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Copper Based Nanoparticle: A Way towards Future Cancer Therapy

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Abstract

Copper based nanoparticles have an immense potential in the future of anticancer therapy. Various copper inorganic nanoparticles and organic framework complexes have been extensively studied since the last decade for their effect on cancer cell growth inhibition and tumor regression. In this review we have summarised the anticancer activity of few such nanoparticles of copper and organo-copper complexes and their mode of action.

Keywords: Anticancer; Copper; Nanoparticles

Abbreviations: APTS: 3-Aminopropyltrimethoxysilane; CUAA: Copper Acetylacetonate; NPs: Nanoparticles; ROS: Reactive Oxygen Species; NM: Nanometres

Introduction

The vast limitations of traditional cancer drugs have pushed researches to advance in the area of cancer nanomedicine. The major drawbacks of the conventional drugs are immense side effects, non-specific tissue absorption, low bioavailability and high cost of production, to name a few. With the advancement in nanomedicine, scientists are aiming to come up with drugs which will have targeted action to cancer cells thus minimizing the side effect on healthy tissue and organs within the body. Various metal and organo metallic compounds are currently in trial to achieve this goal. The major advantage of these metal based nanoparticles is that they can lower the cost of production contrary to the complex structured conventional anticancer drugs like paclitaxel, doxorubicin etc. which are very costly.

Various metal nanoparticles (NPs) have been reported for their anticancer properties like gold [1], Silver [2], Cobalt [3], Cerium [4], but copper nanoparticles have become a favoured choice amongst researchers [5-10]. The reasons being that they are very cost effective compared to Au and Ag NPs and have a longer stability period. Being a transition element, innately they have a high cytotoxic effect on cancer cells even at low doses, mainly due to the oxidative stress it causes inside the cytoplasm of the cells. This review article tries to focus on few of such copper based nanoparticles which have been extensively studied for its anti-cancer activity and mode of action.

Inorganic copper nanoparticles having anticancer activity

There are various inorganic nanoparticles of copper which have been studied for their anticancer activity. Some of them are CuO, CuI, $Cu(PO_4)_2$, $CuCO_3$, CuS, Cu_2O [5-10]. As reported by Laha et al. [6] CuI and $Cu(PO_4)_2$ NPs measured around 35nm and 67nm respectively. CuI NPs were more effective at a lower dose compared to $Cu(PO_4)_2$ as the LD_{50} value for CuI and $Cu(PO_4)_2$ NPs was 2.5 and 10µg/ml respectively. Both these NPs induce ROS-mediated DNA damage causing apoptotic mediated cell death. Guo et al. [10] synthesized amorphous and crystalline NPs of CuS. Both the crystalline and amorphous forms were similar in size around 50-60nm and had effective cytotoxicity on cancer cells. The LD_{50} for amorphous CuS NPs was 18.5µg/ml whereas the nanocrystals had 29µg/ml on HL-60 cell lines. Both the NPs mediated apoptosis of the cancer cells but not in normal cells. Cu_2O NPs were synthesized by Wang et al. [9] and was found that at low concentration these NPs were selective for cancer cell apoptosis whereas not affecting the normal cells. We synthesized $CuCO_3$ NPs which measured 20 nm [7].

It induced ROS-mediated mitochondria and DNA damage leading to apoptosis in cancer cells. $CuCO_3$ NPs were targeted to cancer cells using folic acid. Folic acid is a precursor for DNA synthesis and this machinery is highly active in cancer cells due to its need for fast replication. Most cancer cells over-express this folate receptor which is utilized to internalize the folic acid. Upon treating mice bearing tumor, it was observed that the toxicity level was minimum and the survivability of the mice increased significantly compared to the control group. The tumor volume also reduced [7]. Spherical shaped CuO NPs have been synthesized through green synthesis using plants by Nagajyothia et al. [8,11] as well by chemical reduction process by our group. The size from green synthesis varied from 5-100nm depending on plant species and from chemical reduction, the size was found to be around 30nm. This CuO NPs were very effective on cervical as well as breast cancer cells (HeLa, MCF-7). The mode of action was found to be due to ROS mediated DNA damage which causes stress inside the cells leading to autophagy (a survival strategy of cell to fight against cellular stress) and finally causing apoptosis upon inhibiting autophagy. CuO NPs were further targeted to cancer cells by conjugating folic acid in order to address the selectivity of these NPs. The CuO NPs were conjugated with Folic acid using APTS and then it was observed through *in-vivo* study, that the group of tumor-bearing mice receiving the targeted delivery of this CuO NPs gave a promising result as found in our work of $CuCO_3$ [7-11].

Organic framework copper having anticancer activities

The anticancer activity of copper is not only limited to its inorganic form but also in its organic complexes. Sanghamitra et al. [12] have studied the anticancer activity of $(Cu_2(dppe)_3(CH_3CN)_2][ClO_4)_2$ on lung cancer cells and found its activity to be similar to that of Adriamycin which induced DNA damage and induced the p53 pathway inhibiting the cell growth by cell cycle arrest. Teyssot et al. [13] demonstrated the activity of (CuCl(SIMes)) and compared it with cisplatin. This complex induced cell cycle arrest in G1 phase which inhibited the cancer cells growth. Cu(II) thioxotriazole complex indicated G2/M phase arrest of tumor cells leading to loss of mitochondria function and paraptosis [14]. Kamah et al. [15] reported that $(Cu(PDTA\text{-}H_2)(H_2O)_2)$. H_2O had potential anti-tumor activity on ovarian tumor and solid sarcoma. Their *in-vivo* trails exhibited a complete reduction of tumor size at low doses. Various copper (I), (II) and (III) complexes have been studied likewise by various researchers for their anticancer activity. We have studied one such complex of copper (II) acetylacetonate [16]. This complex exhibited a dose-dependent cytotoxicity on HeLa and MCF-7 cells. More surprisingly when we compared its activity to other transition metal acetylacetonate complexes, it was observed that other metal complexes were having very less activity, thus indicating the role of copper. CuAA induced ROS mediated DNA and mitochondria damage leading to G0 cell cycle arrest causing apoptosis.

Transition of copper complexes to nano-forms for targeted delivery

With the advancement in lipid and polymer nanoparticles it has become very easy to deliver various compounds to diseased cells. These copper-organo complexes can be a field of real interest as they can be very easily synthesized and encapsulated into these biodegradable, non-toxic nano vehicles. We have developed one such polymer nanoparticle of chitosan which has been hydrophobically modified with stearic acid for loading of hydrophobic complexes of copper [16,17]. We targeted this CuAA loaded polymer nanoparticle to folate receptors and HER 2 receptors of cancer cells, which very successfully resulted in regression of tumor in mice model [17].

Conclusion

We summarized various copper inorganic nanoparticles studied by various research groups worldwide which have potential anticancer activity and can inhibit tumor cells of various tissues including cervical, breast, lung etc. Few of these nanoparticles have been successfully targeted to cancer cells using various cancer-specific surface markers to minimize any toxicity to normal tissues. Apart from them, copper complexes have also been studied extensively by many researchers and have been delivered to cancer cells with the help of polymer or liposome nanoparticles. In the current era, this area has a vast opening in the field of developing very cost effective cancer therapeutics which can have minimum toxicity in comparison to the much expensive conventional drugs.

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