

## Organometallic iron complexes as potential cancer therapeutics

Gabriela Mojžišová<sup>1</sup>✉, Ján Mojžiš<sup>2</sup> and Janka Vašková<sup>3</sup>

<sup>1</sup>Department of Experimental Medicine, Faculty of Medicine, P. J. Šafárik University, Košice, Slovak Republic; <sup>2</sup>Department of Pharmacology, Faculty of Medicine, P. J. Šafárik University, Košice, Slovak Republic; <sup>3</sup>Department of Medical and Clinical Biochemistry and LABMED, Faculty of Medicine, P. J. Šafárik University, Košice, Slovak Republic

Metal-containing drugs have long been used for medicinal purposes in more or less empirical way. The potential of these anticancer agents has only been fully realised and explored since the discovery of the biological activity of cisplatin. Cisplatin and carboplatin have been two of the most successful anti-cancer agents ever developed, and are currently used to treat ovarian, lung and testicular cancers. They share certain side effects, so their clinical use is severely limited by dose-limiting toxicity. Inherent or acquired resistance is a second problem often associated with platinum-based drugs, with further limits of their clinical use. These problems have prompted chemists to employ different strategies in development of the new metal-based anticancer agents with different mechanisms of action. There are various metal complexes still under development and investigation for the future cancer treatment use. In the search for novel bio-organometallic molecules, iron containing anti-tumoral agents are enjoying an increasing interest and appear very promising as the potential drug candidates. Iron, as an essential cofactor in a number of enzymatic and physiological processes, may be less toxic than non essential metals, such as platinum. Up to now, some of iron complexes have been tested as cytotoxic agents and found to be endowed with an antitumor activity in several *in vitro* tests (on cultured cancer cell lines) and few *in vivo* experiments (e. g. on Ehrlich's ascites carcinoma). Although the precise molecular mechanism is yet to be defined, a number of observations suggest that the reactive oxygen species can play important role in iron-induced cytotoxicity. This review covers some relevant examples of research on the novel iron complexes.

**Key words:** organometallic iron complexes, cytotoxic and antiproliferative effects, anticancer agents

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### INTRODUCTION

After cardiovascular disease, cancer is the second most frequent cause of death in developed countries. Cancer continues to be a worldwide killer, despite the enormous amount of research and rapid developments seen during the past decade. Global cancer rates have been increasing primarily due to an aging population and lifestyle changes in the developing world (Jemal *et al.*, 2011). The most significant risk factor for developing cancer is old age. Although it is possible for cancer to strike at any age, most people who are diagnosed with invasive cancer

are over the age of 65 (Anisimov *et al.*, 2009; Hajdu *et al.*, 2011). By 2020, the world population is expected to have increased to 7.5 billion; of this number, approximately 15 million new cancer cases will be diagnosed, and 12 million cancer patients will die (Brayand & Moller, 2006).

Many different substances have been tested in anticancer therapy. Only some of them are currently available to treat cancer and many more are being tested for their ability to destroy cancer cells (Desoize, 2004). Cytotoxic drugs used for the treatment of cancer today have the potential to be very harmful to the body unless they are very specific to cancer cells. Moreover, cancer cells have the propensity to become resistant to therapy, which is the major limitation of current therapeutic concepts (Gottesman, 2002). Therefore, novel therapeutic agents for cancer treatment are needed.

Although medicinal chemistry was almost exclusively based on organic compounds and natural products, metal complexes have gained a growing interest as pharmaceuticals for the use as diagnostic/chemotherapeutic agents (Rafique *et al.*, 2010). There is no doubt that the discovery of cisplatin, represents one of the most significant events for cancer chemotherapy in the 20th century. Cisplatin is highly effective in treating a variety of cancers, especially ovarian, lung, head, and neck cancers, as well as testicular and bladder tumors (Galluzzi *et al.*, 2012). Its effectiveness has been hampered by toxic side effects and tumor resistance that often leads to the occurrence of secondary malignancies (Chen *et al.*, 2009). Unfortunately, cisplatin induces cumulative and dose-dependent nephrotoxicity, which restricts the use of high doses to maximize the therapeutic efficacy (Marzano *et al.*, 2009). The cisplatin-induced nephrotoxicity is likely caused by a combination of multiple mechanisms involving DNA damage, caspase activation mitochondrial dysfunction and formation of reactive oxygen species (Pan *et al.*, 2009). In addition, cisplatin is not orally bioavailable, and both inherited and acquired resistance seriously limit its applications (Kelland, 2000).

These unresolved problems in platinum-based anticancer therapy have stimulated increased research efforts in the search for novel non platinum-containing metal species as cytostatic agents with different mechanisms of action, biodistribution and biological activity. A growing number of investigations demonstrate that the development of new metal agents with modes of action different from cisplatin is possible (Ott & Gust, 2007).

✉ e-mail: gabriela.mojzisova@upjs.sk

**Abbreviations:** ER+, positive estrogen receptor; ER $\alpha$ , estrogen receptor  $\alpha$ ; IC<sub>50</sub>, half maximal inhibitory concentration; OH· radicals, hydroxyl radicals; RNS, reactive nitrogen species; ROS, reactive oxygen species; UV radiation, ultraviolet radiation

The antitumor properties of a number of different metal ions and their complexes have been evaluated, but only a few non-platinum metal-based drugs are currently in clinical studies. Some of clinical studies may bring new candidates for modern chemotherapy in the next few years. The most promising ones contain ruthenium and gallium ions (Abu-Surrah & Kettunen, 2006). The search for new effective drugs will remain of the highest priority in the field of cancer research. A major challenge is to design new drugs that will be more selective for cancer cells, and thus have lesser side effects (Jungwirth *et al.*, 2011).

## IRON COMPLEXES AS POTENTIAL ANTI-CANCER COMPOUNDS

As it was mentioned above, current research in the medical field is aimed at the design of new compounds which are active against a wider range of cancers, and have lesser side-effects.

The organometallic sandwich compound ferrocene is an interesting building block for the design of biologically active molecules because of its unique structure, its robustness in aqueous solutions, its favorable redox properties and low toxicity (Dombrowski *et al.*, 1986; Meggers, 2007). It can be injected, inhaled, or taken orally without causing major health problems. The toxicity of ferrocene was also tested in beagle dogs that were fed up to  $300 \text{ mg} \times \text{kg}^{-1}$  per day for 6 months or even  $1 \text{ g} \times \text{kg}^{-1}$  for up to 3 months with no signs of acute toxicity or even deaths (Yeary, 1969). Unsubstituted ferrocene itself is not active as it is not soluble in water. However, appropriately substituted active ferrocenes could interconvert inside the tumour cells between the oxidation state +2 (ferrocene) and the oxidation state +3 (ferrocenium ions). Simple ferrocenium salts were the first iron compounds for which an antiproliferative effect on cancer cells was demonstrated (Köpf-Maier *et al.*, 1984). Although the precise mechanism of antiproliferative action is still uncertain, their potential to induce the formation of reactive oxygen species (ROS), e. g., OH<sup>•</sup> radicals, which may react with DNA or other biomolecules is considered to be important in their mode of action (Os-sela *et al.*, 2000; Gasser *et al.*, 2011; Acevedo-Morantes *et al.*, 2012). Numerous ferrocene derivatives are among the most potential compounds which may be used in cancer research (Al-Bari *et al.*, 2007).

Almost fourthy years ago, Fiorina and co-authors (1978) for the first time reported the anticancer activity of ferrocenyl compounds bearing amine or amide groups against lymphocytic leukemia. They found that some compounds exhibited low but significant antitumor activity.

Since then, several types of ferrocenyl compounds have been synthesized and tested for antiproliferative purposes.

Probably among all the ferrocene derivatives with anticancer properties, the ferrocifens are the most widely studied due to their potential to suppress breast cancer cells growth. Ferrocifens are the complexes of ferrocene with 4-hydroxytamoxifen, an active metabolite of tamoxifen. Tamoxifen is a selective estrogen receptor modulator prescribed for patients diagnosed with positive estrogen receptor (ER+) breast cancer. Jaouen and co-workers (2004) studied antiproliferative effect of hydroxyferrocifens on both, estrogen-dependent breast cancer cells (MCF-7) as well as hormone-independent breast cancer cells (MDA-MB-231). It was found that in MCF-7 cells, the effect of ferrocifens was slightly over the antiprolife-

rate effect of hydroxytamoxifen at concentration  $0.1 \mu\text{M}$  and significantly superior to that of hydroxytamoxifen at  $1 \mu\text{M}$ . It is believed that the activity of ferrocifens against estrogen-dependent cancer cell lines is related to the ability of hydroxytamoxifen competitively to bind to the estrogen receptor (ER $\alpha$ ) subtype, thus repressing estradiol-mediated DNA transcription in the tumor tissue. Impressive results have been obtained in MDA-MB-231 cells. In these cells hydroxytamoxifen has no effect, while ferrocifens significantly decreased MDA-MB-231 cells survival with  $\text{IC}_{50}=0.5 \mu\text{M}$ . This indicates a new and different mode of action for ferrocifens and it is suggested that the ferrocene group may modulate this effect. It may be intracellularly oxidized and the corresponding ferricinium cation may effect an intramolecular oxidation producing cytotoxic species such as quinone methides, which would be responsible for the antiproliferative activity (Hillard *et al.*, 2005). Moreover, Lu and coworkers (Lu *et al.*, 2014) documented that antiproliferative activity of ferrocifen can also be associated with an increased production of reactive oxygen/nitrogen species (ROS/RNS). On the other hand, ROS production was not observed on melanoma cells, while ferrocifen also showed an antiproliferative effect on these cells. As authors suggested, melanocytes due to constant oxidative aggression induced by UV radiation might have developed specific metabolic pathways dedicated to the efficient scavenging of ROS, a necessary for their survival (Michard *et al.*, 2008).

The success with ferrocene-tamoxifen complex prompted the next research in this field. Raloxifene is an another SERM that decreases breast cancer risk in postmenopausal women and may have the benefits of the widely used tamoxifen with fewer side effects. Ferreira and coworkers (Ferreira *et al.*, 2009) replaced a phenyl ring on raloxifene by a ferrocenyl moiety and prepared several 2-benzoyl-3-ferrocenylbenzo[*b*]thiophenes. All tested compounds showed considerable cytotoxic activity against different cancer cell lines. Among them [3-ferrocenyl-6-methoxybenzo[*b*]thiophen-2-yl][4-(piperazin-1-yl)methylphenyl]methanone was even more potent than the reference compound, cisplatin. Moreover, caspase-3 activation analyses revealed a caspase-3-dependent apoptotic cell-death mechanism.

Numerous other ferrocene derivatives have been tested for antiproliferative purposes. Among those, a ferrocene-acridine conjugate was found to be highly cytotoxic. The anticancer activity of acridines is mainly attributed to the planarity of these aromatic structures, which can intercalate within the double-stranded DNA structure, thus interfering with the cellular machinery (Belmont *et al.*, 2007). In 1992 Ong and co-workers synthesized new ferrocene compound by fusion ferrocene with acridine (Ong *et al.*, 1992). When compared its antiproliferative activity with the analogous ferrocenyl derivative lacking the acridine moiety they found that the new ferrocene-acridine was potent cytotoxic agent against four cell lines.

Some research groups tried to increase the anticancer properties of some nucleosides resp. nucleobases by attaching to ferrocene. Simenel and coworkers (Simenel *et al.*, 2009) synthesized several complexes of ferrocenylalkyl with adenine, thymine, cytosine and 5-iodo-cytosine. They found strong antitumor effect 1N-ferrocenylmethyl thymine which suppressed tumor frequency by 70% in mice bearing adenocarcinoma 755 compared to control. Moreover, synergism of antitumor activity with the cyclophosphamide was also demonstrated.

Recently, the synthesis and properties of two chiral ferrocene derivatives containing a nucleobase and a hydroxyalkyl group were reported. The compounds show promising anticancer activity against five different cancer

cell lines. As authors suggested, both functional groups are required for the optimal activity (Nguyen *et al.*, 2014).

Prostate cancer is the second most frequently diagnosed cancer (at 15% of all male cancers) and the sixth leading cause of cancer death in males worldwide (Jemal, 2011). Current treatments for these cancers include anti-hormone therapy in the early stages of disease, surgery, radiotherapy and chemotherapy but these frequently affect quality of life and have significant side effects. The promising strategy to create efficient drugs for hormone-dependent prostate cancers is an idea of attaching ferrocene to androgens and antiandrogens.

Top and coworkers (Top *et al.*, 2009) synthesized and studied biological activity of a series of organometallic complexes of the steroidal androgens testosterone and dihydrotestosterone substituted at the C-17 position of the steroid skeleton with ferrocenyl. Among them two ferrocenyl derivatives of ethynyl testosterone showed a strong antiproliferative effect on the hormone-independent prostate cancer cells PC-3 with  $IC_{50}$  in the micromolar range.

The modification of the biological effects of some biologically active molecules by ferrocene is an active field of study and many other complexes were synthesized and studied for their biological activity including ferrocenyl-phenols (Hillard *et al.*, 2007; Hamels *et al.*, 2009), ferrocenyl-ampicillin and ferrocenyl-6-aminopenicillanic acid (Skiba *et al.*, 2012) or ferrocenyl-flavonoids (Monserrat *et al.*, 2013). Also, our preliminary results with ferrocenyl-chalcones confirmed antiproliferative potential of these compounds. We found significant suppression of growth of several cancer cells (human acute T-lymphoblastic leukemia, cervical carcinoma, breast cancer and lung carcinoma) in the low-micromolar range. Moreover, we found that some steps of angiogenesis (endothelial cells migration and matrix metalloproteinase activity) were inhibited with the studied compounds (Mojzisoava *et al.*, 2014).

Another interesting approach for the development of anti-tumourally active iron species was taken by preparing iron carbonyl nucleosides, which were able to induce apoptotic effects.

Treatment of melanoma cells with the cytosine analogue ferropoptoside, which contains an iron carbonyl complex, resulted in strong induction of apoptosis. Surprisingly, caspases were not involved in the initial phase. On the other hand, production of ROS appeared as an early effect, and antioxidant vitamin E completely prevented induction of apoptosis (Franke *et al.*, 2010). Recently, it was documented apoptosis-inducing properties of iron-containing nucleoside analogues containing a butadiene  $Fe(CO)_3$  substructure in Burkitt-like lymphoma cells. The highest cytotoxicity was also observed in compounds with cytosine as a nucleobase. However, in contrast to above mentioned results, activation of caspase-3 was observed (Hirschhäuser *et al.*, 2013).

Apoptosis-inducing effects could also be noted with other iron species. For example, iron (II) complexes containing pentadentate pyridyl ligands displayed high cytotoxic activities and induced apoptosis (Wong *et al.*, 2005).

It has been shown that the nontoxic ferric-sorbitol-citrate complex (FSCC) inhibited the proliferation of malignant cells, but did not appreciably alter proliferation of normal cells. An increased number of cells in G1 and early S phase suggested that iron excess blocked the cell cycle before the onset of DNA synthesis. Since FSCC could block DNA synthesis and probably can induce oxidative stress in cells, the question then arises as to which type of mechanism is responsible for this anticancer action. As authors suggested, free radicals damage

cellular lipid membranes, proteins, DNA and may induce cell death by apoptosis or other forms of cell death. (Flajsig & Poljak-Blazi, 1990; Poljak-Blazi *et al.*, 2000).

The aim of the Zhivkova *et al.*, (2010) study was to evaluate the effect of two newly synthesized Fe mixed ligand complexes on viability and proliferation of cultured tumor cells. Among the cell lines used as experimental models in their investigations, the chicken hepatoma cells were found to be the most sensitive to the cytotoxic and antiproliferative effects of the tested compounds.

Woldemariam and Mandal (Woldemariam & Mandal, 2008) synthesized a water soluble Fe(III)-salen complex and investigated its biochemical effects on DNA *in vitro* and on cultured human cells. They showed that it produces free radicals and induces DNA damage. Interestingly, upon treatment with Fe(III)-salen at concentration as low as 10  $\mu$ M, human cells showed morphological changes, nuclear fragmentation, and nuclear condensation that are typical features of apoptotic cell death. Furthermore, treatment with Fe(III)-salen resulted in translocation of cytochrome *c* from mitochondria to cytosol affecting mitochondrial membrane permeability. Their results demonstrated that Fe(III)-salen not only damages DNA *in vitro*, but also induces apoptosis in human cells via mitochondrial pathway. Iron (III)-salophene with selective cytotoxic and antiproliferative properties have also been used in platinum resistant ovarian cancer cells (Rafique *et al.*, 2010).

At present, research is going on to design new compounds which are active against a wide range of cancers and have lesser side effects. Among the available strategies to design affordable and efficient drugs, the use of organometallics (Allardyce *et al.*, 2005), and especially of ferrocene (Fouda *et al.*, 2007), clearly offers new possibilities since these compounds may exhibit enhanced chemical and pharmacological properties compared to the purely organic parent drugs (Quirante *et al.*, 2011).

## CONCLUSION

Much work has been done on metals and metal compounds. A surprising number of drugs contain metals. Every year thousands of new metal compounds are prepared and identified by analysis and characterized by spectroscopia and other physical methods. Only some of them play a serious role in chemotherapy. Organometallic compounds of iron constitute a very large group of substances, which in recent years has attracted considerable attention. Although iron has a long history of medical application, coordination compounds of iron have been investigated as potential antiproliferative agents only in the last few decades, particularly after the discovery of cisplatin, the most widely used anticancer metallodrug. Iron, as an essential cofactor in a number of enzymes and physiological processes, may be less toxic than non essential metals, such as platinum. Up to now, a great variety of iron complexes have been tested as cytotoxic agents and found to be endowed with an antitumor activity in several *in vitro* tests and few *in vivo* experiments. Some of them e. g. ferrocene showed interesting and promising anti-tumor effects especially in *in vitro* experiments. On the other hand, knowledge of the exact mechanism of their potential antiproliferative and antiangiogenic mechanisms are still limited and therefore, requires more intensive pharmacological research.

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