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Inorganic nanocarriers for platinum drug delivery

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Nowadays platinum drugs take up almost 50% of all the clinically used anticancer drugs. Besides cisplatin, novel platinum agents including sterically hindered platinum (II) drugs, chemically reductive platinum (IV) drugs, photosensitive platinum (IV) drugs, and multinuclear platinum drugs have been developed recently, with a few entering clinic trials. Rapid development of nanobiotechnology makes targeted delivery of anticancer platinum agents to the tumor site possible, while simultaneously minimizing toxicity and maximizing the drug efficacy. Being versatile drug carriers to deliver platinum drugs, inorganic nanovehicles such as gold nanoparticles, iron oxide nanomaterials, carbon nanotubes, mesoporous nanosilica, metal-organic frameworks (MOFs), have been extensively studied over the past decades. In contrast to conventional polymeric and lipid nanoparticles, inorganic nanoparticles based drug carriers are peculiar as they have shown excellent theranostic effects, revealing themselves an indispensable part of future nanomedicine. Here, we will elaborate recent research advances on fabrication of inorganic nanoparticles for platinum drug delivery.

Introduction

Cancer is a major public health problem in the world. A total of 1,665,540 new cancer cases and 585,720 cancer deaths are estimated in the United States in 2014 [1]. However, over the last 50 years, there has been sluggish improvement in cancer therapeutics to help increase the lifespans of cancer patients. It is therefore imperative to constantly develop competent treatments for cancer therapy.

Since the discovery of the anticancer activity of cisplatin by Rosenberg [2], platinum drugs have been of great importance in cancer treatment and are now widely administered in cancer therapy to treat various solid tumors, including ovarian, head and neck, colorectal, and non-small cell lung cancers, etc. [3,4]. Platinum drugs are enrolled in standard chemotherapy regimens either as a single therapeutic agent or in combination with other cytotoxic agents such as doxorubicin [5], paclitaxel [6] and gemcitabine [7] or radiotherapy [8], covering almost 50% of cancer chemotherapy agents. Following the clinical success of the first-generation of platinum drug cisplatin, other major platinum drugs such as the second-generation carboplatin and the third-generation oxaliplatin were developed and approved around the world (Fig. 1) [9–11]. Other cisplatin derivatives such as nedaplatin, lobaplatin and hetaplatin were also clinically applied all over the world [12].

Platinum compounds with the general formula of cis-$[PtX_2(Am)_2]$ (Am is an inert amine with at least one N–H moiety as stable group and X is leaving group) show a similar mechanism of action. Cisplatin for one example, once entering the blood stream where a higher chloride concentration (100 mM) exists [13], the chloride ligands in platinum compounds stay close with the Pt atom [14]. Furthermore, on encountering cancerous cells, cisplatin is taken up through passive diffusion or by copper transporter proteins (such as CTR1) [15]. Cisplatin is then aquated to lose one or two chloride ligands due to a greatly lowered concentration of chloride (4–20 mM) inside the cancer cells, followed by the attack of aquated cisplatin species toward the nuclear DNA, finally leading to apoptosis [16]. This process is depicted in Fig. 2.

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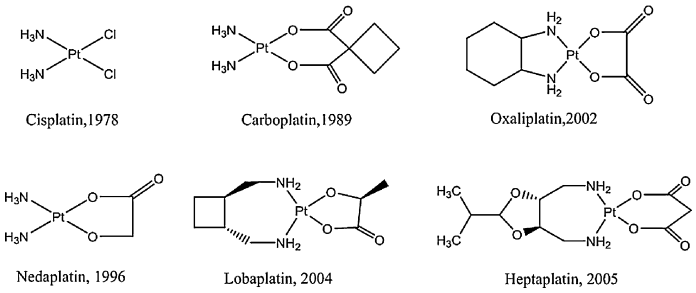

FIGURE 1

Classical platinum drugs in clinic use.

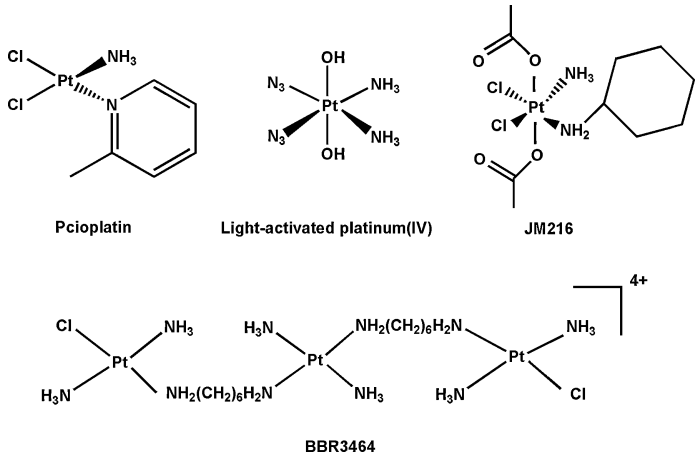

FIGURE 3

Representative unclassical Pt drugs developed till far: picoplatin, photosensitive platinum (IV), chemically reductive platinum (IV) drug JM216 and multinuclear platinum drug BBR3464.

Although platinum drugs have shown great potency on a variety of cancers, they also possess drawbacks such as drug resistance [17]. The drug resistance of platinum agents is mainly attributed to: (1) reduced drug uptake [18]; (2) enhanced drug detoxification by thiols [19]; (3) increased DNA repair [20]; and (4) altered cell signaling pathway [21]. To overcome the drug resistance, non-classic platinum drugs which violate the structure–activity relationship were first developed as representative ones are shown in Fig. 3. Picoplatin, a sterically hindered platinum drug, was designed to reduce the glutathione mediated detoxification. Introduction of picoline as one of the stable ligands would retard the binding rate of GSH (glutathione) with the platinum atom, offering an opportunity to increase the drug efficacy and thus overcome drug resistance [22]. The second strategy to nullify platinum drug resistance is to design chemically reductive platinum (IV) compounds [23] in replacement of active platinum (II) drugs. Considered prodrugs of their platinum (II) counterparts, platinum (IV) drugs possess elevated chemical inertness along with lower toxicity and fewer side effects. They can be reduced by intracellular chemical reductants such as GSH and ascorbic acid to release antineoplastic species that can further attack cellular DNA [24]. A representative in this category JM216 was the first platinum (IV) prodrug that was orally administered and entered clinic phase II for treatment on solid tumors [25]. As an alternative to chemical reduction, photo irradiation can also activate platinum (IV) prodrugs in a non-invasive manner. For the first time, the Sadler group developed a series of photosensitive platinum (IV) azide complexes that could be decomposed into platinum (II) species and nitrogen gas upon UV irradiation [26,27]. By tuning the amine ligands, they can shift the activation light from UV to green light.

To mitigate drug resistance of platinum compounds efficiently, Farrell *et al.* reported another strategy to synthesize platinum agents with two or more platinum atoms in one molecule, as-named multinuclear platinum drugs [28]. An elite member of multinuclear platinum drugs, BBR3464 compound targets DNA

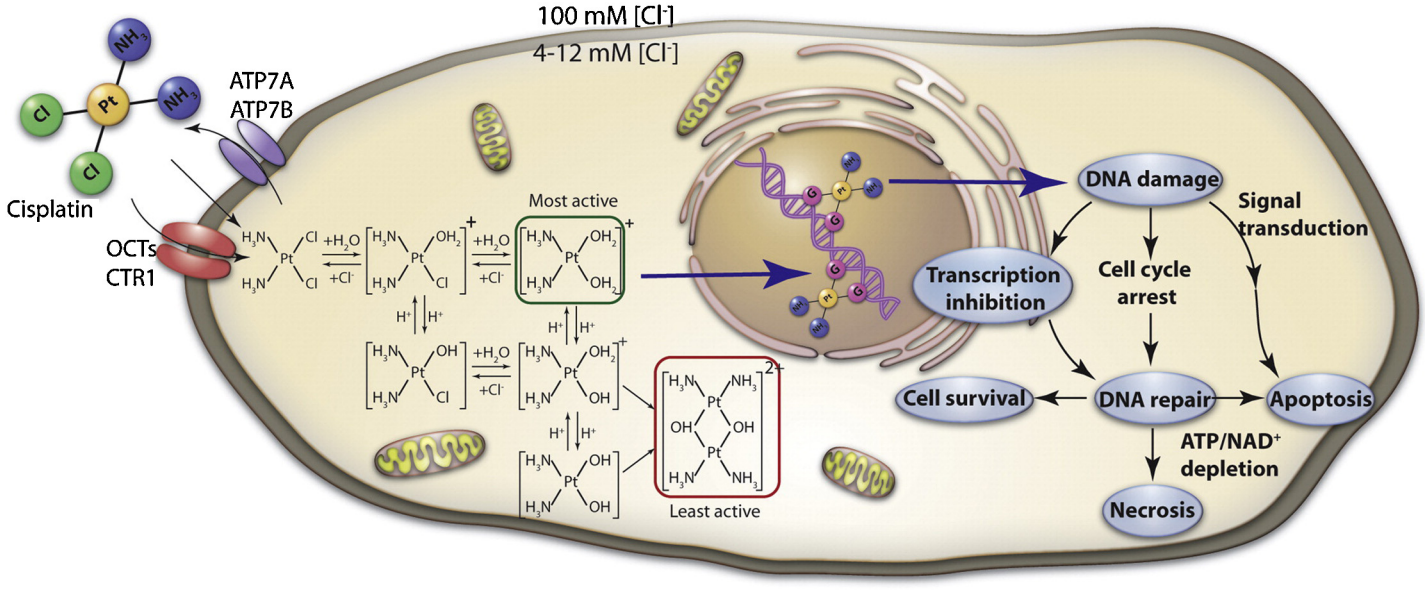

FIGURE 2

The mechanism of cisplatin. Cisplatin is internalized into the cancer cells by passive diffusion and via copper transporter 1 (Ctr1) mediated transportation. Due to the decrease of chloride concentration from outside the cells (100 mM) to within the cancer cells (4–12 mM), cisplatin is aquated to mono-aquated cisplatin and bis-aquated cisplatin, which then attacks nuclear DNA, blocks DNA replica and induces apoptosis.