From Amino Acids to Proteins as Targets for Metal-based Drugs

Ondrej Zitka[1,2], Marketa Ryvolova[1,2], Jaromir Hubalek[3], Tomas Eckschlager[4], Vojtech Adam[1,2] and Rene Kizek[1,2*]

[1]*Department of Chemistry and Biochemistry, Faculty of Agronomy, Mendel University in Brno, Zemedelska 1, CZ-613 00 Brno, Czech Republic-European Union;* [2]*Central European Institute of Technology, Brno University of Technology, Technicka 3058/10, CZ-616 00 Brno, Czech Republic-European Union;* [3]*Department of Microelectronics, Faculty of Electrical Engineering and Communication, Brno University of Technology, Technicka 10, CZ-616 00 Brno, Czech Republic-European Union;* [4]*Department of Paediatric Haematology and Oncology, 2nd Faculty of Medicine and University Hospital Motol, Charles University, V Uvalu 84, CZ-150 06 Prague 5, Czech Republic-European Union*

Abstract: Metallomics and metalloproteomics are emerging fields addressing the role, uptake, transport and storage of trace metals ions both toxic and essential for an organism. Research areas related to the understanding of the mechanisms of life processes associated to metals are covered. Similarly to the genome and proteome terms, metallome was introduced to refer to metalloproteins, metalloenzymes and other metal-containing biomolecules in a biological system. This review aims to give an overview of metal ions behaviour in organisms. The interactions of metals with biomolecules such as amino acids, peptides and protein are the main focus. Special attention is paid to the application of nanotechnology-based techniques using these interactions for medical purposes such as diagnostics, imaging and therapy.

Keywords: Metallomics, metals, amino acid, peptide, protein, interactions, nanotechnology.

1. INTRODUCTION

Across the broad scientific community, there can be recognized group of scientific branches containing the suffix "-omics". These branches are quite extensive, but they have a common feature to target on one type of substances. The question is why metallomics is among the other "-omics" so little recognized as a comprehensive area of the study? The answer is not simple. One explanation may be using the physico-chemical methods for the invetisgation of inorganic substances and materials. Most of the instrumentation as atomic absorption spectrometry (AAS), mass spectrometry (MS), emission spectrometry with inductively coupled plasma (ICP-OES), X-ray crystallography (X-ray), nuclear magnetic resonance (NMR) and electrochemical techniques, has not served for biochemical and biological purposes for decades. Most of these methods over time, however, have found more than a major application in biochemistry, genetics and proteomics. Together with the evolving the main applications of these analytical methods, the understanding of the role of metals in organisms has been also developed. Thanks to methods such as AAS, MS, ICP-OES and electrochemical techniques we can accurately identify and quantify the different metals in animal tissues and body fluids. Using structural methods such as X-ray or NMR we are able to explore more structural roles of metals in catalytic centres of enzymes. It is more than obvious that the re-orientation of these techniques from the physico-chemical direction toward the biological and biochemical purposes gave the basis to create new branch called metallomics as a multidisciplinary science that has long been established, but unfortunately without fast progression and much-needed euphoria. Thanks to this, there have been created several smaller branches, however, with common denominator including the medical inorganic chemistry, which deals with three main objectives as (i) the uptake of metal ions in biological systems, (ii) handling and redistribution of metal ions in an organism and (iii) the transfer of ions [1]. These objectives are basically a general nature metallomics. We need one or more robust sequence analysis approaches, using that it is possible to monitor metal-organism interactions at the molecular level, and then create the database. This is one of the milestones, which needs to be reaching to obtain of more popularity for metallomics among chemists, biochemists, molecular biologists and physicists.

2. METALLOMICS

Metallomics is a new interdisciplinary science that arises from the growing needs of the knowledge of metals in the biochemistry of organisms. At the end of 2003, the term "Metallomics" was defined by J. Szpunar [2], who refers to the author H. Haraguchi, indicating also metallomics as a new branch of science to integrate research directions that are associated with a biologically active metals [3]. A half year later, this concept was applied in practice for computational and experimental studies in the field of structural genomics [4]. Since then, more than 80 articles containing the metallomics in their title, abstract and/or key words have been published. However, thematically related works as those that contain amino acid and metal*, or peptide* and metal*, or protein* and metal*, or nucleic acid* and metal* in their title, abstract and/or keywords, is published annually in the hundreds of thousands, and their number has been increasing. The term “metallome” has been introduced by R.J.P. Williams by analogy with proteome as distribution of free metal ions in every one of cellular compartments [5]. Subsequently, the term metallomics has been coined as the study of metallome. Metallomics is then defined as a scientific branch, similar to genomics and proteomics, which examine the presence of metals (qualitatively/quantitatively), function, interaction and transformation in biological systems. From a physiological point of view, biologically active metals can be divided into two groups: i) essential metals, which are crucial for numerous biochemical processes; ii) toxic metals, which are harmful to the body.

Cobalt, copper, iron, manganese, molybdenum, nickel, selenium, vanadium, calcium, zinc and tungsten are generally classified among essential metals. Essential metals are particularly important due to their occurrence in proteins. The functionality of up to one-third of all described proteins is closely associated with the binding of a metal [6-8]. Zinc belongs to the most abundant ones [9]. Zinc(II) ions are important part of more than three hundred from more than two thousands enzymes, stabilizes DNA structure and influences gene expression [10]. Iron is important for the transfer of

*Address correspondence to this author at the Department of Chemistry and Biochemistry, Mendel University in Brno, Czech Republic-European Union; Tel: +420-5-4513-3350; Fax: +420-5-4521-2044;
E-mail: kizek@sci.muni.cz

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oxygen in the haemoglobin and myoglobin proteins similar to copper in crustaceans and arthropods. Copper also involves in carbohydrate metabolism in mammals. Other metals such as selenium, tungsten and molybdenum are also important for human health. Selenium is part of the amino acid selenocysteine, which has its place in the antioxidant enzymes, playing a key role in protection of an organism from antioxidants. It is assumed that there are at least 25 proteins containing selenocysteine in humans including glutathione peroxidase 6, selenophosphate synthetase and thioredoxin reductase [11]. Majority of epidemiological studies have demonstrated selenium mediated decreased incidence of malignant tumours. Recently published studies showed that selenium increase effect of chemo and radiotherapy, because it acts on cancer cells more likely as prooxidant than antioxidant [12-15].

Toxic metals can be defined as all d-elements of the periodic system beyond third groups and transuranium elements, and all p-elements with the properties of metals excluded the above-mentioned essential metals. Toxicity is a property that expresses the degree of harm (toxicity) of the substance on an organism, respectively, on its part. The degree of toxicity for the organism depends on the dose of the substance, the size of the organism, the mode of entry into the organism, duration of exposure, metabolism, etc. Toxic heavy metals for humans are often referred to arsenic, cadmium, lead and mercury. Recently, there are increasingly discussed the impact of heavy platinum metals (platinum, palladium and rhodium), primarily because of their intensive use in the automotive industry as a part of catalysts [16].

Effects of unbalanced homeostasis or intoxication by different metal ions can result in numerous other pathological conditions such as Parkinson's disease, which was found elevated levels of iron in the cells that produce dopamine, which may indicate the interaction between iron and dopamine [17]. In Alzheimer's disease it was again referred to the connection with the homeostasis of zinc, copper and iron [18]. Aluminium has been implicated as a factor in this disease but whether it is a sole factor and whether in all cases is not known until now [19]. A similar relation to different metals was found for other diseases or pathological conditions such as atherosclerosis, Menkes' and Wilson's disease, cardiovascular disease, osteoporosis, hemochromatosis, tooth decay, epileptic seizure, and infectious diseases [20].

3. AN EFFECT OF METALS ON AN ORGANISM

Lack of some metals as well as their presence at higher concentrations can cause serious disruption of homeostasis in organism. The metals are known for more types of toxicities. Brief summary of symptoms of acute and chronic intoxications by different metals are shown in Table **1**. Besides "standard" metal ions and their effects, platinum complexes play an important role in the chemotherapy of various malignancies [21-25]. The biological activity of the first platinum based cytostatic drug – cisplatin (*cis*-diammine-dichloroplatinum(II)), which is still one of the most frequently used cytotoxic agent, was discovered in 1965 by Rosenberg during his studies on the effects of an electric current on bacterial growth [26]. Since then hundreds of platinum(II) and platinum(IV) complexes have been synthesized and evaluated as anticancer agents over past 40 years. To be specific, the "second generation" Pt drug carboplatin [*cis*-diammine(1,1-cyclobutane-dicarboxylato) platinum(II)] was develop in the 1980s as a less toxic alternative to cisplatin, providing less severe nephrotoxicity, vomiting, neurotoxicity and ototoxicity [27-29]. Oxaliplatin [oxalato-1,2-diamino-cyclohexane platinum(II)] was developed in the 1990s as a novel ("third generation") Pt drug to overcome cisplatin and carboplatin resistance [21, 30, 31]. Besides these commonly used anticancer drugs, many research groups around the world still develop new ones such as LA-12 [(OC-6-43)-bis-(acetato)(1-adamantylamine) amminedichloro-platinum(IV)] [32-34] or analogues of clinically ineffective transplatin [35, 36]. In addition, behaviour of these platinum compounds in an organism with respect to kinetics of different complex formation has not been well described. Based on *in vitro* experiments influencing of platinum complexes stability by pH, concentration of ions and biologically active compounds in blood has been described [37, 38]. Particularly, serum concentration of chloride (about 100 mM) is meaningfully higher than its intracellular concentration (about 4 mM). Due to this difference structural changing of a platinum based cytostatics passing through cytoplasmic membrane appear as was discovered by mathematical modelling. It clearly follows from published papers [37, 39] that the predominant complex among others is $[Pt(NH_3)Cl_2]$. Total content of this complex is about 80 % in comparison with others where their content does not exceed 1 – 3 %. On the other hand, distribution of the complex in cell cytoplasm differs markedly. Here predominates $[Pt(NH_3)OH_2]$ complex, whereas content of other forms of cisplatin is higher in comparison with their blood concentration. It is supposable that these complexes can coordinate to DNA [40-42]. Chaney et.al. [42-44] and others [40, 45] have found that cisplatin, carboplatin and oxaliplatin form the same types of adducts at the same sites on the DNA. Particularly, a platinum based cytostatic drug can coordinate to N7 of two neighbouring guanine and/or adenine bases, as this nitrogen does not form H bonds with other bases, in the same or in opposite DNA strands (approximately 60 – 65 % intrastrand GG, 25 – 30 % intrastrand AG, 5 – 10 % intrastrand GNG, and 1 – 3 % interstrand GG diadducts) [40, 42].

Given the emerging resistance of some cancer cells, there are also investigating effects of other metals as potential anticancer drugs. It was found that similar effects as platinum has a kinetically inert cobalt(III) complex, which is suitable for treating tumours in the absence of oxygen [46], because a resistance of tumour cells to anticancer drugs is widely observed in hypoxically growing tumours. Under hypoxic conditions cobalt(III) can be reduced to cobalt(II), which is associated with dissociation of ligands with cytotoxic effects [47]. Arsenic has similar effects as copper, which were discovered due to long-term consumption of arsenic contaminated water. The long-term intoxication by arsenic increases the risk of skin, kidney, bladder and other organs cancers [48, 49]. On the other hand arsenic trioxide as a commercial product called "Trisenox" is registered by Food and Drug Administration (USA) for the treatment of acute promyelocytic leukaemia refractory to conventional therapy because As_2O_3 induces leukemic blast to undergo apoptosis [50].

Ruthenium is another metal that could have anticancer potential and would also reduce the increasing resistance of tumour cells [51], which is studied quite intensively in the emerging field of inhibition of cyclin-dependent kinases, together with osmium [52]. Chromium(VI) is considered as a carcinogen, particularly in lung cancer, but compared to the chromium(III) has a positive effect on lipid metabolism, reducing the risk of cardiovascular disease and reduce cholesterol serum levels [53]. Lanthanum carbonate could also serve as the active ingredient in the suppression of hyperphosphatemia in chronic kidney diseases [54, 55].

Unlike the toxic properties, physical properties of metals can be also used in medicine. Due to the large ion radius gadolinium and certain lanthanides are used in medicine [56, 57]. Their salts serve as contrast substances in investigations of patients using magnetic resonance imaging (MRI) [56]. Hypoxic tumours can be observed using gadolinium by MRI due to the increased oxygen content [58]. Similarly, other metals such as cadmium, zinc, copper, iron, and others, may be used for mapping the distribution of oxygen in tissues due to tumour angiogenesis [55].

4. ENTERING OF METAL IONS TO AN ORGANISM

Entry of metal ions into body can be performed at different levels by food, air, through skin or intravenously usually in a medical procedure. At the cellular level the situation is more complex. Unlike gases, metals generally cannot penetrate through the plasma

Table 1. Main Symptoms of Acute and Chronic Intoxication by Silver (Ag), Arsenic (As), Beryllium (Be), Bismuth (Bi), Cadmium (Cd), Cobalt (Co), Chromium (Cr), Copper (Cu), Iron (Fe), Mercury (Hg), Manganese (Mn), Nickel (Ni), Lead (Pb), Antimony (Sb), Tin (Sn), Thallium (Th), Vanadium (V), Zinc (Zn). The Oral Lethal doses Were Determined for Rats (if Not Stated Otherwise).

	Symptoms of Acute Intoxication	Symptoms of Chronic Intoxication	Lethal Dose (LD_{50})* [mg/kg of Body Weight]	Reviews on the Topic
Ag	Very high doses: haemorrhage, bone marrow suppression, pulmonary oedema, hepatorenal necrosis	Argyria = blue-grey discoloration of skin, nails, mucosae	125 (AgCN)	[189-192]
As	Nausea, vomiting, diarrhea, encephalopathy, painful neuropathy	Diabetes; hypopigmentation/ hyperkeratosis; cancerogenic – mainly lung, bladder, skin cancer	20 (As_2O_3)	[146, 193]
Be	Nasopharyngitis, tracheobronchitis and pneumonitis; systemic granulomatous diseasse	Inflammatory reaction principally of respiratory system and skin: fatigue, weakness, night sweats, weight loss, anorexia, cyanosis, clubbing of fingers, cancerogenic – mainly lung cancer	0.6 ($BeCl_2$)	[194-197]
Bi	Renal failure; acute tubular necrosis	Diffuse myoclonic encephalopathy	> 2000 (metallic)	[198-200]
Cd	Flu-like syndrome, nausea, vomiting, diarrhoea, pneumonitis, acute kidney, lung and heart failure	Proximal renal tubular dysfunction and renal failure; osteomalacia that may cause spontaneous fractures, anosmia, cancerogenic- mainly lung cancer	203 (Cd ($C_{18}H_{35}O_2)_2$)	[146, 201-205]
Co	Cardiomyopathy; vertigo, deafness	Pneumonitis; goitre; optic nerve atrophy; peripheral neuropathy, cognitive problems, including dementia	42 ($CoCl_2$)	[206-208]
Cr	Gastrointestinal haemorrhage, haemolysis, acute renal failure (Cr^{6+} ingestion); irritant or contact dermatitis, ulceration of the skin	Pulmonary fibrosis, hepatotoxicity, cancerogenic mainly lung cancer, premature dementia (Cr^{5+}), rhabdomyolysis	160 ($K_2Cr_2O_7$)	[202, 209-211]
Cu	Vomiting, gastrointestina irritation/ haemorrhage, haemolysis, hypotension; multi-organ dysfunction syndrome (ingested); metal fume fever (inhaled)	Vineyard sprayer's lung (inhaled); Wilson disease (hepatic and basal ganglia degeneration caused by mutations in the Wilson disease protein (*ATP7B*) gene)	66 ($CuCl_2$)	[212-215]
Fe	Vomiting, GI haemorrhage, cardiac depression, metabolic acidosis	Hepatic cirrhosis (usually after multiple transfussions)	30 (Fe_20_3)	[216-219]
Hg	Elemental (inhaled): fever, vomiting, diarrhoea, acute lung injury, erosive bronchitis and intersticial pneumonitis profuse sweating, tachycardia (persistently faster-than-normal heart beat), increased salivation, and hypertension. Inorganic salts (ingestion): caustic gastroenteritis	Nausea, metallic taste, gingiva-stomatitis, tremor, neurasthenia, nephritic syndrome; hypersensitivity (Pink disease)	10 ($HgCl_2$,) mice	[203, 220-223]
Mn	Hepatotoxicity, flu-like syndrome	Parkinson-like syndrome, respiratory, manganism (mimics manio depressive psychosis or schisophrenia)	260 ($MnCl_2$)	[224-228]
Ni	Alergic reaction- dermatitis and asthma. Nickel carbonyl: myocarditis, acute lung injury, encephalopathy	Occupational (inhaled): pulmonary fibrosis, reduced sperm count, cancerogenic mainly lung and nasopharyngeal cancer	29 ($NiCl_2$)	[229-232]
Pb	Nausea, vomiting, encephalopathy (headache, seizures, ataxia, obtundation)	Encephalopathy, anaemia, abdominal pain, nephropathy	11 (organic)	[203, 233]
Sb	Vomiting, diarrhoea, muscle pain, dermatitis, resembles arsenic poisoning	Arythmia, lichen planus, weight loss, indigestion	300 ($K_2[Sb_2(C_4H_4O_6)_2]$)	[234-236]

(Table 1) Contd….

	Symptoms of Acute Intoxication	Symptoms of Chronic Intoxication	Lethal Dose (LD_{50})* [mg/kg of Body Weight]	Reviews on the Topic
Sn	Nausea, vomiting, diarrhoea, headache, chills	Hepatotoxicity, genotoxicity	4 ($C_8H_{18}O_2Sn$)	[237, 238]
Th	Vomiting, diarrhoea, painful neuropathy, coma, autonomic instability, multi-organ dysfunction syndrome	Alopecia, peripheral neuropathy	15 (Th_2SO_4)	[239-244]
V	Bronchitis and bronchopneumonia	Nephrotoxicity, hepatotoxicity, eczema, diffuse pneumosclerosis, chronic rhinitis	10 (NH_4VO_3)	[245-247]
Zn	Metal fume fever (oxide fumes); vomiting, diarrhoea, abdominal pain (ingestion)	Copper deficiency: anaemia, neurologic degeneration, osteoporosis	794 ($Zn(O_2CCH_3)_2$)	[248-252]

* LD_{50} determined for rats (if not stated otherwise). LD_{50} is influenced by both central atoms as metal ion and anions and/or ligands. Based on the current state of the art, the lowest LD_{50} for the certain metal ion is listed.

membrane spontaneously. Cells have evolved a variety of mechanisms for transport of various metallic elements. For the metal ions there exist different receptors and special transporters in cytoplasmic membranes recognizing type of metal ions *via* its ionic radius and operate under the energy consumption. The transport mechanisms are different for different metallic elements. There are many carriers for the transfer of metal ions, either in free form or bound in complexes with proteins, and new ones are still being discovered and structurally characterized [59]. The preview of the up-to-date characterized transporters is shown in Fig. **1**.

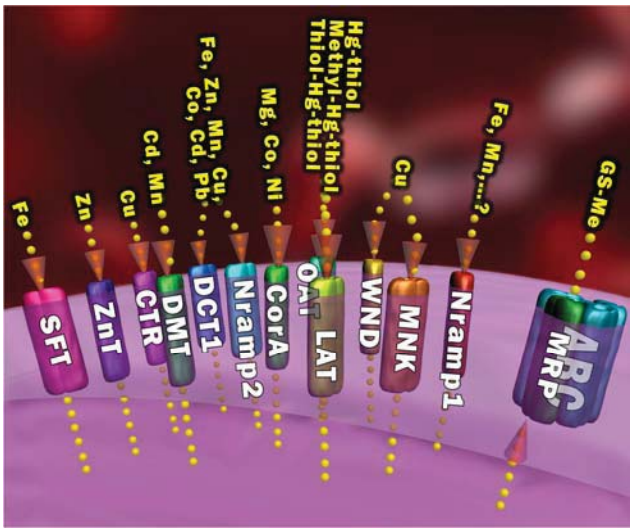

Fig. (1). Preview of metal transporters in eukaryotic cells. Stimulator of Fe transport (SFT) is used for transporting of iron. Zinc transporters (ZnT) serve as a specific transporter for zinc. Copper transport proteins (CTR) as their name indicating are utilized for copper transporting. Divalent metal transporter (DMT) is used for cadmium and manganese transporting. Complex of natural resistance-associated macrophage protein-2 (Nramp2) and divalent cation transporter-1 (DCT1) can be employed for transporting of iron, zinc, manganese, copper, cobalt, cadmium and lead. CorA transporter (named the cobalt-resistant phenotype in E. coli that was caused by the gene's inactivation [188]) is responsible for transporting of magnesium, cobalt and nickel. Organic anion transporter (OAT) and L-type large neutral amino transporter (LAT) serve for handling with mercury ions. Multidrug resistance protein (MRP) belonging to ABC transporter family can transport reduced glutathione-metal (GS-Me) species. Menkes protein (MNK) and Wilson protein (WND) are transmembrane proteins responsible for transporting of copper. Natural resistance-associated macrophage protein-1 (Nramp1) is used for transporting of magnesium and iron, however, other metal ions are discussed.

Knowledge about the transport of metals across membranes is still insufficient and varies for different metals. The main attention is paid to the membrane transporting of essential metal ions in eukaryotes as transferrin cycle responsible for transporting of iron homeostasis in mammals, because this metal is important for erythropoiesis. Iron is firstly transported to a cell membrane by transferrin family proteins such as lactoferrin [60], which binds to the transferrin receptor (TfR-1) on the cell surface. Further, apotransferrin binds iron. Interestingly, the affinity of TfR-1 to iron-bound transferrin is app. 2,000 times higher compared to apotransferrin [61]. To release the iron from the complex, reducing the pH to ~ 5.5 with the ATP proton pump inside the vesicle is used. Iron(III) ions are then reduced onto iron(II) ions by STEAP enzyme family (DcytB) and transported by symport with protons into the cytosol [62].

Transfer of one type of ions can be done using more types of carriers. On the other hand, there are carriers that transport strictly only one type of ion as hCTR1, which carries the copper or ZnT-1, 2, 3 and 4 transport zinc [63]. Zinc may be also transported with CDF transporters [64] and/or ZIP proteins [65]. However, the mechanism of zinc, cadmium and manganese transfer based on ZIP transporters is unknown in eukaryotic cells [64]. The family of copper transporters (CTR) is widespread in the most eukaryotic organisms [66, 67]. Copper is also transported out of cells by the Wilson disease protein (WND), whose gene is ATP7B [68] or using Menkes' protein (ICD, gene ATP7A). At the end of the 20th century, it was assumed that the mammalian transporter DCT-1 carries only the iron atoms, but in fact this transporter is able to transfer also zinc, manganese, copper, cobalt, cadmium and lead in cooperation with Nramp-2 transporter. Conversely, Nramp-1 transports iron and manganese ions out of cells [69].

Study of metal ion transport in humans is most intense in the area of "metal drugs" or toxic metal ions effects on an organism. The phenomenon of resistance across-cancer drug has one of its origins in the transport of xenobiotics across membranes. This is mainly due to the ABC transporters, which are sophisticated ATP-binding protein complexes (cassette) [70]. ABC transporters are a large and highly studied group involved in many physiological and pathological processes [71]. MRP proteins belong to a subfamily of ABC transporters, able to transfer various forms of glutathione (GSH), as oxidized glutathione (GSSG) and nitroso-glutathione

(GSNO), both alone and in complex with metal [72]. There are known types as MRP-1, 2 and 3, able to carry nearly identical substrates, but varies in their occurrence in different tissues [73]. ABC transporters are present both in prokaryotes and in eukaryotic cells, like CorA family transporters, carrying manganese, cobalt and nickel [74]. In the case of toxic metal transport through the cytoplasmic membrane there are known carriers, transporting mercury complexed with thiols. These are organic anion transporter (OAT) in kidney, MRP transporters in liver, or protein for activation of T cells called LAT in endothelia's lining the blood-brain barrier [75]. Cadmium can be transported by divalent metal transporter (DMT-1) in liver cells [75], but its ion radius (0.94 nm) is very similar to that of calcium with ions radius 1.00 nm. Therefore it can be also transported by calcium ion channels [76]. Manganese can be transported using DMT-1 [77]. Receptor proteins called metallo-chaperones play an important role in the transporting of metal ions across the membrane also [78]. Generally, even though the transport of metal ions through the organism is a complex process, the monitoring of metal behaviour in the body provides valuable information for designing of new metal-based drugs [70, 79].

5. AMINO ACIDS-METAL INTERACTIONS

Amino acids are molecules containing at least one carboxyl group (-COOH) and at least one primary or secondary amino group ($-NH_2$). The general formula of amino acids is then H_2NCHR COOH. Due to the acido-basic behaviour amino acids are considered as ampholytes, which means that they can with the negatively charged-COO-group or a positively charged-NH_3^+ behave outwardly as acids or as basis.

In an organism, amino acids can be both free and bound. Bound amino acids are either permanently or temporarily incorporated into proteins or other biochemically functional structures. Among bound amino acids, both biogenic amino acids and their precursors can be included. Free amino acids comprise other amino acids generated by modifying the known biogenic amino acids. These are known as biogenic amines, including histamine, dopamine, noradrenaline, ornithine, taurine, or growth factors sarcosine, spermine and spermidine. The methods using for the determination of free amino acids in blood plasma [80] or in human milk [81] have been still developed. Several scientific groups have found similar concentrations of amino acids in human milk as app. 3 mM [82]. Determination of free amino acids or biogenic amines is insufficient to understand the metal biochemistry. It needs to deal directly with their own interactions between the metal and amino acids.

Uncontrolled move of metal ions in the body leads to formation of reactive oxygen species such as superoxide anion radical ($O_2^{\cdot-}$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), and the highly reactive hydroxyl radical ($^{\cdot}OH$). These inorganic compounds can then oxidize biochemical molecules and disrupt the homeostasis in an organism. The first-line defence against these free radicals is always a compound able to mitigate these effects, or completely scavenge these species, without harming the body or the disruption of homeostasis (Fig. **2**). This is done by chemical reduction using hydrogen transfer. Cysteine is the best compound for this purpose followed by methionine, histidine or tryptophan due to the nucleophilic properties of their side chains. Cysteine is one of the two biogenic sulphur containing amino acids. It is biosynthesised from two amino acids as methionine and serine. Methionine is firstly converted to homocysteine *via* S-adenosylmethionine and S-adenosylcysteine [83]. Cysteine contains sulphur atom in the form of a thiol group, which is located on the last γ-carbon. Due to redox properties and the ability to be a donor of electrons, cysteine is very important in the formation of large-scale structural interactions including binding of metal ions [84]. It is not surprising that cysteine is the part of many metal-binding peptide proteins and enzymes, which perform these functions. Based on this the cysteine was formerly used as a remedy for poisoning by heavy metals. Its derivative N-acetyl-L-cysteine is used as mucolyticum, as antidotum in paracetamol poisoning and as nephroprotective agents. In particular, the mercury is known to be present in the body in the

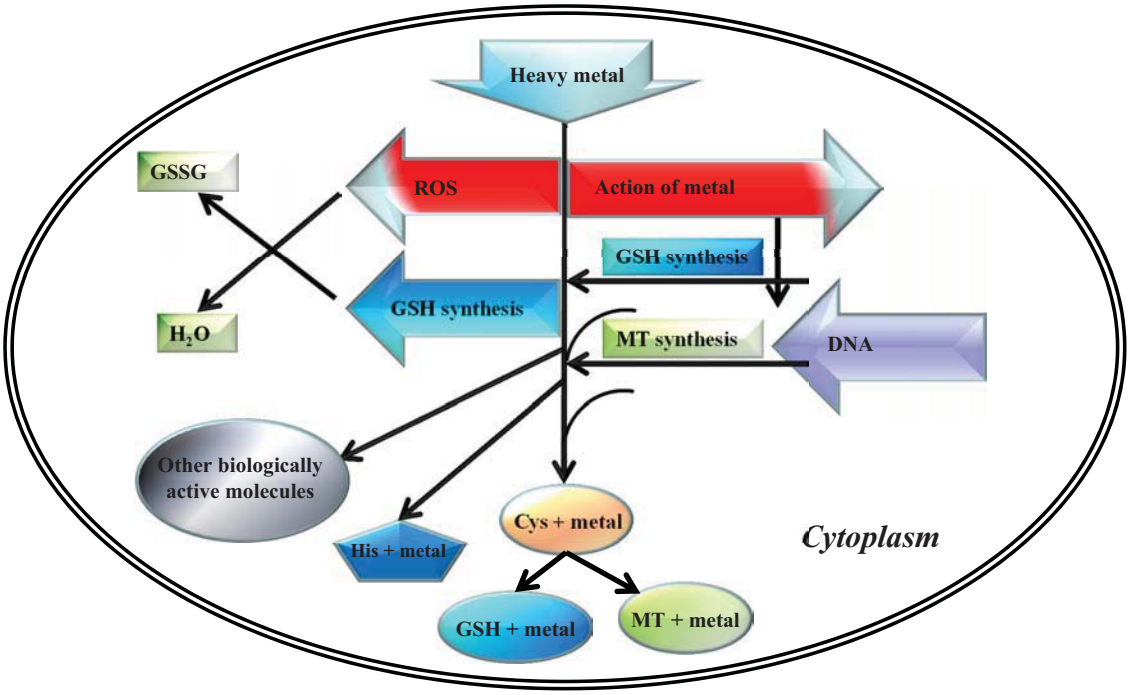

Fig. (2). Scheme of various mechanisms triggers due to presence of toxic and/or excess of essential metal ions in a cell. (**I**) Metal ions can generate reactive oxygen species (ROS). The presence of the generated ROS enhances synthesis of main redox maintainer, reduced glutathione (GSH). This peptide scavenges ROS and oxidized glutathione (GSSG) and H_2O are products of this reaction. (**II**) Presence of metal ions can also alter some biochemical pathways including DNA replication and protein expression through binding to active sites of enzymes involved in these pathways. This action enhances synthesis of reduced glutathione, metallothionein and other compounds rich in cysteine and histidine. The formed complexes are then excreted out of a cell.

form of salts or bound to biomolecules such as cysteine, homocysteine, N-acetyl-cysteine, glutathione, metallothionein and albumin but not free [75].

Methionine is the second of two sulphur amino acids and compared to its precursor cysteine, methionine has a less pronounced metal-binding properties, because the sulphur atom is not present as an easily accessible thiol group, but as a disulphide. Therefore, the methionine is more likely as donor of electron pairs during interactions with metal ions, by which this aminoacid can then coordinate the metals in protein complexes [75, 85]. Methionine also plays a role in the transport of drugs *via* hCtr transporters [86] and ensures a high specificity of copper transport [87]. It has two biologically significant derivatives. Homocysteine is the first one [88]. The metal binding potential of homocysteine is essentially analogical to cysteine, because it does not contain a methyl group bound to a sulphur atom as methionine. Thus it can be assumed to structural similarity of its dimer, which is homocystine, with the above mentioned cystine. This similarity has a profound effect on differentiation of molecules passing through transmembrane transporters [75]. Formylmethionin is the second derivative serving as the first amino acid in the process of translation in prokaryotic organisms. S-adenosylmethionine is also an important compound, which is produced from methionine and ATP by the enzyme methionine-adenosyltransferases. S-adenosylmethionine is involved in many biochemical reactions that are associated with methylation of various substrates such as nucleic acids, proteins and lipids. Interactions of cysteine and methionine cisplatin were also studied to found the impact of platinum-based drugs [89-91].

The amino acid histidine is studied for its potential metal-binding properties due to the imidazole nitrogen acting as a nucleophile [92-95]. The histidine-rich glycoproteins, known as HRG-proteins can bind to cadmium(II) ions [96]. Further, glutamic and aspartic acids were studied due to the possible complexation of metal ions *via* carboxyl [97]. Attention was also paid to other amino acids and their metallic complexes [98, 99]. A formation of less reactive metal ions complexes compared to above-mentioned ones with other amino acids can occur in organism and for this purpose, advanced computer technologies can be used for theoretical studies, in which models of the most probable form of interaction are suggested [100].

6. METAL-OLIGOPEPTIDES INTERACTION

A number of various peptide molecules occur naturally in organisms. The metal ions coordinated in these peptides are often involved in a range of catalytic or other biochemical processes. Also the presence of the metal ion in the peptide structure leads to the significant conformational changes of the biomolecule. Systematic investigation of the metal-peptide interactions started in the middle of the 20th century, when the copper(II) and nickel(II) coordination by the –CONH– peptide bond have been confirmed [101]. Metal ions are coordinated *via* two types of interaction: (i) peptide backbone including the interaction of the metal ion with the terminal $–NH_2$ and/or –COOH group as well as coordination by the nitrogen atoms of the peptide amide bonds due to the delocalization of the lone pairs of the nitrogen atoms; (ii) amino acid side chains. There are three groups of side chain types which can be classified according to the ability of ion coordination. First group of non-coordinating side chains including Ala, Val, Leu, Ile, Phe, Trp. Ser, Thr, Tyr, Lys, Arg, Asp, Glu, Asn, Gln, Arg, Met belong to the group of weakly-coordinating side chains, and His and Cys are strongly-coordinating side chains. The metal binding abilities of oligopeptides, including the effect of the number of histidines and their position within the peptide amino acid sequence have been recently summarized [102, 103]. In addition, an exhaustive review focused on the mechanisms of metal ion-peptide interaction was published in 2006 [101]. Intensive study of metal ion interactions with oligopeptides covers both synthetic as well as naturally occurred oligopeptides [104-107].

Reduced glutathione, tripeptide with the composition of γ-L-glutamyl-L-cysteinyl-glycine (Fig. **3**), is probably the most widely studied biologically active oligopeptide especially due to the crucial function in detoxification of heavy metals. Glutathione occurs in cells on the millimolar level and represent over 90% of the total non-protein -SH groups [108]. Glutathione plays an important role in cell protection against reactive oxygen species, xenobiotics as well as heavy metals. Two forms of glutathione can occur as reduced glutathione (GSH) having the antioxidant properties and its oxidized form called glutathione disulphide (GSSG) [109-111]. The GSH/GSSG ratio is generally accepted as a marker of the oxidative stress [112]. Glutathione-ascorbate cycle belongs to the most important processes, which employs the activity of cysteine thiol groups in the tripeptide called glutathione [113]. The cycle is shown in Fig. **3**. In the first step, hydrogen peroxide is reduced to water by ascorbate peroxidase. Ascorbate is used as an electron donor. Oxidized ascorbate is reduced again by monodehydroascorbate-reductase (MDAR). Monodehydroxyascorbate is a radical, which, if not rapidly reduced, forms the ascorbate and dehydroxyascorbate. Dehydroxyascorbate is then reduced on ascorbate by dehydroxyascorbate-reductase under the simultaneous reduction of two molecules of reduced glutathione (GSH) to one molecule of oxidized glutathione (GSSG). Finally, GSSG is reduced by glutathione reductase using NADPH as an electron acceptor.

Interactions of glutathione with the physiologically occurring metal ions such as Cu and Zn [114-116] as well as with the potentially toxic heavy metals Cd, Pb, Hg, Al and Ni were described [109, 117-119]. These interactions mostly exhibited a stoichiometry of 1:2, Metal:GSH [120]. Recently the effect of lithium(I) ions was also investigated [121] regarding to the use in psychiatry for therapy of bipolar disorders. Due to the exclusive possibility of the interaction between cisplatin and glutathione in the organism [122-124], these interactions have been studied both theoretically [100] as well as by real *in vivo* experiment [125]. Model of interaction between two molecules of GSH and one metal(II) ion is shown in Fig. **4**.

Generally, the complexes of the metal ions with peptides were studied by a wide range of analytical methods including atomic absorption spectroscopy [126], high performance liquid chromatography coupled to inductively coupled plasma atomic emission spectroscopy (HPLC-ICP-AES) [127], NMR analysis [109, 128, 129], UV spectroscopy [129] as well as mass spectrometry [119]. Moreover the practical exploitation of the metal coordination is represented by immobilized metal ion affinity chromatography (IMAC), routinely utilized in molecular biology for purification of protein products by hexahistidine. [130-132]. Metal ion-peptide interactions in combination with the possibility of immobilization on either bulk or nanoparticle-based surfaces are enabling the advances in the area of miniaturized instrumentation and consequently in point-of-care and lab-on-chip field. Miniaturized and portable devices are typically based on low size sensors providing simple and easy to use analyses. The interactions of oligopeptides with metal ions are widely utilized in construction of sensors [133-135].

7. METAL-PROTEINS INTERACTION

Similarly to peptides, proteins have number of functions in the body including the binding of inorganic elements including metal ions. These ions can be bound to proteins due to various purposes as transportation, implementation of structural features, cofactor in enzymes, transcription regulation, and last but not least, the creation of deposits mainly for storage of essential metal ions (Fig. **5**). Immediately after entering the body, free metal ions present in body fluids are bound by metal transporting proteins. These proteins can be both highly specific for certain metals, or can bind more metals

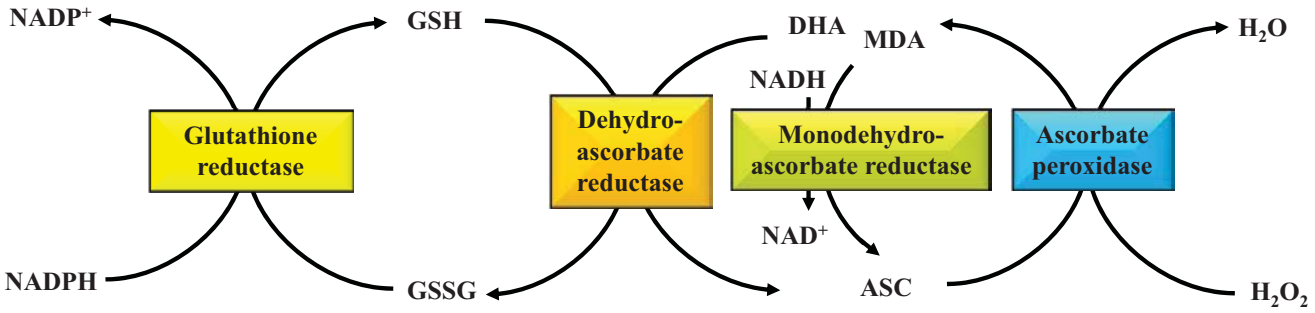

Fig. (3). Glutathione-ascorbate cycle. In the first step, hydrogen peroxide is reduced to water by ascorbate peroxidase. Ascorbate is used as an electron donor. Oxidized ascorbate is reduced again by monodehydroascorbate-reductase (MDAR). Monodehydroxyascorbate is a radical, which, if not rapidly reduced, forms the ascorbate and dehydroxyascorbate. Dehydroxyascorbate is then reduced on ascorbate by dehydroxyascorbate-reductase under the simultaneous reduction of two molecules of reduced glutathione (GSH) to one molecule of oxidized glutathione (GSSG). Finally, GSSG is reduced by glutathione reductase using NADPH as an electron acceptor.

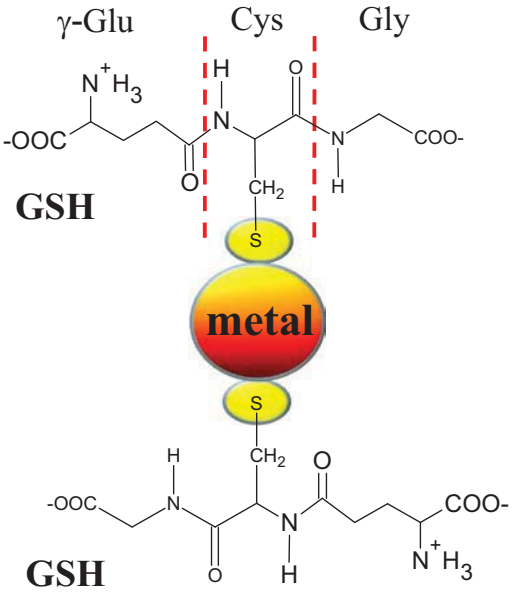

Fig. (4). Complex of two molecules of reduced glutathione with divalent metal ions.

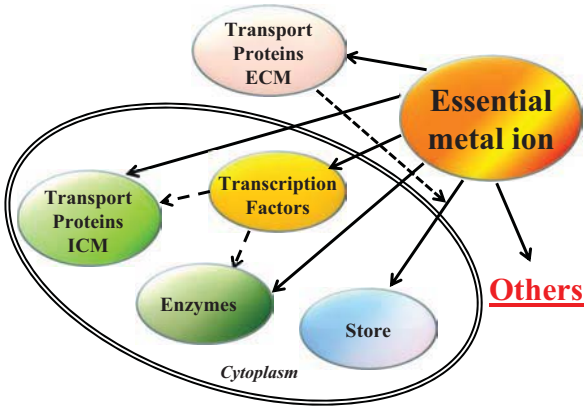

Fig. (5). Essential metal ions are, after their entering into a cell milieu various targets. Primarily, they are used for activation of transcription factors, which is responsible for translating of proteins, mainly for enzymes and transporting proteins in intracellular matrix (ICM). Slight excess of essential metal ions can be also stored. Some of the ions can be also used for activation and synthesis of transporting proteins in extracellular matrix (ECM).

simultaneously. Metal-specific proteins such as transferrin, ceruloplasmin, transcobalamin and nickeloplasmin, binding iron, copper, cobalt and nickel respectively, are the most known and studied vertebrate metal-binding proteins. On the contrary, metals such as calcium, zinc and cadmium are nonspecifically bound by serum albumin [96]. Zinc is transported by large family of ZIP proteins in blood plasma [136] and copper is transported extracellularly through protein ceruloplasmin, which can also oxidize Fe(II) ions to Fe(III) [137]. In addition to ceruloplasmin, the transport of copper in plasma can be performed by albumin, binding copper(II) ions with lower strength [138].

Metal ion entering the body as a part of other structure can be either component of smaller organic molecule – drug, or a complex with biomolecule – protein. One may mention iron transporting protein lactoferrin, which belongs to the transferrin family entering into mammalian body in the form of milk [139]. Lactoferrin is also found in tears, saliva and sweat secretions [140]. After the metal is transported *via* transporting proteins to the cytoplasmic membrane of cells, it is as a free metal ion transferred to the cytosol using various types of carriers mentioned-above. Free ion also interacts with intracellular proteins, which have different functions. Transport of metal ions on the intracellular level is mostly performed by metallothionein proteins, which have the ability to bind most of the essential and toxic metals. The most important biological function of MTs is probably homeostasis of heavy metal levels. Gene transcription is initiated when metal ions associates with the metal-regulatory transcription factor-1 (MTF-1). MTF-1 is the only known mediator of metal responsiveness of MTs [141-143]. MTF-1 binds to metal responsive elements (MREs) that regulate MTs expression. MREs are located in the promoter regions of MT genes [142] and are present in multiple copies in the promoter/enhancer regions of almost all metal-inducible MTs [144, 145]. Further, various studies have demonstrated that the presence of other metals can also activate redox-sensitive transcription factors such as NF-κB, AP-1 and p53 [146].

Excessive metal ions can be stored in so-called deposits utilizing the interaction with proteins. This is known especially in the case of essential metals. The accumulation of toxic metals, known in plants, has not been satisfactorily demonstrated in higher animals. Free iron ions in higher concentration toxic for a cell are stored in the protein ferritin in both plant and animal cells. This protein has 24 subunits and is able to bind up to 4,500 iron ions to its structure [147].

Enzymes are great group of molecules, functionally dependent on metal ions, , binding most essential metals such as iron, magnesium, selenium, manganese, zinc, copper and calcium in their active

sites, and performing its function only if the metal is present in the active and other sites in the enzyme molecule. From the intracellular ones dimeric metalloenzyme alkaline phosphatase can be mentioned. This enzyme requires two zinc ions, or magnesium for its proper function namely the hydrolysis of phosphate esters at pH 9.8 to 10.0 and [148]. Superoxide dismutase (SOD) is another important enzyme responsible for reducing superoxide anions. SOD requires copper cation but some isozymes may also contain iron, nickel and manganese [149]. Hydrogen peroxide, which can be also produced by SOD, may be effectively reduced to water by glutathione peroxidase with the assistance of two molecules of GSH. Glutathione peroxidase is present in several isoenzymes both intra and extracellularly [150], and its activity requires the presence of selenium. Matrix metalloproteinases belong to other large group of metalloenzymes, which, although expressed intracellularly, acts extracellularly for cleaving and rearranging extracellular matrix composed primarily of collagen [151]. These enzymes require calcium(II) and zinc(II) atoms [152]. Enzymes may not be only molecules functionally dependent on the presence of metal ion. A number of oxygen carriers depend on the presence of iron. In the case of mammals, haemoglobin is iron carrier, consisting of protoporphyrin and iron atom that is coordinated *via* histidine moieties [153].

8. NANOTECHNOLOGY BASED ON METALS

Nanotechnology is an area of development, production and utilization of materials, equipment and systems on the nm-length scale, i.e. at the level of molecules and supramolecular structures. It may be applied in biotechnology and medicine. Development of materials and devices for diagnostics and drug delivery systems are the main applications of nanotechnology in medicine (nanomedicine). Due to the metallic nature of a wide range of nanomaterials, studying of their interactions with biomolecules is attracting a great interest of numerous researchers. Physico-chemical properties of newly developed nanomaterials enable their utilization in nanomedicine, particularly in targeted drug delivery, laboratory diagnostics and/or imaging techniques.

Molecular nanotechnology appears from measuring scale, in which is operating [154-157]. This measuring scale is within the range from tens to thousandths nanometres, whereas the basic structural element of molecular nanotechnology is an atom with diameter < one nm. By various organizations of atoms such as carbon or silicon, properties of resulting product, including elasticity, plasticity, strength, or conductibility can be modified. Nanomedicine, one the newest member of branches in molecular nanotechnology, can be defined as monitoring, repairing, building, and control of biological systems on molecular level carried out by nanocomponents and nanosystems. Dramatic advancement of these technologies can be expected, especially in diagnostics of diseases in their early stages [158-162]. Nowadays, we can divide nanomedicinal approaches into two sections i) currently in use and ii) real future perspectives. In the approaches with real future perspectives, we may see therapeutic abilities of nanorobots in microsurgery and in treatment of various types of diseases, such as coronary thrombosis or malignant tumours [163]. We can expect that medical nanorobots with size up to 1,000 nm can be injected into human body (several milliards of nanorobots correspond to one millilitre). They can help the immune system, participate in metabolic processes, perform repairing operations, eventually cluster together into higher structures and form more complex and effective repairing and protective systems. Bio-implants in the field of skin regeneration (special polymers, silver nanoparticles) are very important nanomedicinal group currently used.

8.1. Drug Delivery

Drug nanodelivery belongs to another nanomedical area, which is already implementing. Concerns connected with the drug delivery, such as troublesome solubility and biological availability, short time of circulation in blood vessels and/or inconvenient biodistribution to the target organ may occur. On the other hand, nanoparticle-mediated targeted delivery of drugs might significantly reduce the dosage of the drugs, increase its specificity and bioavailability, overcome chemoresistance and reduce side effects of therapy which makes possible to increase doses of active compound [164-166]. Mainly in cancer therapy, targeted delivery in a localized way is one of the key challenges. The first mentioned improvement is based on the enhanced permeability and retention effect of the vasculature surrounding tumours. The active way relies on ligand-directed binding of nanoparticles to receptors expressed by tumour cells [167]. These ligands comprise antibodies, peptides, nucleic acid aptamers, carbohydrates and small molecules [165]. The key features of anticancer nanoparticles are mainly nanoparticles size, surface properties (e.g. hydrophobicity) and targeting ligands. Generally, 200 nm is considered as upper limit for nanoparticles size, while the minimal diameter should be about 10 nm. Certainly, nanoparticles property requirements also depend on tumour characteristics including cancer type, stage of disease, site in the body and host species. All strategies are summarized in review of Adiseshaiah *et al*. [168].

Nanoparticles designed for tumour targeted therapies consist of various components in most cases from nanocarrier (in some literature called nanovector) and an active agent (drug) [169]. Drug-carrier nanoparticles are considered as submicroscopic colloidal systems that may act as drug vehicles, either as nanospheres (matrix system in which the drug is dispersed) or nanocapsules (reservoirs in which the drug is confined in a hydrophobic or hydrophilic core surrounded by a single polymeric membrane) [170]. Nanoparticle carriers are mostly composed of iron oxides, gold, biodegradable polymers, dendrimers, lipid based carriers such as liposomes and micelles, viruses (viral nanoparticles) and even organometallic compound [165, 171, 172]. A detailed summary on nanocarriers was recently reviwed by Peer *et al*. [173]. The drug encapsulation in nanocarrier provides better biocompatibility and hence its potential use in clinical oncology. Several such engineered drugs are already in clinical practice, including liposomal doxorubicin and albumin conjugate paclitaxel [174]. However, the potential success of these particles relies on consideration of above mentioned important parameters, but most importantly, minimum toxicity of the carrier itself [175]. Concerning the nanoparticles shape, following nanostructures are frequently cited in literature: nanoshells, nanorods, nanocages, nanocubes or nanotubes. Adsorption of oligopeptides on silver [176, 177] and/or gold [135, 178, 179] nanoparticles were described.

8.2. Imaging

The targeted drug delivery and *in vivo* imaging employing nanoparticles-based contrast agents are one of the most extensively studied areas of nanotechnology field [180-182]. Molecular imaging refers to the characterization and measurement of biological processes at the cellular and/or molecular level, its modalities include optical bioluminescence, optical fluorescence, ultrasound, X ray methods including CT, MRI, magnetic resonance spectroscopy (MRS), single-photon-emission computed tomography (SPECT) and positron emission tomography (PET). In the last decade, molecular imaging, a subfield of functional imaging, became an essential tool in the arsenal of bio-imaging, understood as the range of all imaging technologies covering the full scale of biological and medical applications from a molecule to a patient. Molecular imaging (MI) can be defined generally as the science and the techniques for *in vivo* extraction of biological information on the spatiotemporal distribution of molecular, biochemical, biological, and cellular processes for diagnostic or therapeutic applications, or their application to visually represent, characterize or quantify biological processes at the cellular levels within intact living organisms. The recent arrival of MI research is the result of the development in cellular and molecular biology, genomics and proteomics,

nanotechnologies, and increased sophistication of imaging technologies, combined with a large diversification in new contrast agents and probes. MRI is a powerful imaging tool producing high resolution images with excellent soft tissue contrast without the application of harmful radiation. MRI can provide both physiological and anatomical details of *in vivo* systems simultaneously and in real time, which is not possible with other imaging techniques. For example there were developed highly lymphotropic superparamagnetic iron oxide nanoparticles having diameter 2 to 3 nm that have been used as contrast for high-resolution MRI to diagnose otherwise undetectable small lymph node metastases of prostate cancer [183]. In MRI, all nuclei with spin can be employed for image creation. However, mostly hydrogen protons of water molecules are exploited to report on biological processes of interest because of their high abundance. Optical imaging belongs to another important group of imaging techniques using metal particles. This group includes several modalities based on *in vivo* bioluminescence and fluorescence and is probably the fastest growing biomedical imaging technology nowadays. In general, optical imaging techniques are non-invasive, fast, very sensitive, and relatively inexpensive. Bioluminiscence is characterized by extremely high sensitivity. In fluorescence imaging, an external light source excites fluorophores (fluorescent protein or dye), which emit the transferred light energy at a different wavelength. Fluorescence imaging can be performed at different resolution and depth penetrations ranging from micrometers to centimetres. Since no single imaging technique can provide complete information about the subject´s structure and function, using multiple imaging methods, followed by image fusion, is required. Nanostructures provide an outstanding platform to integrate different functional nanocomponents into one single nanoentity to exhibit multifunctional properties. Quantum dots (QDs) portion of matter whose excitons are confined in all three spatial dimensions, such materials have electronic properties intermediate between those of bulk semiconductors and those of discrete molecules [184]. They can be combined with MNPs to exhibit magnetic and fluorescent properties concurrently. Unlike MRI, *in vivo* optical imaging utilizes the incomparable fluorescent properties of QDs such as small size (tens of nm) and unique tuneable optical features. QDs are widely being used in place of organic dyes for imaging applications in biological systems due to their much greater temporal stability and resistance to photobleaching than fluorescent dyes do. The combination of superparamagnetism and fluorescence at nanometre scale should increase the biological applicability of multifunctional nanomaterials. The desirable physical and chemical properties of contrast agents required for bimodal optical and magnetic imaging can be combined in a single nanoparticle [185]. Utilization of nanomaterials, particularly nanoparticles for the *in vivo* monitoring of cell transplantation is one of future perspectives. Currently MRI provides low resolution and no difference, between original and transplanted cells, is registered. Basically any cells can be labelled as stem cells, Langerhans cells, tumour cells, immunocompetent cells. Incorporation of the contrast agents into the cells can be done either by fagocytosis or conjugation of the contrast agent to the cell surface *via* antibody- antigen or ligand-receptor interaction. Labelled cells can be transplanted into the animal.

8.3. Laboratory Diagnostics

Molecular markers, (cellular changes of DNA, RNA, metabolites or proteins) may be used for diagnosis and therapeutics. They have been detected by nanotechnology and they can be used as diagnostic markers of diseases or therapeutic target. Markers of bacteria and viruses have been detected by nanotechnological assays, and they improved the possibilities of microbiological diagnostics, because nanotechnology enable an RNA, DNA and protein analysis with higher speed of examination and increased accuracy and sensitivity compared to classical molecular diagnostics [186]. Antibody conjugated nanoparticles that can recognize a specific cancer cell may be applied for the fast and accurate diagnostics and investigation of prognostic markers and/or therapeutic targets. Streptavidin-coated quantum dots (QDs) conjugated to anti-EGFR antibodies bind selectively to glioblastoma multiforme and oligodendroglioma cells expressing EGFR, which demonstrated that antibodies labelled QD can afford fast, specific and accurate method for detection of specific cellular marker that is useful not only for diagnose of glioblastoma or oligodendroglioma but also as a target for cetuximab therapy [187].

9. CONCLUSION

Metallomics as a wide area of studies focused on the interactions of metal ions with biomolecules, transport and behaviour of metals in organisms as well as the general impact of the exposure to the metal ions has a great share of the current state of knowledge in the field of biochemistry and biomedicine. The main advances in the cancer treatment based on metallic pharmaceuticals were enabled by the understanding of the reaction mechanisms between the drug and the surrounding environment in the living cell. New generations of metal-based cytostatics as well as nanomaterials-based targeted pharmaceuticals are developed paying particular attention to the interaction of metal ions with, amino acids, peptides, and proteins.

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