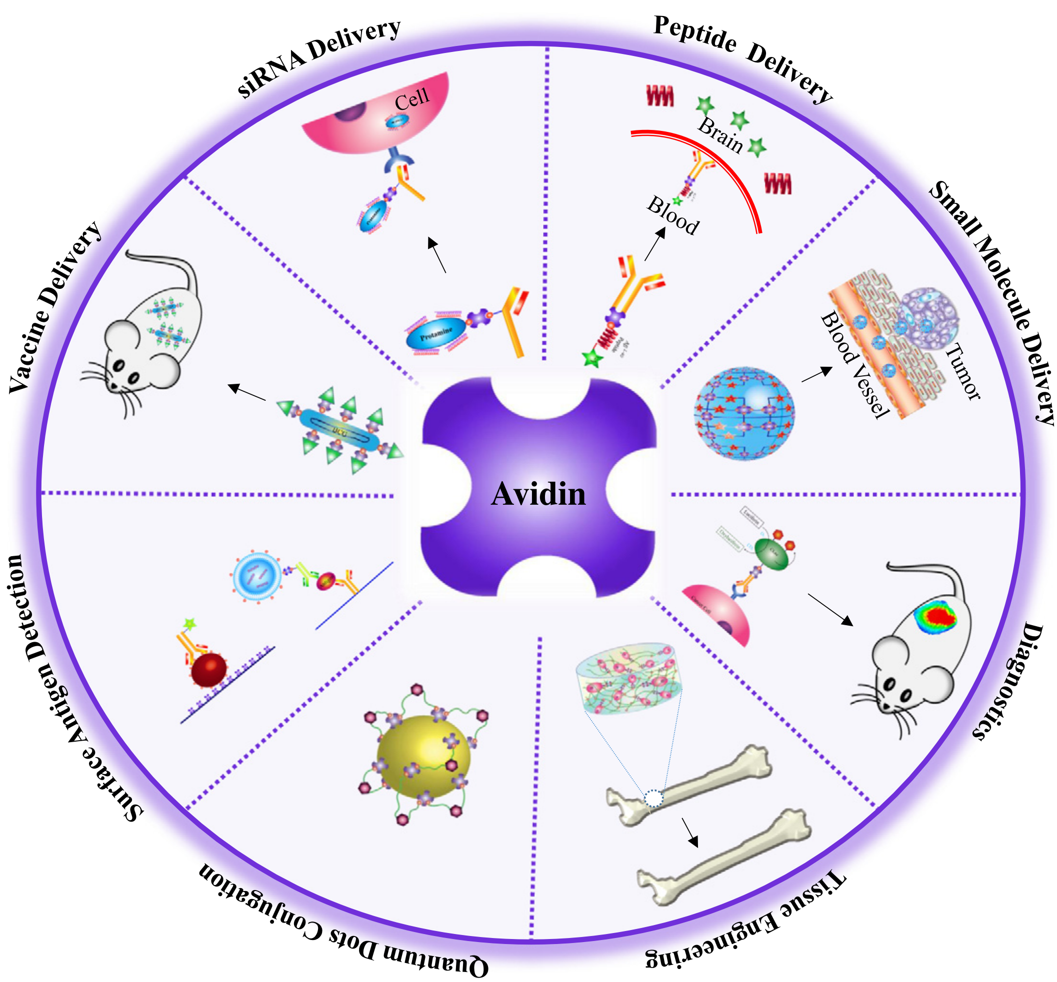

Fig. 1. Avidin-based nanoscale systems in various applications.