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Review

Metal-binding protein: Metallothionein

Faiz Marikar[1], Hua Zi-Chun[2]

[1]Department of Biochemistry, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka
[2]State Key Laboratory of Pharmaceutical Biotechnology, College of Life Sciences, Nanjing University, Nanjing, China

Abstract

More than a century ago, the very first adverse human health effects of metalloproteins were reported after the usage of cadmium-containing silver polishing agents. It was first observed in the Horse population. The discovery of the low-molecular-weight protein Metallothionein (MT) in 1957 was an important milestone as this protein was shown to bind cadmium and to cause cellular cadmium toxicity. The mentioned authors contributed evidence in the 1970s concerning cadmium binding to MT and synthesis of the protein in tissues. We showed in our previous studies that binding of cadmium to MT in tissues can prevent some toxic effects; yet, further, identification of these macro and micro-molecules is required at the biochemistry and genetics levels. As with the recent studies, novel biochemical functions of MTs are introduced, for example, a new application of Mts, which are being used in protein purification by affinity chromatography. The trend is used to cure neuron disorders and even cancer. This review summarizes that this evidence in a genetic experiment is still needed for find out the function of MTs; it is an open area of research even in the 21st century.

Keywords: Cytology, genetics, metallothionein, therapeutic use

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Metallothioneins (MTs) were first discovered from horse kidney by Morgoshes and Vallee in the 20th century (1957) and was subsequently purified and characterized by Kägi and Vallee [1]. This discovery marked a field of research focused on the study of a low-molecular-weight polypeptide superfamily, the MTs. MTs are cysteine rich, low-molecular-weight (6–7 kDa), non-enzymatic, intracellular proteins ubiquitous in all eukaryotes (often discovered in encoded multiple copy genes), as well as some prokaryotes [2, 3]. In the mouse, there are four MT genes (MT-1, 2, 3, and 4) that reside in a 50 kb region on chromosome 8, whereas in the humans in addition to the four genes, numerous isoforms of MT-1 are clustered on chromosome 16q13 [4, 5]. Human MT proteins are encoded by ten genes: MT-1A, MT-1B, MT-1E, MT-1F, MT-1G, MT-1H, MT-1X, MT-2A, MT-3, and MT-4. In addition to these ten functional isoforms, there are seven non-functional isoforms encoded by, in mice MT-1C, MT-1D, MT-1I, MT-1J, MT-1K, MT-1L, and MT-2B [6]. The MT-1 and MT-2 in addition to these isoforms, which differ by only a single negative charge, are the most widely expressed isoforms in different tissues. In the human, MT2A gene is clusterd on chromosome 16q12 (Fig. 1).

Synthesis and Regulation of Synthesis

MT harbors high metal content. Mammalian MTs contain 20 cysteine residues, which are central to the binding of metals. The stoichiometry is such that there are seven bivalent ions for every 20 cysteines, which form metal thiolate complexes, therefore enabling the MT to bind between 7–10 atoms of metal/mol MT in a two domain structures [6]. The protein has the shape of a dumbbell and envelops the metals that it contains in two separate domains. It is most remarkable that the metals are arranged in a cluster structure unique to biology. Total length of the MT2A is 60 amino acid long protein. Its molecular weight is about 6 kD. In one cluster (N-terminal α-domain), four metal atoms are bound to 11 cysteines, five of which bridge the metals in a two domain structures; the other (C-terminal β-domain) has three metal atoms and

Address for correspondence: Faiz Marikar, MD. Department of Biochemistry, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka
Phone: +941 112 635268 **E-mail:** faiz@kdu.ac.lk **ORCID:** 0000-0003-4579-7263

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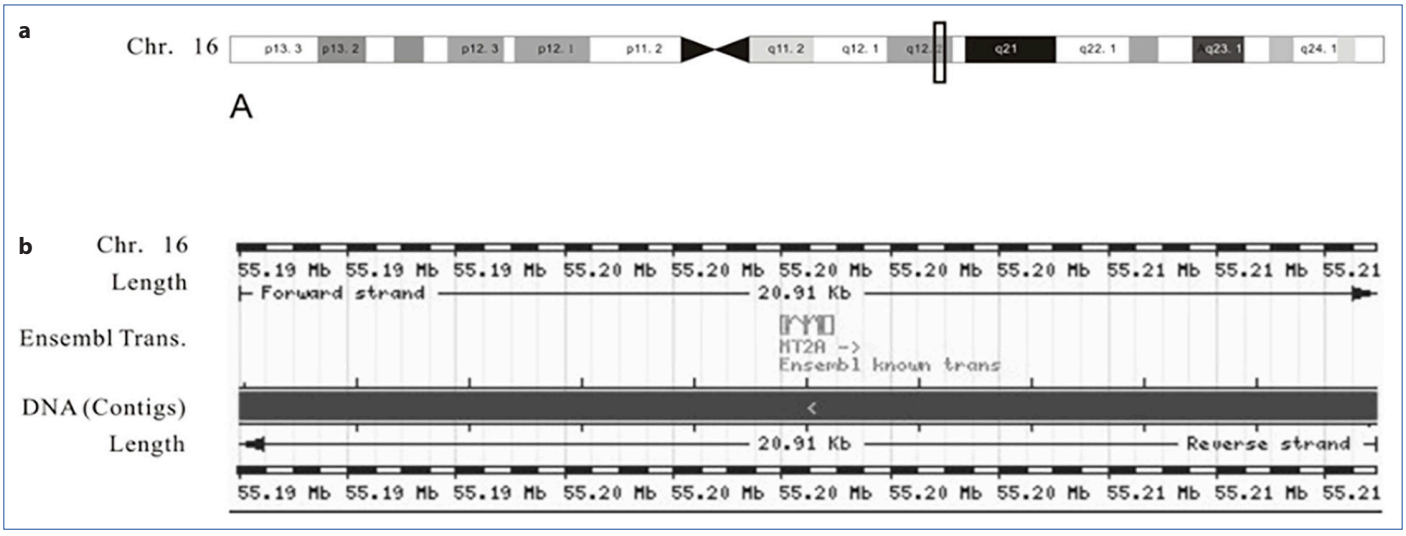

Figure 1. (a) The CCDS10763 (MT2A) locus on human chromosome 16q12. (b) Physical map of the CCDS10763 (MT2A) locus on chromosome 16 showing the relative position of MT2A gene in humans, MT2A gene is clustered. Image generated from http://www.ensembl.org/Homo_sapiens/index.html.

nine cysteines with three bridges (Fig. 2) [7]. Zinc is bound extremely tightly to α-domain and cupper is mostly bound to β-domain of MT2A.

Intramolecular metal linkages can stabilize the MT protein secondary structure; therefore, loss of metal can cause structural changes, rendering the polypeptide chain vulnerable to proteolysis [8]. Stability is also influenced by the nature of the metals bound to MT. Predominantly, Zn^{++} but sometimes also Cu^{++} are bound *in vivo* under physiological conditions. However, several less abundant transition metals, such as Cd^{++}, Bi^{+++}, Pt^{++}, Ag^{+}, and Hg^{++} also bind eagerly to MT *in vitro*. The binding affinity of different metals for MT2A varies considerably and has the following order: $Zn^{++}<Pb^{++}<Cd^{++}<Cu^{+}<Ag^{+} = Hg^{++}$ is bound Bi^{++}, therefore making zinc readily displaceable by other metal ions [9].

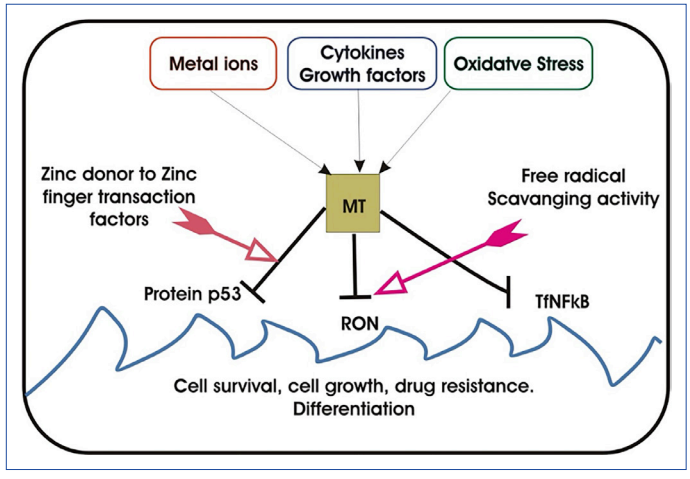

Figure 3. Schematic drawing of mts functions.
MT: Metallothionein.

Function

Despite the accumulation of detailed information on both the biochemical and molecular aspects of MT structure and expression, its biological role is still not clearly understood more that 40 years after its discovery. The fact that there are multiple copies of MT genes expressed in distinct patterns, and the relatively rapid turnover of the protein suggests that they should have important functions. Its biological role has not been clearly understood for more than 40 years since its discovery. Zn^{++} provides essential structural and catalytic functions to a variety of proteins. Zn^{++} is also crucial in the regulation of gene expression because numerous transcription factors have "zinc finger motifs" that are maintained by Zn^{++}. Apo-MT (MT with no metals bound) role in maintaining the essential metal homeostasis is a Zn^{++} acceptor due to the abundance of free sulfhydryl groups and their high affinity for Zn^{++}. However, the sulfhydryl groups are highly reactive, and Zn^{++}, although bound with high affinity, can undergo exchange reactions, which allows Zn^{++} to be transferred from MT to other proteins [10–13]. The affinity of sulfhydryl groups for Zn^{++} can also make MT an efficient metal ion scavenger. This implies a possible regulatory role of MT in the activation or inactivation of various molecular effectors is a Zn^{++} acceptor due to the abundance of free sulfhydryl groups and its high affinity for Zn^{++}. Such a possibility was demonstrated by showing that apo-MT can chelate Zn^{++} out of the transcription factor IIIA (TFIIIA), a process that inactivates TFIIIA [14]. Therefore, it is tempting to speculate that MT might be essential for Zn^{++} homeostasis by regulating Zn^{++} absorption or as a donor of Zn^{++} to various enzymes and transcription factors during development or protein synthesis. The affinity of sulfhydryl groups for Zn^{++} can also turn MT into an efficient metal ion scavenger.

There is strong evidence that MTs play an important role in protection against metal toxicity. In unicellular eukaryotes,

MTs bind copper predominantly [2, 3]. Mutations that prevent MT synthesis confer copper sensitivity, whereas excess expression of MTs confers resistance to copper toxicity [7, 15]. There is strong evidence that MTs can play an important role in the protection against Cd^{++} toxicity and lethality, but it provides much less protection against the lethality of the other metals such as, Zn^{++}, Cu^{+}, Fe, Pb^{++}, Hg^{++}, and As [15]. Cadmium is a ubiquitous and insidious pollutant. A by-product of zinc production by humans and a component of volcanic eruption by nature, the element is chiefly used in the industrial plating process and can be found in products as diverse as solder, artists' pigments, and rechargeable batteries ubiquitous and an insidious pollutant. It is even used to absorb neutrons in the control rods and shielding of nuclear reactors. Depending on the dose, route, and duration of exposure, Cd^{++} can cause damage to various organs including the lung, liver, kidney, bones, testis, and placenta [16–20]. It is even used for absorbing to Cd^{++} produces hepatic, pulmonary, and testicular injury, whereas chronic exposure results in renal and bone injury and cancer [21]. The Agency for Toxic Substances and Disease Registry currently ranks Cd^{++} 7^{th} on its priority list of hazardous substances. Moreover, various mammalian cell lines that cannot synthesize any MT are sensitive to cadmium toxicity, whereas mice and the cells that overexpress MT are resistant to Cd^{++} [22, 23]. In fact, selection for cadmium resistance with mammalian cells results in up to 80-fold amplification of the entire MT-locus. MT that is sensitive to cadmium toxicity disposition has been examined in MT-transgenic mice. In this model, MT does not inhibit intestinal Cd^{++} absorption, nor does it affect initial Cd^{++} distribution to various tissues [24, 25]. However, MT decreases Cd^{++} elimination through the bile and is a major factor for tissue retention of Cd^{++} [25–27]. The results of a number of studies with humans environmentally exposed to Cd^{++} demonstrated that proteinuria is the main renal injury in these subjects [28]. The results of several studies Cd^{++} injures proximal tubules of kidney, an increased excretion of protein into urine is observed. A novel fusion expression vector for *Escherichia coli* was developed based on the pTΩRG plasmid, a derivative of the pET32a. This vector, named pT7MT (GenBank access No: DQ504436), carries a T7 promoter and it drives the downstream gene encoding MT 2A (MT2A) [29].

MTs are cysteine-rich molecules. Therefore, it is reasonable to expect that sulfhydryl-rich MTs may function in a manner similar to GSH, wherein MT provides an intracellular nucleophilic sink to "trap" electrophiles, alkalyting agents, and free radicals [30, 31]. The multiple cysteine residues of MT can be oxidized during oxidative stress, and the subsequent release of alkylating Zn^{++} has been proposed to be important in protecting against oxidative damage [32, 33]. However, it has been difficult to demonstrate oxidation of MT *in vivo*. Therefore, there have been controversial reports on the role of MT during oxidative stress. While it has been difficult to demonstrate the oxidation of MT *in vivo*, reports on the role of MT during oxidative stress show controversial results.

Role in the Pathogenesis of Diseases Including Apoptosis/Angiogenesis/Oxidative Stress

A variety of stimuli such as metals, hormones, cytokines, and a range of other chemicals, inflammation, and stress can induce MTs. Some of these stimuli include metals, hormones, cytokines, a range of other chemicals, inflammation, and stress [34]. The most extensively studied of these inducers are metals and glucocorticoids, both being efficient inducers of MT. However, both of these entities display species differences in isoform induction. In mice, both metals and glucocorticoids equally induce MT-1 and MT-2; in man, metals induce all the MT isoforms, whereas glucocorticoids only induce MT-2A and MT-1E [35, 36]. In human, MT isoforms are regulated independently of each other, whereas, in mouse, the MT-1 and MT-2 isoforms are co-ordinately regulated [34, 37, 38]. With the exception of glucocorticoids, only metals have been shown thus far isoforms, whereas mice MT-1 and MT-2 isoforms are to be capable of inducing the human MT-1. This demonstrates the apparent simplicity of the human MT-1 promoter region compared with that of MT-2A, which contains several enhancer regions [36]. Considerable progress has been made in the mechanism by which metals induce MT and the way, in which expression of this protein is regulated, even though the regulation of protein expression not yet fully understood [39]. Exposure to heavy metals leads to a significant MT synthesis and this synthesis is the regulation of protein expression which is not yet thought to be mediated through *cis*-acting DNA sequences or metal responsive elements (MREs) which are present as multiple copies in the promoter region of all the MT genes [40, 41]. These cis-acting regions are conserved among many diverse organisms but are not all functionally equivalent [42]. Moreover, variations in the ability of different MREs to mediate metal-activated transcription of MT genes have been reported [43].

Proteins which are thought to be positively acting transcription factors bind with MREs in a metal-dependent manner during metal induction of MT [44]. Following metal exposure, different proteins from nuclear extracts of cells of both rodent and human origins have been identified as possible regulators of metal mediated gene transcription [45]. These include metal response element binding factor-I, zinc-activated protein, and zinc-regulated factor. These proteins have different binding affinities for the various MREs and it is not clear if the binding of these proteins is metal specific [46]. These proteins are metal specific which is identified from nuclear extracts of HeLa cells do affect metal-mediated MT gene transcription. These are MREBP (MRE binding protein) that specifically binds MREs of the human MT-2A gene and MTF-1 (MRE binding transcription factor), constitutively active zinc sensitive factor. MREBP is thought to inhibit transcription, whereas MTF-1 is thought to have an important role in the control of MT gene expression [41, 47–49] (Fig. 3).

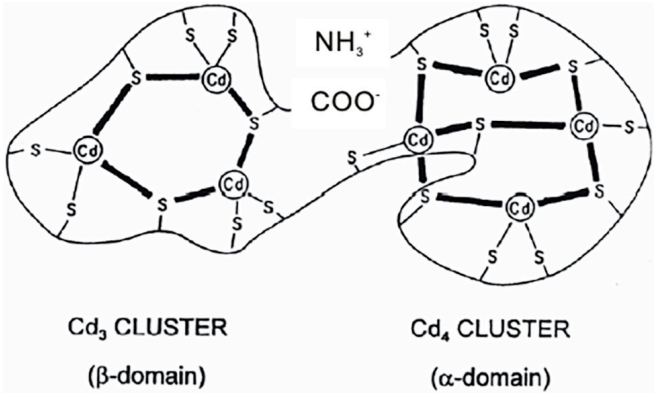

Figure 2. Schematic drawing of zinc thiolate clusters in MT based on both X-ray diffraction and NMR spectroscopy data. (Adopted from Edmont H. Fischer and Earl W. Davie, Recent excitement regarding metallothionein, *Proc. Natl. Acad. Sci. USA, Vol. 95, pp 3334, 1998*).
MT: Metallothionein; NMR: Nuclear magnetic resonance.

Cancer, Diabetes mellitus, Atherosclerosis, and Other Related Diseases

In resting cells, most MTF-1 localizes in cytoplasm from which it is translocated to the nucleus under several different stress situations [50, 51]. The finding that MTF-1 requires elevated concentrations of zinc for strong binding to DNA suggests that MTF-1 is activated by allosteric regulation of DNA binding through binding of metals to the transcription factor itself [48, 52, 53]. Although heavy metals readily induce MT gene transcription in cultured cells, none of them can substitute zinc in cell-free DNA binding reaction of MTF-1 [52]. The most likely scenario is the replacement of zinc by other heavy metals in cellular and/or extracellular zinc storage proteins, which leads to concomitant activation of MTF-1 by the released zinc. In addition, MTF-1 can be phosphorylated on metal induction, as a result of the activation of a complex kinase signaling transduction pathway which includes protein kinase C, phosphorinositol-3 kinase, c-Jun N-terminal kinase, and a tyrosine-specific kinase [54].

The accumulation of the MT 1/2 protein as detected through immunohistochemistry has different prognostic significance in various human tumors [55]. In tumors such as colonic and bladder cancers, MT 1/2 overexpression is frequently associated with well differentiated and lower histological grade tumors [56, 57]. Whereas in tumors such as ductal breast cancer, cervical carcinoma, endometrial carcinoma, and pancreatic carcinoma, MT over expression appears to be predominantly associated with more aggressive and higher-grade tumors [58, 59]. The expression of MT was also analyzed in normal breast tissue and in variety of benign, preinvasive, and malignant breast lesions. Normal breast tissue did not stain for MT [60]. The available information on the character and consequences of MT overexpression associated with human cancer is presently too limited to offer a complete understanding.

Moreover, MT may potentially activate certain transcriptional factors by donating zinc. A number of studies have shown an increased expression of MT in various human tumors of the breast [61, 62], colon, kidney, liver, lung, nasopharynx, ovary, prostate [63, 64], salivary gland, testes, thyroid, and urinary bladder [64]. However, MT is down-regulated in certain tumors such as hepatocellular carcinoma and liver adenocarcinoma. The first and second MT protein has been shown to be a useful prognostic and diagnostic marker in a variety of human cancers. Subset of MT protein has been documented to be overexpressed in a sub-set of human breast cancers and that overexpression correlates to poor prognosis. There is strong evidence that overexpression of MT isoform 3 (MT-3) protein correlates to poor disease outcomes in subset of human breast cancers [64]. They reveal that certain isoforms are expressed in specific cell types. The factors which can influence MT induction in human tumors are not yet understood.

Projection for Future Studies

The four isoforms of MT are identified in mammals, three of which, MT-I, II and III are found in the central nervous system and MT-IV is found in the skin and upper gastrointestinal tract. tract. In the past decades, mostly isoforms such as MT-I, MT-II, MT-III, and MT-IV. MTI and II were demonstrated and the studies have mainly focused on oncogenesis, tumor progression, therapy response, and patient prognosis. Studies have reported increased expression of MT-I and II mRNA and protein in various human tumors; such as breast, kidney, lung, nasopharynx, ovary, prostate, salivary gland, testes, urinary bladder, cervical, endometrial, skin, and pancreatic cancers, as well as in melanoma and all, where, in some cases, MT-I and II expression correlates with tumor grade/stage, chemotherapy/radiation resistance, and poor prognosis. It is especially important in case of heart cells. Analysis of MT expression in tumor cells may be useful in choosing a method of treatment. It is difficult to determine whether increased expression of MT is only an inducing factor of the development of the carcinogenesis, its malignances, and multidrug resistance, or it is a factor inhibiting the induction and development of cancer.

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Conflict of Interest: None declared.

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