Open access Journal of
Neurology & Neurosurgery
ISSN: 2476-0501

Juniper Publishers
key to the Researchers

Mini Review
Volume 14 Issue 2 - October 2020
DOI: 10.19080/OAJNN.2020.14.555884

Open Access J Neurol Neurosurg

The Role of Metallothionein-3 in Brain Diseases

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Submission: September 28, 2020; **Published:** October 09, 2020

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Abstract

Metal imbalance plays a key role in diverse brain pathologies. Metallothionein-3 (MT3), which is abundant in the central nervous system (CNS), has affinities for various metals. Abnormal expression and distribution of MT3 in the brain is closely linked to many CNS dysfunctions, including acute brain injuries due to oxidative stress caused by altered metal mobility as well as neurodegenerative diseases from abnormal protein circulation and cytoskeletal dysfunction. MT3 has a high affinity to zinc, iron, and copper, and is capable of maximal binding to seven zinc metals within its structure. Zinc-binding MT3 has a different function from copper- or iron-binding MT3. Independent of its role in other organs, there are many reports describing the role of MT3 in CNS homeostasis. Here, we aimed to provide an in-depth understanding of MT3 by describing its effect on CNS function and association with diverse CNS diseases.

Keywords: Actin; Autophagy; Lysosome; Metallothionein; Neurodegenerative disease; Oxidative stress

Introduction

Transition metals play diverse roles in the physiology of the central nervous system (CNS). They may be present in the free from or attached to different proteins. Intracellular labile metals are dynamic and involved in a variety of cellular homeostasis processes including immunity, metabolism, growth, and differentiation [1]. In addition, labile metals may cause cellular toxicity. The most prominent characteristic of metal toxicity is the close association with redox imbalance because most cellular metals including copper, iron, and zinc contribute to Fenton reaction and the regulation of reactive oxgen species (ROS) including peroxides, superoxides, hydroxyl radicals, singlet oxygen, and alpha-oxygen [2]. This is why proper concentration of transition metals is important for the normal biological activity of cells. Exogenous sources of ROS may be pollutants, heavy metals, smoke, drugs, and radiation [3]. ROS may be endogenously stimulated by a variety of biochemical reactions in the cells and within cellular organelles such as mitochondria, endoplasmic reticulum, and peroxisomes [4,5]. Aging also causes the ROS levels to rise in the body. Transient increase in ROS is beneficial for the immune system and may initiate apoptosis. However, chronic increase in ROS levels can cause many diseases such as cancer, inflammatory disease, neurodegeneration, cardiac diseases, and vascular diseases [6]. Metallothioneins (MTs) are one of the transition metal-binding proteins, and their affinity to metals is flexible, depending on specific cell conditions. Since its discovery in the horse renal cortex as Cd-binding proteins [7], many researchers have reported the functional features of these proteins. MTs in humans are divided into four subfamilies, designated as MT1, MT2, MT3, and MT4, and are differentially distributed in tissues. MT1 and MT2 are ubiquitously found in every organ; however, MT3 and MT4 are expressed in the CNS and stratified squamous epithelia, respectively [8]. Of these, MT3 is known as the growth inhibitory factor in the CNS with high affinity for zinc and copper; it is of high relevance in Alzheimer's disease (AD) [9]. Here we address the characteristic functions of MT3 in the CNS by focusing on the different brain disease conditions.

Structural characteristics of MT3

MT3 is a small protein with a molecular weight of ~7 kD. It contains ~ 20 cysteine resides with thiol groups, which provides it the ability to possibly bind with diverse metals depending on the intracellular metal concentrations and the stress situation. Most functions of MT1 and MT2 are mainly focused on their capacity for regulation of metal homeostasis and redox control [10]. However, MT3 has its own structure, and this enables dynamic changes in its structure and consequent differentiation from other MTs

in function [11]. All MTs have common structure: they have α (C-terminal)- and β (N-terminal)-domains, each containing eleven and nine cysteines with thiol groups, comprising a four-metal cluster (M_4S_{11}) in the C-terminal α-domain and a three-metal cluster (M_3S_9) in N-terminal β-domain [12]. The sulfur ligands residing in cysteine improve the chance for bonding with various metals, thus enabling the molecule to bind with up to seven atoms of Zn or Cd [13].

The first unique structure in MT3 is an EAAEAE (55-60) insert in the α-domain in the C-terminal. This site is located far from the metal-thiolate cluster and is less restricted, thereby making alternative conformation possible [14]. The second unique structure in MT3 is the KCE (21-23) sequence in the β-domain of the N-terminal. This site regulates interaction with the thiolate group of MTs, thus leading to the releases of zinc ions [15]. Lastly, the TCPCP motif of the β-domain of the N-terminal is representative of MT3's functional structure. This site is very special for the MT3 molecule because it is the main site associated with its activity as a growth inhibitory factor (GIF) [16,17]. The TCPCP sequences are flexible, thus contributing to the dynamics of the β-domain of MT3 [14]. Only MT3 possesses Thr5, and this amino acid plays a key role in the optimal GIF activity of MT3 [16].

Functions of MT3

Unlike MT1/2, MT3 has a broader range of functions in cells. The structural characteristics of MT3 have already mentioned; here we enumerate the various functions of MT3. MT3 exhibits responsiveness to ROS similar to that exhibited by MT1/2. The flexible β-domain enables an easier access for the larger molecules to the metal-thiolate cluster of MT3, which results in changes in the cluster structure of the protein when it reacts against diverse radicals. This is proven by the higher reactivity of nitric oxide(NO) and S-nitrosothiols, which are molecules with larger stoichiometric characteristics, when compared to small molecules such as hydrogen peroxide and superoxide radicals [18]. MT3 regulates metals in the cytosol as well as within a variety of cellular proteins. There are controversial reports about MT3-triggered response to a great number of oxidative stressors. Several reports have proven that MT3 protects cells by swapping out the intracellular ROS, the stress-inducing component, into the cysteine-thiol cluster of MT3, thus rescuing the cells from damage [19]. On the other hand, another study reported that MT3 knock-out (KO) mice showed less neuronal or astrocytes damage than wild-type (WT) mice via reduced release of metals like zinc from inside each metal-thiol cluster [20,21]. Interestingly, MT3 did not show any alteration in gene expression in response to oxidative injury, whereas MT1/2 showed significant increase in ROS-regulated gene expression under a similar stress condition [22]. This suggests that MT3 may have functions other than ROS control. Another function of MT3 is the regulation of actin cytoskeleton. Actin cytoskeleton has many roles in the normal cell homeostasis such as maintenance of cellular structure and shape, export or import of diverse molecules via endocytosis or exocytosis, and cellular cytokinesis and division via chromosomal segregation [23]. Recently, it has been postulated that MT3 regulates cAbl activity via controlling filamentous actin (F-actin) and cAbl binding in epideral growth factor (EGF)-stimulated cortical astrocytes [24], and the TCPCP motif is at the center of this reaction. In line with this, MT3-induced actin dynamics may control amyloid beta $(Aβ)_{1-42}$ endocytosis into cortical astrocytes [25], suggesting its possible role in the clearing of Aβ plaques in patients with AD. MT3 is also associated with lysosomal biogenesis. In the cortical astrocytes of MT3 KO mice, lysosome-associated membrane proteins (Lamp) 1/2 were hyperglycosylated and lysosomal enzymes such as cathepsin D, cathepsin L, acid phosphatase, and neuramidase were decreased [20]. These alterations protected the MT3 KO cortical astrocytes from lysosomal rupture, and thereby apoptotic death via rupture of the diverse lysosomal enzymes. Although the correct mechanism should be elucidated in detail, abnormal localization and expression of vacuolar-type H^+-ATPase subunit Voa1 (V-ATPase Voa1) and resultant slight increase in lysosomal pH may, in part, be associated with these phenomena in MT3 null astrocytes [26].

Lysosomal biogenesis is very important in the process of normal autophagy. In conjunction with the modified lysosomal functions seen in cortical astrocytes of MT3 KO mice, it has been reported that MT3 KO cortical astrocytes showed accumulation of enlarged autophagosomes without any fusion with lysosomes [27]. Increased lysosomal pH caused stagnation of autophagy and resulted in accumulation of bulky molecules inside the cells [28]. Protein recycling via optimal degradation is pivotal to maintain cell health. However, if the smooth flow of macromolecular cycling in a living body is stagnated, normal cellular signaling may be impaired, resulting in metabolic disorders. In addition to autophagy, release of zinc from MT3 also controls apoptosis via the upregulation of the fork-head box protein 1 (FOXO1), p38 kinase, caspase9, and poly (ADP-ribose) polymerase (PARP) [21, 29]. It is not clear if zinc liberated from MT3 is directly associated with all these alterations or not. However, MT3 may function as a key modulatory molecule in intracellular homeostasis.

MT3-associated diseases

MT3 may be associated with a variety of diseases because it controls multiple processes in the cells. As explained previously, MT3 started getting attention due to its role in ROS regulation. MT3 is dominant in the CNS, and zinc liberated from MT3 has a role in the process of neuronal death after ischemic brain injury [30]. In kainate-induced seizure, MT3, to a large extent, causes an increase in intracellular zinc by releasing it from within itself [31, 32]. This injures hippocampal neurons via zinc-induced oxidative stress. The relevance of zinc in seizure-induced damage in MT3 WT mice also proven by the application of a zinc chelator, N, N, N' N'-tetrakis-(2-puridylmethyl) ethylenediamine (TPEN), because TPEN treatment almost completely blocks the

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intracellular zinc-mediated toxicity [32]. Besides ROS regulation, the function of MT3 on actin cytoskeleton is associated with many cellular processes. The role of actin in the endocytosis process is known. Destruction of actin polymerization either by in vitro MT3 silencing or by in vivo MT3 KO contributes to abnormal endocytosis in cortical astrocytes, preventing normal signal transmission or uptake of abnormal proteins via astrocytic endocytosis [24, 25]. Interestingly, in an animal model with diverse neurodegenerative diseases, there was injured expression of MT3 mRNA and the protein level was significantly altered. In the case of AD, the MT3 level was reduced in the vicinities of senile plaques [33]. In patients with amyotrophic lateral sclerosis (ALS), the intensity of immunostaining for MT3 in astrocytes is closely related to the number of motor neurons in the ventral horn [9]. During ALS progress in mice, MT3 KO significantly shortens survival time [34]. In addition, the level of MT3 was reduced in the brain of a patient with Parkinson's disease (PD) [35]. However, the mechanism of action of MT3 in different neurodegenerative diseases should be elucidated in detail. Nevertheless, it is safe to assume that in most cases, abnormal MT3 expression causes an imbalance in ROS or lysosomal function, which in turn induces Aβ and mutant huntingtin (mHtt) aggregation and deposition in the brain of AD or huntington disease (HD) animal models [36].

MT3 is also expressed outside the CNS, in organs such as pancreas, testis, and prostate [37]. Consistently, MT3 mRNA is highly expressed in pancreatic islets and is closely associated with zinc dysregulation. It has been reported that MTs protect β-islet cells from oxidative stress inducers, thereby rescuing animals with obesity and type 2 diabetes from disease severity [37]. This report is consistent with the study about polymorphisms of MT1A and MT2A in humans showing a greater risk of progression of type 2 diabetes and its complications [38]. MT3 null mice were less sensitive to streptozotocin (STZ)- and Sodium Nitroprusside (SNP)-induced toxicity due to reduced Zn release linked with oxidative injury and decreased phosphodiesterase 3a (PDE3a) expression [39].

MT3 is also associated with cancer tissues. In tumor cells, ROS may be overproduced because of excessive metabolism. Diverse stressors-induced ROS accumulation may result in DNA mutation of proteins specifically essential for cell cycle control, leading to irrecoverable cell proliferation. Therefore, MT3-triggered scavenging of the excessive ROS via swapping various toxic metals or radicals may prevent carcinogenesis. Moreover, autophagy activation acts as a tumor suppressor in the early stages of a tumor. However, once the cells become malignant, autophagy may contribute to tumor survival [40]. Therefore, autophagy induction during tumor treatment may induces side effects that eventually result in the survival of tumor cells. This is proven by the post-radiation survival of glioma cells seen in MT3 KO [41] and contribution of MT3 to the growth inhibitory effect on MCF-7 breast cancer cells [42]. Recently, the expression level or polymorphisms of MT3 have been used as diagnostic and progression indicators of various tumors including colorectal cancer, breast cancer, hematological malignancies, and gastric cancer [43].

Conclusion

MT3 expression is present in several organs and it has unique features that sets it apart from the other MT subtypes. The other subtypes of MTs are primarily involved in various diseases through ROS regulation. However, in addition to regulating ROS, MT3 is more delicately involved in various intracellular processes. In other words, MT3 controls lysosomal biogenesis by catching or releasing zinc from its own structure, thereby regulating zinc concentration in lysosomes, changing lysosomal pH appropriately, modifying lysosome membrane proteins, and regulating the activities of many enzymes in lysosomes. For this reason, abnormal MT3 expression changes lysosome dynamics and consequently affects the autophagy process via blocking a fusion process between the lysosome and the autophagosome. The sequential processes may cause a variety of neurodegenerative diseases, diabetes, and cancers. Although further research on how MT3 specifically affects each intracellular process is still needed, many researchers have shown that MT3 polymorphisms cause cancer and various abnormal metabolic conditions. Therefore, in-depth study on customized targeting of MT3 in a variety of diseases should be performed in future.

Acknowledgement

This work was supported by Basic Science Research Program through the National Research foundation of Korea (NRF) funded by the Ministry of Education (2016R1D1A1B04934383). It was also supported by Jeonbuk National University, Republic of Korea..

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