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 ASSIGNMENT

1. Write a comprehensive note on the role of cisplatin as anticancer agent

Cisplatin is a metallic (platinum) coordination compound with a square planar geometry. It is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimanide and N,N-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the trans-isomer (Akron, 2009).

Cisplatin was first synthesized by M. Peyrone in 1844 and its chemical structure was first elucidated by Alfred Werner in 1893. The initial observations of Rosenberg at Michigan State University pointed out that certain electrolysis products of platinum mesh electrodes were capable of inhibiting cell division in Escherichia coli. This observation gave insight as to how cisplatin can be used in chemotherapy. Cis-dichlorodiammineplatinum (II) (cisplatin, r) was identified as the agent responsible for the chemotherapeutic activity cisplatin confers and this in turn made researchers shift much interest to the use of coordination complexes of platinum, palladium, and other noble metals in the treatment of cancer.

Cisplatin is clinically proven to combat different types of cancers including sarcomas, cancers of soft tissue, bones, muscles, and blood vessels (Desoize and Madoulet, 2002) .Drug resistance and some side effects have developed and this has led to combination therapy of cisplatin with other cancer drugs have been applied as novel therapeutic strategies for many human cancers.

At present, platinum based treatments are key drugs for SCLCs (Small Cell Lung Cancers) ([Abrams, Lee et al., 2003](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4146684/#R1)) (Abrams, Lee *et al*., 2003). Cisplatin and carboplatin are two of the most common types of platinum based treatments used in SCLC chemotherapy (Go and Adjei, 1999). In clinical trials, cisplatin is often selected due to its strong antitumor activity, but its adverse effects include renal toxicity (Nagata *et al*., 2005). Therefore, to avoid renal toxicity, urine volumes should be monitored and large-dose infusion is mandatory in cisplatin based chemotherapy. Cisplatin is an important chemotherapeutic agent used widely or the treatment of a variety of malignancies, including breast, testicular, ovarian, cervical, prostate, head and neck, bladder, lung and refractory non-Hodgkin's lymphomas (Braiteh *et al*, 2009). The cytotoxic effect is likely a result of inhibition of replication by cisplatin-DNA adducts and induction of apoptosis (Siddik, 2003).

Cisplatin combination chemotherapy is the basis of treatment of many cancers. Platinum responsiveness is high primarily but many cancer patients will ultimately relapse with cisplatin-resistant disease. Hence, drug resistance has been observed in many patients who have relapsed from cisplatin treatment. The proposed mechanisms of cisplatin resistance include changes in cellular uptake and efflux of cisplatin, increased biotransformation and detoxification in the liver, and increase in DNA repair and anti-apoptotic mechanisms (Gottesman, 2002). To overcome resistance, cisplatin is commonly used in combination with some other drugs in treating ovarian cancer, biliary tract cancer, lung cancer (diffuse malignant pleural mesothelioma), gastric cancer, carcinoma of salivary gland origin, breast, colon, lung, prostate, melanoma and pancreatic cancer cell lines, squamous cell carcinoma of male genitial tract, urothelial bladder cancer, and cervical cancer

Cisplatin becomes activated once it enters the cell. In the cytoplasm the chloride atoms on cisplatin are displaced by water molecules. This hydrolyzed product is a potent electrophile that can react with any nucleophile, including the sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids. Cisplatin binds to the N7 reactive center on purine residues and as such can cause deoxyribonucleic acid (DNA) damage in cancer cells, blocking cell division and resulting in apoptotic cell death.

Apoptosis is a controlled type of cell death which is energy-dependent leading to cell shrinkage, chromatin condensation, membrane budding, phosphatidylserine externalization, and activation of a family of cysteine proteases called caspases (Lasker *et al.,* 2000). Cisplatin primarily induces cell death by apoptosis and a defect in apoptotic signaling could also confer cisplatin resistance. There are two major pathways of apoptotic cell death. The extrinsic pathway is initiated when ligands bind to the tumor necrosis factor-α (TNFα) receptor super family followed by oligomerization and recruitment of procaspase-8 via adaptor molecules to form the death-inducing signaling complex (DISC). The intrinsic pathway is initiated by cellular stress, such as DNA damage, resulting in release of cytochrome-c from the mitochondria causing activation of procaspase-9 through the interaction with apoptosis promoting activating factor-1 (APAF-1) and formation of an active apoptosome complex. Bcl-2 family proteins regulate DNA damage-induced apoptosis by regulating the release of mitochondrial cytochrome c in response to DNA damage. Cisplatin-induced genotoxic stress activates multiple signal transduction pathways, which can contribute to apoptosis or chemo resistance.

2. Write briefly on the role of vanadium as antidiabetic agent

Vanadium constitutes 0.015% of the earth's crust and is almost as abundant as zinc. It is omnipresent in the biosphere which is another precondition for general availability for living organisms. Vanadium is present in the human body tissues in smallest concentrations around 60 nM. Its daily intake comes from eating food, drinking water or industrially prepared nutrition supplements (Shechter, 2003). Its presence in the human body seems not to be essential - at least until now - and vanadium bearing coenzymes or enzymes has not been identified. Its presence seems more a matter of tolerance. Vanadate (H2VO4ˉ in oxidation state +5) geometrically resembles the ubiquitous biological messenger phosphate (H2PO4ˉ or HPO42ˉ in formal state +5). The charges and structural match may explain its physiological role in analogy to phosphate ions in biochemical reactions.

Under physiological conditions, vanadium shows two stable oxidation states: IV and V. In strongly reducing conditions, the oxidation state III can also exist. In both more common states, vanadium complexes lower pathologic blood sugar levels. Because of their insulin-like activities, they are sometimes denominated as insulinomimetics, insulin-mimetics or insulin enhancers (Cusi, 2001).

Anti-diabetic vanadium salts act by separate pathways: vanadate (V) yield several beneficial effects concerning glucose and fat metabolism within the cells (cytosolic activity), while vanadyl salts (in form of vanadium IV) normalize glucose concentration in blood plasma by ameliorating the glucose uptake across cytoplasma membranes and inhibit lipolysis (Kiss, 2008).

Common bioligands of organically chelated vanadium compounds coordinate vanadium as their central atom through their O-, N- and S-functions like citrate, oxalate, nucleotides or ascorbic acid, as well as certain peptides (Thompson, 2006).

The anti-diabetic effects of vanadium are probably linked to the ability of its complexes to exchange ligands or chelators with the environment (Rehder, 2013). Structural requirements are reflected by either one or more unoccupied coordination sites, especially for weakly coordinating monodentate chelators (Nilsson, 2009). Moreover, the change of oxidation state of bicationic vanadyl (IV) to vanadate (V) was reported in NADPH-dependent enzymatic redox reactions and later reviewed (Shechter, 1995). Under oxidative stress conditions (reactive oxygen species) VO2+ is oxidized to H2VO4ˉ. Moreover, the structural, electrostatic and chemical features of oxidovanadates (IV: O=V(OH)3ˉ V: O=V(OH)2(O)ˉ) resemble those of monoanionic phosphate (O=P(OH)2(O)ˉ). Of note, vanadate is reactive because it can undergo chemical reactions in solution, e.g. readily redox-convertible to vanadyl complexation by biogenic and reversible ligands. Yet, in biochemical pathways a sort of phosphate - vanadate antagonism could take place with vanadate substituting agonistic phosphate in all sorts of phosphate-regulated enzymatic reactions (phosphatases, kinases or phosphorylases) (Rehder, 2015). Concerning the molecular mechanism(s) of action, reports diverge and give rise to two controversial tenets.

Other enzymes (mostly phosphatases and kinases) in the glucose uptake pathway have been considered as targets (Goldwaser, 2000). In the first biochemical step, the insulin hormone binds to the extracellular domain of the insulin receptor (IR) and activates the IR which is a membrane-spanning protein tyrosine kinase complex (PTK). The blood glucose uptake (by insulin responsive glucose transporter GLUT-4) into the tissue cells is triggered which describes the physiological (or normal) signaling protein network. Shechter et al. summarized the biochemical underpinnings of the insulin-mimetic effects of vanadium salts coining the two fundamental aspects: (1) enhancing the glucose utilization; and (2) its storing after entering the cells. Certain metabolic enzymes in key positions for incoming glucose utilization and storage are located in liver, muscle tissue or adipocytes. Some are blocked by vanadate (V). A cytosolic PTK can be activated by vanadate (V) in addition to another mechanism with similar metabolic effect: a cytosolic PTP can be inhibited by this metalooxide. Generally, vanadate is more active in the cytosolic compartment, enhancing glucose and fat metabolism, while vanadyl (IV) acts on the membranes of the cell plasma facilitating the cell permeation of glucose and possibly inhibiting lipolysis. In literature, the glucose metabolism was found to be modulated at a site which is located further upstream to the phosphatidylinositol-3-kinase. Lipolysis was inhibited by a vanadate-dependent mechanism further downstream to the aforementioned kinase but not by insulin. Another vanadate-dependent inhibition was reported for the liver enzyme glucose-6-phosphatase and the hexose-6-phosphatase in muscles and adipose tissues of hyperglycemic diabetic rats, all of which led to the restoration of glucose-6-phosphate levels (Shechter, 2003).

Of note, tenet (2) makes also sense since vanadate as a phosphate-replacing antagonist is not chemically substituted and cannot exercise (enzyme-independent) exclusive binding (specificity) to target PTP1B. Thanks to its similarity to phosphate (geometry, charge and volume), vanadate is recognized by phosphatases and kinases (Kuznetsov, 2012). However, for being not exactly identical (hydrogen-bonding geometries, electronic mesomerism, redox, volume) it may possess different affinities as a binder in the enzyme network. It may stay longer at the active site of one or another enzyme, and thereby modulates the access for the endogenous (weaker) binder phosphate. With differential binding preferences for both enzyme families vanadate can be considered as a typical surrogate to phosphate. During eons of time, agonistic phosphate anions have been moved around in an evolutionary adapted network of kinases and phosphatases. Its binding strength has not been challenged in the absence of vanadium or in the presence of a negligible natural pool of intracellular vanadium. However, when vanadium supply increases, the cellular systems respond with a plethora of signaling changes.

3. Account on the role of selenium as an anticancer agent

Selenium (Se) is known to be an essential micronutrient implicated in many biological processes. Se is necessary for well-balanced functioning of many organs such as thyroid, brain, muscle, prostate, testis. Both organic and inorganic chemical forms are specific to naturally occurring Se. It is known that Se intake range between deficient and toxic levels is very narrow. It has been demonstrated by many researchers that low Se intake is associated with cancer risk. However, data on the anticancer properties of Se is still contradictory. Different Se species such as inorganic, organic compounds and Se-nanoparticles possess anticancer activity, but it depends on many factors such as chemical form, dose, cancer cell type, bioavailability, stage of disease. Se asserts chemopreventive activity when used at concentrations higher than optimal. Se also is applied for cancer treatment combining with chemotherapy and radiation. The utmost anticarcinogenic Se effect has been obtained when administered before or at early stage of disease development. Se supplementation along with conventional anticancer therapies was shown to enhance the efficiency of chemotherapeutic drugs, decrease side effects and improve general condition of the patients. However, more clinical trials are needed to estimate safety and efficiency of Se compounds in modulation both effectiveness and toxicity of common anticancer therapies. The data obtained from already performed clinical trials are not sufficient and some of them are ambivalent.

Many in vivo and in vitro studies at supranutritional level demonstrated an anticarcinogenic effect of Se. It has been demonstrated that the incidence of liver cancer was reduced by 35% in a society of 21,000 persons in China taking selenite salt supplementation. It was revealed by several studies that a 200 μg of Se per day intake, in the form of Se yeasts, reduced the risk of lung, colon, rectal, and prostate cancers. Se supplementations at the same dose reduced the stomach cancer risk in subjects with low Se levels (Fairweather-Tait, 2010). It was detected that low level of SelP is associated with higher risk of prostate, kidney, esophagus, colon, lung cancers. Moreover, it has been demonstrated that Se rich plants of the genuses *Brassica* and *Allium* reduce the risk of colon cancer (Lavu, 2016).

Se has so different anticancer effects and it is difficult to establish one predominant. Oxidative stress is known to be one of the major factors in the initiate on of carcinogenesis. It has been reported that Se exhibits its anticancer effects by protection against oxidative injury. Se anticancerogenic activity is related with the regulation of the expression of redox active proteins and the modulation of intracellular redox status. Se is involved in the antioxidant defense system and consequently plays a relevant role in protection against oxidative stress. Many studies demonstrated that Se as an integral part of GPx increases antioxidant capacity of intracellular redox system (GSH/GSSG) and reduces cellular damage by preventing accumulation of free radical species. GSH as an antioxidant effectively removes free radicals and other reactive oxygen species through the GPx activity, which oxidizes GSH to GSSG, and the action of NADPH-dependent glutathione reductase, which generates GSH (Farhat, 2018). Some types of GPxs are Se-dependent, while others are not. Hence, Se is an important element of antioxidant system that protects against metal-induced ROS. El-Demerdash demonstrated that administration of Se along with other antioxidants such as vitamin E, caused reduction of oxidative stress in the brain and other organs. However, there are data about toxic dose-dependent effects of Se. The excess of Se is able to negatively affect redox status of the cell directly by oxidizing thiols, and indirectly—by generating ROS, leading to decreased redox status in body cells and thereby oxidative cellular damage. Moreover, synthetic compound methyl-seleninic acid was reviewed to inhibit thiol biosynthesis due to targeting oncogene c-Myc in melanoma cells. It is known that interaction of Se with metals such as cadmium, cobalt, gold, platinum, mercury can shift redox status in cells. It was found recently that interaction of Se with zinc is important; metallothionein system can by negatively affected by Se due to impairment of zinc homeostasis and losing antioxidant role of this system. Such dysregulation can lead to oxidative DNA damage and cancer development (Yildiz, 2019).

Different other mechanisms, identified at both molecular and genetic levels, are involved in Se anticancerogenic activity. These mechanisms include the ability to counteract heavy metals toxicity, maintenance of DNA stability, stimulation of DNA repair, regulation of inflammatory and immune responses, induction of cell cycle arrest and apoptosis, inhibition of local invasion and migration, blocking of angiogenesis, modulation of cell proliferation, and enhancing phase II-carcinogen-detoxifying enzymes. Different Se compounds were reviewed to induce apoptosis due to different cellular effects and signaling pathways. Only at higher than optimal doses Se compounds display cell growth inhibiting and cytotoxic activities. It should be noted that these activities depend on Se species, dose and experimental model applied. Due to high reactivity and pro-oxidative nature both metabolites selenide and monomethylselenol are effective in cancer treatment. However, there are few human trials on this issue.

Redox active Se compounds can be used for cancer treatment due to specific features of cancer cells: elevated basal ROS level, upregulated antioxidant system of protection and low tolerance to increased ROS level. Se compounds assert pro-oxidative effect on neoplastic cells by some main pathways: ROS generation, oxidation of thiols in proteins and DNA binding. As mentioned above, it is known that Se compounds can shift redox balance by oxidation of intracellular thiols, which are implicated in metabolism, transcription and signaling

Due to both reduced toxicity and improved targeting Se-nanoparticles are more effective in cancer treatment in comparison with other Se compounds. Diversity of nanoparticles is caused by different methods of their synthesis, i.e., chemosynthesis, biosynthesis and physical synthesis. Besides, their decoration design enables convey them to appropriate target. Poor uptake of nanoparticles by cells can be increased by changing surface charge or/and binding particular ligands on the outside surface of particles during synthesis. Supposedly, uptake of nanoparticles by malignant cells occurs via endocytosis, inside the cells nanoparticles act as prooxidants, they increased ROS formation leading to endoplasmic reticulum stress, mitochondrial membrane cleavage, apoptosis, DNA fragmentation and cell cycle arrest. Se-nanoparticles have been applied in treatment of various disturbances associated with oxidative stress and inflammation, such as cancer, diabetes, arthritis, nephropathy, liver fibrosis, drug induced toxicity

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