Advances in the study of DNA-metal complexes in biomedical applications

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Abstract. DNA-metal composites are emerging as emerging materials for biomedical applications due to their unique DNA and metal nanoparticle properties. DNA is a multifunctional macromolecule that enables targeted drug delivery through aptamer selection and gene silencing through nuclease activity. These properties make it highly selective and targeted in therapy. While conventional chemotherapy faces significant drawbacks, including poor targeting and severe side effects, DNA-metal composites with their excellent targeting and therapeutic efficiencies can significantly enhance therapeutic efficacy. This paper first describes the structural properties, synthesis methods of DNA-metal composites and their therapeutic applications. The combination of DNA and metal nanoparticles provides a novel approach to improve the effectiveness of anticancer and antimicrobial therapies, addressing key limitations in current therapeutic strategies. Innovative applications of DNA-metal composites in the anticancer and antimicrobial fields are then explored, highlighting their multiple synthesis and application possibilities through interactions with metal ions or particles. DNA-metal composites address several of the limitations of conventional chemotherapeutic and antimicrobial drugs, providing better targeting and resolving the issue of drug resistance. DNA-metal composites in biomedicine show DNA-metal composites show great promise in the biomedical field, and future research will continue to promote their application and development in clinical therapy.

Keywords: DNA; metal; targeted therapy; anti-cancer; antibacterial.

1. Introduction

DNA is a chain macromolecule, and two complementary DNA strands can be bonded to each other by hydrogen bonds. Double-stranded DNA acts as a store of genetic material in the cell. Artificially designed DNA sequences can be made to have more diverse functions, for example, in vitro screening of nucleic acid aptamers can play a role similar to that of antibodies to improve drug targeting [1], some DNA fragments have nuclease activity, which can recognise and cleave specific mRNA fragments in order to silence the expression of certain intracellular genes [2].

Metal nanoparticles or materials containing metal ions have been developed for use in a variety of biomedical applications, and a variety of transition metals can be used in anticancer therapies as well as antibacterial reagents [3]. Nanoscale metals have many excellent physicochemical properties that are different from those of macroscopic metallic materials [4], and exhibit a variety of uses [5].

Direct intracellular application of metal nanoparticles or metal ions is uncontrollable and poorly targeted, and using DNA alone faces inefficiencies. These drawbacks make the therapeutic approach challenging in many ways [2, 4].

DNA can be bound to metal nanoparticles or metal ions [6], and reduction of the latter with a reducing agent produces DNA-bound metal clusters or metal particles embedded in DNA [7]. The use of DNA-metal complexes allows for the use of metals to enhance the effects of DNA zymes [4], as well as to use DNA to enhance the dispersion, stability and targeting of metals for better therapeutic effects [5]. In this paper, we will present the structure and properties of DNA metal composites and thus discuss their applications in the field of anticancer and antibacterial properties.

2. Structure of Nucleic Acid Metal Complexes

2.1. DNA Structure

DNA and RNA have similar structures, the monomers of single-strand DNA and RNA consist of three parts: one pyrimidine or purine base, a D-ribose or D-2-deoxyribose and phosphoric acid. The hydroxyl group of the phosphate is dehydrated and condensed with the 5' hydroxyl group of the sugar, and the hydrogen of the base is dehydrated and condensed with the 1' hydroxyl group of the sugar to give the monomer: ribonucleotide or deoxyribonucleotide. The monomers form polymers by dehydration condensation of the 3'hydroxyl group of the sugar moiety with phosphoric acid. DNA is more commonly used in nucleic acid metal material due to the fact that the monomer of RNA has a 2'hydroxyl group, thus is more unstable than DNA, and the ubiquitous existence of RNA hydrolases [8].

DNA often consists of double strands, stabilized by the formation of hydrogen bonds between bases between the strands and by van der Waals forces between adjacent parallel base pairs, with the phosphate group exposed. Notably, the phosphate group is negatively charged and can interact with cations by charge interaction, while the bases have nitrogen atoms that can act as ligands [9].

2.2. Metal Ions Containing DNA Structures

The phosphate group is negatively charged, and the native neutralizing cation is the magnesium ion. Under artificial conditions, various metal ions can interact with DNA, which can be differentiated using the soft and hard characteristics of the ions: hard cations tend to bind to the phosphate backbone, soft cations tend to coordinate to the bases, and the metals in the first transition region are moderately soft and hard and can bind to both sites [9]. The binding of metals to bases may alter the structure of DNA and this ability may lead to toxicity, e.g. platinum and ruthenium binding to bases can lead to drastic changes in the structure of DNA, which can then become components of anti-cancer drugs. Some metals can be inserted between base pairs and have coordination interactions with the bases, replacing the original hydrogen bonds and forming metal-mediated base pairing. while base pairs mediated by metal ions may not need to satisfy the rules of complementary pairing [6].

The use of nucleoside analogs or artificial nucleosides can expand the range of available metals by providing better metal binding sites [6], But if nucleoside substitutes or artificial nucleosides are used, their effects on metabolism in organisms need to be further evaluated.

2.3. Metal Nanoparticles Combining DNA

Metal nano-ions due to their nano-size thus produce many excellent physical and chemical properties different from those of macroscopic metal blocks.

The size of the particles is small enough to allow the electrons confined in the metal to exhibit quantum mechanical properties, producing discrete energy levels, whereas the macroscopic metal block has only continuous energy bands due to the large space in which the electrons can move. This gives metal nanoparticles surface plasmon resonance effect and allows metal particles to strongly absorb and scatter light at resonant frequencies, which can be used for imaging [10]. Strong absorption means strong thermal energy conversion, allowing metal nanoparticles to be used in photothermal therapy [11]. At the same time, metal nanoparticles have a high specific surface area and therefore can perform a good catalytic activity and play a role in chemical kinetic therapies.

There are several ways to synthesize composites of DNA with metal nanoparticles, one of which is to make spherical nucleic acids, which were invented in 1996 and can be obtained by sulfur-containing moiety-modified DNA combined with already synthesized metal nanoparticles [4]. Directly, the surface of the nanometal particles is positively charged and can be stabilized by citrate, and the phosphate groups on the surface of the DNA are negatively charged and can displace citrate in electrostatic interactions with the nanometal particles. Gold and silver have a high affinity for sulfur atoms and can form strong Au-S bonds and Ag-S bonds, which can be self-assembled on the surface of metal particles by modifying the thiol groups on DNA to obtain stable spherical nucleic acids [12].

Another approach is through DNA template-mediated. Using the characteristics of DNA binding metal ions, heating to make the DNA deconvoluted to expose the bases, at this time the metal ions can be coordinated, and then a reducing agent (such as sodium borohydride) to reduce these ions, to obtain metal nanoparticles[7] because the metal ions were previously bind to DNA, the resulting particles are still closely bound to DNA, or the DNA will be embedded in it, this method to DNA as a template, the and the DNA does not need to be modified, which is more convenient. However, the type of reducing agent used may be related to the toxicity of the metal particles, so bacteria or plant extracts may be used as reducing agents to reduce the toxicity of the complex [13].

3. Anti-cancer Applications

Traditional anti-cancer chemotherapy achieves its effect by destroying the DNA of the tumor cells or inhibiting their division by drugs, but the targeting of chemotherapy drugs is insufficient, thus causing a lot of side effects such as hair loss, immunosuppression, and organ toxicity. Additionally, the development of drug resistance by cancer cells over time can diminish the efficacy of chemotherapy [14].

Less toxic metal nanomaterials have been developed for several anti-cancer therapies. DNA can be used as an aptamer to bind to target cells, improving drug targeting, and can also improve the biocompatibility of metallic materials [1]. Thus therapeutic regimens based on metallic DNA composites as an improvement or alternative to previous chemotherapy.

3.1. Enhanced Chemo-dynamic Therapy

Transition metal nanoparticles delivered into tumor cells can catalyze a Fenton or Fenton-like reaction by releasing ions that generate reactive oxygen species (ROS) within the cell, killing cancer cells through oxidative stress. Autophagy in cancer cells can diminish the effectiveness of chemokinetic therapies by removing damaged organelles and providing energy to the cells.

The efficacy of CDT can be improved by inserting nuclease fragments into the DNA bound to the metal nanoparticles, enabling them to cleave autophagy-associated mRNA and silencing autophagy gene expression [15]. The use of zinc-containing nanoparticles in addition to manganese, which catalyzes the Fenton or Fenton-like reaction, can increase the intracellular concentration of zinc ions and enhance DNA nuclease activity [2].

3.2. Medical Imaging and Photothermal Therapy

Metal nanomaterials have the property of scattering near-infrared light due to surface plasmon resonance, and can be imaged on cancer cells through surface aptamers that bind specifically to cancer cells, or after being cytosolised, and the scattering can be observed using dark-field microscopy and light-scattering imaging techniques [11].

At the same time, gold and silver nanomaterials can be used as photothermal agents, absorbing near-infrared light and converting it into heat energy, causing thermal ablation of cells, and also improving the efficacy of certain drugs through high temperatures [11].

4. Anti-bacterial Applications

Antibiotics are commonly used antimicrobial agents, but the emergence of bacterial resistance accompanying the use of antibiotics is gradually becoming a serious problem, and metal nanoparticles, as an alternative antimicrobial material, show strong antimicrobial activity. The antimicrobial mechanism of metal nanoparticles includes the release of reactive oxygen species, cation release, biomolecule damage, ATP depletion and membrane interactions, etc [3].

It has been shown that the antimicrobial activity of nanoparticles is based on the release of ions and is directly proportional to the release of ions [16], and that DNA as a capping agent can improve

the dispersion and stability of metal nanoparticles and maintain a high specific surface area, which is conducive to the play of catalytic activity as well as to the release of ions.

4.1. Disruption of Bacterial Wall Membrane Structure

The cations released by metal nanoparticles can bind to and aggregate with the cell wall and cell membrane of bacteria, which may lead to damage to the cell wall, increased permeability of the cell membrane and dissipation of the membrane potential, thereby disrupting the structure of the bacterial cell membrane and cell wall [17].

4.2. Sulfur-atom Affinity

Sulfhydryl groups are common groups on proteins and are derived from cysteines, which are essential for the catalytic activity of enzymes with the formation of the correct structure of proteins. The binding of metal ions to sulfhydryl groups can lead to a decrease in the catalytic ability of certain enzymes and prevent protein synthesis [18]. Also, metal ions can bind to low molecular weight thiols and work with reactive oxygen species.

4.3. Reactive Oxygen Species (ROS)

Producing excessive levels of ROS is destructive and can disrupt the normal metabolism of bacteria thus killing them. At the same time, low molecular weight thiols in bacteria maintain redox homeostasis. Thiol depletion leads to rapid accumulation of ROS in bacterial cells, further amplifying the oxidative stress response.

5. Conclusion

DNA-metal composites are increasingly becoming a promising material for biomedical applications due to their unique properties derived from DNA and metal nanoparticles. DNA, as a multifunctional macromolecule, enables targeted drug delivery through aptamer selection and gene silencing through nuclease activity. Metal nanoparticles, on the other hand, have demonstrated great potential due to their unique physicochemical properties in the face of significant drawbacks of conventional chemotherapy, including severe side effects. DNA-metal composites enhance targeting and therapeutic efficacy through functional and designed DNA sequences and the unique properties of nanometals, such as surface plasmon resonance and catalytic activity. This study reviews the synthesis and structure of DNA-metal composites and their therapeutic applications, demonstrating their potential as advanced alternatives to conventional therapies. The combination of DNA and metal nanoparticles provides a novel approach to improve the effectiveness of anticancer and antibacterial therapies and to address key limitations in current therapeutic strategies. This paper explores the innovative applications of DNA-metal composites in the anticancer and antimicrobial fields, highlighting their multiple synthesis and application possibilities through interactions with metal ions or particles. DNA-metal composites address several limitations of conventional chemotherapeutic and antimicrobial drugs, providing better targeting and addressing drug resistance issues. Although more diverse synthesis methods and therapeutic options based on metal-DNA interactions are not covered in this paper, the application directions explored are representative of such materials. In addition, the toxicity and metabolic pathways of these materials are still understudied, and further studies on their metabolic pathways in animals are needed before they can be used as drugs.

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