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Applications of Polydopamine - Platinum Nanoparticle in Cancers

Jiayu Liu[1, *]

[1]Department of Biology, University of Oregon, Eugene, Oregon, the United States
*Corresponding author: jliu5@uoregon.edu

Abstract:

Platinum nanoparticles (Pt NPs) are effective anticancer small molecule drugs. Cisplatin, which platinum particles generate when they enter the cell body, effectively kills cancerous cells. However, the specificity of Pt NPs targeting to cancer cells without affecting normal cells remains a big challenge. Due to the emphasis on the effectiveness of Pt NPs, researchers tried to decrease its toxicity by creating an organic metal framework (MOF) structure to envelope Pt NPs. Polydopamine (PDA), with its good biocompatibility and antioxidant properties, can be a carrier for transporting Pt NPs into cancerous cells. The PDA-Pt NPs combination has shown a significant increase in efficacy and fewer side effects. EpCAM antibody and Pt fixed with PDA carbon dots were used to target liver cancer cells specifically. Clinical trials on hepatocellular carcinoma treated with multi-functional NPs after traditional interventional treatment showed significant beneficial effects on outcomes. This review summarizes the individual compositions and functions of Pt NPs and PDA, as well as the combined complex and its clinical application. Future *in vitro*, *in vivo*, and clinical research is required to modify the structure of PDA-Pt NPs to reduce side effects and make them fit for more types of cancers.

Keywords: Platinum nanoparticles; polydopamine; molecular pharmaceutical; cancer.

1. Introduction

Cancers have been the leading cause of mortality among non-epidemic diseases for decades. Unlike other diseases, the majority caused by viruses or bacterial infection, cancer is an unfavored mutation of cells from the host. Precisely because this mutation comes from the patients themselves, the cancerous cells can easily bypass the detection function of the immune system. Not only that, the muted cells have much more livability than normal cells. Thus, it is hard to be exterminated by normal small molecular medicine for similar symptoms. Fortunately, in the early 70s, a biophysicist, Burnett Rosenberg, noticed this discovery in his experiment of charged platinum particles (Pt NPs) killing bacteria [1]. After over a decade of experiments by multiple research groups, the first prototype of a Pt NPs drug was invented. The researcher noticed there was a compound that they named cisplatin, which was produced by the Pt NPs when they entered the cell body of the cancer cells. Cisplatin shows significant efficacy in killing cancer cells. Hence, it was extensively employed in cancer treatment, but its efficacy is hampered by poor stability and selectivity, not to mention significant toxicity towards non-target cells [2]. Biopharmacists noticed that a newly developed material enlightened by mussel, called polydopamine (PDA), was especially suitable for the carrier of Pt NPs. As a compound akin to melanin, owing to its excellent biocompatibility and antioxidant properties, it has found broad application in the modification of diverse biological materials. The fusion of PDA and Pt NPs maximizes the stability and minimizes the side effects it might cause, creating the PDA-Pt NPs. Thus, PDA-Pt NPs are a promising complex for the base of target cancer treatment. This review summarizes the function of PDA-Pt NPs by introducing the composition and function of Pt drugs, the reason for choosing PDA as the carrier of the drug, and the potential applications.

2. Molecular Basis of Pt NPs

Platinum-based anti-cancer drugs were first discovered by accident in 1969 by an American biophysicist, Barnett Rosenberg [1]. Platinum has been disclosed to generate some compounds that inhibit growth and multiplication and eventually kill the bacteria of the experiment. Later, the compound in question was discovered to be a complex of platinum II, in which the central ion is bonded to 2 chloride anions and 2 ammonia molecules [3]. Because the ligands are situated next to the same type in the sic-position, the compound was also called Cisplatin.

2.1 Cisplatin

Cisplatin, also known as (SP-4-2)-diamminedichloridoplatinum(II), stands as one of the premier and earliest metal-based chemotherapeutic drugs employed in the treatment of various solid cancers (Figure 1) [1]. Cisplatin's structural function explains its very high efficiency in

killing cancer cells. Cisplatin's mechanism involves three key components: cisplatin itself, DNA, and the HMG protein.

Due to its size, cisplatin can readily traverse the cell membrane. The majority of cisplatin enters the cell body through active transport, although some molecules diffuse passively through the membrane. Upon arrival in the nucleus, cisplatin can form an adduct with two consecutive guanine bases within a DNA strand. Subsequently, the molecule replaces its chlorine atoms with the nitrogen atoms of the targeted guanine. Cisplatin exhibits a stronger binding affinity with nitrogen due to its ability to effectively balance the platinum charge compared to guanine. This adduct-induced DNA bend facilitates the binding of proteins containing the high mobility group (HMG) domain. Once the protein binds to the DNA, it inserts a wedge-like phenyl group of phenylalanine 37 into the widened minor groove formed by the binding. The tightly bound HMG protein induces the de-stacking of nucleotide bases, causing the DNA helix to become kinked. Hence, cisplatin is regarded as a disruptive element in the DNA repair mechanism. The altered strand, with the HMG protein bonded to the DNA, is not adequately repaired, ultimately resulting in cell death [1]. The efficacy of cisplatin depends on its effectiveness in targeting cancerous cells compared to healthy cells. It is frequently employed in clinical settings alongside 5-fluorouracil, capecitabine, and calcium formyl tetrahydrofolate for treating colon cancer while also being utilized to modify ligand structures and develop drug delivery systems for cancer treatment [3].

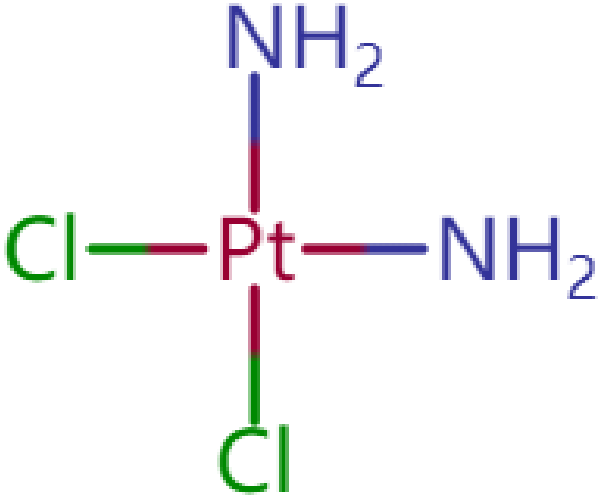

Fig. 1 Molecular structure of cisplatin. Figure credit: original.

2.2 Metal-Organic Framework (MOF)

As efficient as the Pt-NP is in cancer treatment, the negative effect of toxicity on cells, especially kidney cells, should not be ignored. In the quest for safer and more efficient therapeutic outcomes, researchers have turned to nanoparticle delivery systems to encapsulate platinum drugs, thereby improving their bioavailability and reducing toxicity to organisms. This advancement has facilitated progress in the field of biomedicine [3]. Novel metal-organic backbone (MOF) materials have been engineered. These materials are versatile and capable of performing various functions by forming complexes between metal ions and organic ligands [3]. Due to their framework structure, MOFs possess larger specific surface areas and spacious pores, making them ideal carriers for containing and transporting drug particles for medical applications.

Platinum nanoparticles and their derivatives (like cisplatin) are capable of killing cancer cells, which can be transported by MOFs to address bodily ailments and can be incorporated with other metals to craft fresh MOF materials, each with distinct effectiveness. Subsequently, these materials can be co-administered with other therapeutic drugs for clinical interventions [3]. In both approaches, platinum assumes distinct functions, with the primary distinctions rooted in how it binds to the MOF substance. In the first form, platinum joints with other materials to composite the mainframe work of MOF, but the principle can be further delineated into two main categories: firstly, where platinum serves as a metallic junction to construct the MOF framework, typically resulting in a bimetallic MOF material; secondly, where platinum is employed as an exogenous element [3]. The other form is to use platinum as the effective drug, where the Pt NPs are doped into complete MOF materials. However, this form does not include the construction or the encapsulated in the outer layer of the MOF materials [3].

2.3 Synthesizing Porous Pt NPs (pPt NPs)

pPt NPs were synthesized using a modified porogen-assisted reduction method [4]. Initially, 24 mL of a 10 mM K2PtCl4 solution was combined with 60 mL of a 100 mM CTAB solution and heated to 70 ℃ [4]. Subsequently, 36 mL of a 20 mM ascorbic acid solution was gradually added to the mixture while stirring at 600 rpm [4]. After a continuous reaction period of 3.5 hours, the precipitated pPt NPs were harvested via centrifugation and subjected to repeated washing with distilled water and ethanol [4]. Following, the resulting pPt NPs (20 mg) were dispersed in 40 mL of a 10 mM Tris-HCl solution (pH 8.5) and sonicated for 5 minutes [4]. Subsequently, 4 mg of DA·HCl was added, and the mixture was magnetically stirred at 600 rpm for 1 hour. The pPt@PDA NPs were then collect-

ed post-centrifugation and washed with deionized water [4].

3. PDA and PDA-Pt

PDA, a polymer with near-infrared absorption properties, has garnered significant interest (Figure 2). As a crucial constituent of melanin found extensively in the human body, PDA exhibits distinct advantages in terms of biological safety. Research indicates that PDA does not impede the activity or proliferation capacity of various mammalian cells and does not induce notable cytotoxic effects even at significantly elevated doses. Furthermore, PDA has demonstrated complete in vivo degradation, thus presenting a superior safety profile to other conjugated polymers [5]. The artificially synthesized PDA is an emerging biopolymer material inspired by nature, boasting numerous intriguing properties such as self-assembly and universal adhesion. Furthermore, PDA exhibits the capability to form coordination bonds with various metal ions, which can subsequently be reduced to metal nanoparticles through thermal annealing in a protective environment [6]. In the medical field, researchers have employed PDA as a support material to synthesize Pt nanoparticles in an aqueous solution at room temperature, facilitating the transportation of these nanoparticles to cancer cells [6, 7].

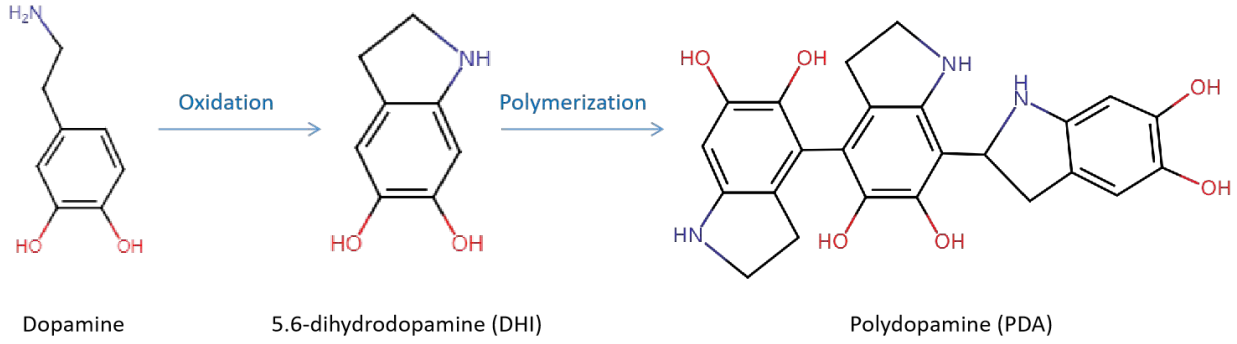

Fig. 2 Molecule structure of Polydopamine (PDA). Figure credit: original.

Pt NPs have been found to exceed exceptional success in anti-cancer treatment. However, in the early days, although researchers understood the significance of optimizing nanocarriers for metallodrugs in clinical applications, customized nanocarriers for metal-based photosensitizers were still uncommon [7]. A PDA hybrid nanocomposite PDA-Pt was designed. The structure of PDA-Pt undergoes modification with cyclodextrin (CD) groups and incorporates a Ru (II) complex (RuFc) through host-guest interactions, resulting in the formation of PDA-Pt-CD@RuFc nanoparticles [7].

4. Applications

During interventional treatment, materials are introduced into the blood supply artery and transported directly to tumors, offering promising avenues for the clinical application of nanomedicine [8]. Although trans-arterial chemoembolization (TACE) and transarterial radioembolization (TARE) are effective treatments for hepatocellular carcinoma (HCC), the presence of residual tumors after surgery can result in intrahepatic recurrence and distant metastasis [8]. The utilization of multifunctional NPs in combination therapy involving both TACE and TARE is anticipated to surmount drug resistance in hypoxic tumors and enhance therapeutic outcomes [8].

One of the main problems for NPs in targeted therapy is finding cancerous cells through the blood stem. Li et al. conducted a study using imaging-guided chemo-photothermal PDA carbon dots to deliver the drug EpCAM directly to the liver tumor [9]. They introduced a multifunctional nanoparticle capable of conducting imaging-guided chemo–photothermal synergistic therapy while facilitating targeted delivery to liver tumor cells through EpCAM [9]. Via an amidation reaction, EpCAM antibody (anti-EpCAM) and Pt(IV) were attached to polydopamine carbon dots (PDA-CDs) [9]. The EpCAM antibody segment of the particles enables specific interaction with liver progenitor cells due to their heightened expression of the EpCAM protein [9]. The tetravalent platinum prodrug [Pt(IV)] triggers apoptosis with minimal side effects by interacting with the DNA of tumor cells [9]. Additionally, the nanoparticles display stable photothermal characteristics and exhibit significant anti-tumor therapeutic efficacy *in vivo* [9].

5. Conclusion

The PDA-Pt NPs complex is a core of platinum drug for cancer treatment, and in combination with other compounds, conforms to target treatment for various cancer types. After entering the cancer cell body, Pt NPs free a compound called cisplatin that can kill the cancerous cells very efficiently by binding to and breaking down the DNA

helix of the cancer cell nucleus. In order to increase its efficacy and minimize its toxicity to other organs, researchers create MOF material as a carrier to contain it. PDA was a later discovered material, and the idea was derived from mussels. It has been largely popular in nanotechnology and biomedical fields since it was introduced. As a similar compound to melanin, due to its high biocompatibility and antioxidant activity, it has been widely used to modify various biological materials, including Pt NPs. In the future, researchers can use PDA-Pt NPs as a base to construct more complex target treatments for cancerous disease and other illnesses.

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