Metallothionein and cancer

Soňa Křížková1, Markéta Vaculovičová1, Vojtěch Adam1 and René Kizek1,*

1 Central European Institute of Technology, Brno University of Technology, Technicka 3058/10, CZ-616 00 Brno, Czech Republic - European Union, E-Mails: kizek@sci.muni.cz (R.K.)

* Author to whom correspondence should be addressed; E-Mail: kizek@sci.muni.cz; Tel.: +420-5-4513-3350; Fax: +420-5-4521-2044.

Received: 6.5.2015/ Accepted: 13.5.2015/ Published: 1.7.2015

Metallothioneins (MT) are small (molecular weight in range 500 – 1400 Da) intracellular proteins rich in cysteine content. In humans four main isoforms of MTs have been discovered so far – MT-1, MT-2, MT-3 and MT-4. All of MTs functions – heavy metals binding, antioxidative, regulation and immunomodulation are involved in MTs roles in cancer. MTs role is double-edged in carcinogenesis; in healthy cells with high MT content it has protective effects, while in healthy cells with low MT content, carcinogenesis via environmental factors occurs, on the other hand, at cancer-transformed cell the high MT content increases the tumour malignancy and chemotherapeutics resistance. Expression of MT can be used as marker of tumour diseases. Increased level of MT in serum or full blood was found in many cancer diseases and can be used as early stage biomarker. To decrease tumour resistance, or on the other hand, to improve non-target cells tolerance to chemotherapeutic multiple approaches are tested, including specific increasing or decreasing of MT expression based on specific compounds or targeted gene therapy.

Keywords: metallothionein; cancer; biomarker; chemoresistance; epigenetics

1. Metallothionein

Metallothioneins (MT) are small (molecular weight in range 500 – 1400 Da) intracellular proteins rich in cysteine content. In 1957 MT was discovered in horse liver as cadmium binding and detoxification protein [1]. With progressing research it has been discovered, that metallothioneins are found in all kingdoms – bacteria, animals, fungi and even plants and that they are involved in numerous cell processes according their isoform, oxidation state and metals content [2].

In humans four main isoforms of MTs have been discovered so far – MT-1, and MT-2, which are ubiquitous, MT-3 and MT-4, which are specific for neuronal tissue, but their expression also in skin was found. Human MT genes are localized on chromosome 16q13 and are encoded by a multigene cluster of closely linked genes. Genes for MT consist of 11 MT-1 genes and one gene for every other MT isoform (the MT-2A gene, MT-3 gene and MT-4 gene) [3]. A gene called MT-like 5 (MTL-5) that encodes a testis-specific MT-like protein called tesmin was described in the 11q13 [4]. A number of other MT or MT-like genes and pseudogenes with significant homology to functional MT genes exist in human genome, but their functionality is unknown.

2. Roles of metallothionein in the cells

The first discovered and still not fully understood roles of MT-1 and MT-2 are transporting of essential heavy metals, detoxification of toxic ones and protection against oxidation stress. MT by interaction with other proteins fulfils its function, resulting in different effects in the organism [5]. Interaction of MT with other proteins occurs either directly or via heavy metals administration and redox reactions.
Interaction of MT with ferritin, which causes a redox reaction leads to reduction of Fe\textsuperscript{3+} stored in ferritin with consequent releasing of harmful Fe\textsuperscript{2+} [6]. Interaction of MT with GSH/GSSG modulates Zn transfer between MT and zinc-binding proteins [7]. Apo-MT is able to deactivate Zn-transcription factors and Zn-dependent enzymes, while Zn-MT can activate them. Interaction of MT with zinc-dependent enzymes such as carbonic anhydrase, Cu/Zn SOD, δ-aminolevulinic acid dehydratase via zinc binding is known [5,8]. After interaction of MT with endocytic LDL receptor megalin the uptake of CdMT occurs, resulting in disruption of proximal tubules [9]. MT is involved in many cellular processes, which are regulated by protein-protein interaction. The most known are transcription, apoptosis, immunomodulation and cancerogenesis, interacting with NF \kappa B, p53, specificity protein 1 (Sp1), transcription factor IIA (TFIIA), estrogen receptor (ER), Gal4, and tramrack (TTK), matrix metalloproteinasises and other [5,10].

MT-3 has been discovered as neuronal growth inhibition factor. It is involved in growth of neuronal tissue, but its expression has also been found in skin, and epithelial tissues. It also binds heavy metals, but its main function is regulation of neuronal development [11].

MT-4, discovered few years ago is the least known MTs isoform. It is found in stratified squamous epithelia, including the oesophagus, upper stomach, tail, footpads and neonatal skin [12]. It helps to regulate stomach acid pH, taste and texture discrimination of the tongue and help protect against sunburn and other skin traumas [13].

3. Connection of metallothionein with cancer diseases

All of MTs functions – heavy metals binding, antioxidative, regulation and immunomodulation are involved in MTs roles in cancer. MTs role is double-edged in carcinogenesis, in healthy cells with high MT content it has protective effects, while in healthy cells with low MT content, carcinogenesis via environmental factors occurs, on the other hand, at cancer-transformed cell the high MT content increases the tumour malignancy [14]. Proliferative, anti-apoptotic function of MTs, (de)activation of transcription factors, ROS scavenging are beneficial for cancer cell to survive, proliferate and defend against organisms’ immune system.

All isoforms, except the least known MT-4 have been found to be involved in cancer. However, according to last findings MT-4 – expression at mRNA level was found in lung cancer (NSLC) [15] and squamous cell carcinoma [16]. The most about MT up/down regulation is known about MT-1 and MT-2 [8,17-19]. Disclosed MT expression as a useful diagnostic factor for tumour progression and drug resistance was reported in a variety of malignancies e.g. leukaemia, melanoma, breast, ovarian, renal, lung, pancreatic, gall bladder, oesophageal, and basal cell carcinomas [20-27]. One may suggest that MTs may lead to a protection of tumour cells against apoptosis and support the metastatic behaviour of tumours and/or cancer cell proliferation. On the other hand in some other studies devoted to colorectal and bladder cancer and others, no significant correlation between MT expression and prognosis was observed [28,29]. In recent years, common MT polymorphisms were identified and associated with, particularly, western lifestyle diseases such as cancer, complications of atherosclerosis, and type 2 diabetes mellitus along with related complications [30]. MT is often downregulated at epigenetic level in numerous cancers [31-36].

MT-3 expression was found to be corrected with lung cancer [20], skin cancer [37], breast cancer [38], prostate cancer [39], oesophageal squamous cell carcinoma [40], bladder cancer [41] and renal carcinoma [42]. Moreover, MT-3 is a putative tumour suppressor gene, that is frequently inactivated in paediatric acute myeloid leukemia [33].

4. Metallothionein and resistance to chemotherapeutics

In MT-related chemoresistance heavy metals chelation and antioxidative functions are involved. It can contribute not only to cancer cell survival, but also to decreasing of side effect of chemotherapy, especially anthracyclines [8]. To decrease tumour resistance, or on the other
hand, to improve non-target cells tolerance to chemo-therapeutic multiple approaches are tested, including specific increasing or decreasing of MT expression based on specific compounds or targeted gene therapy, including using antisense mRNA, siRNA, microRNA, and DNA methylation, can be considered [8,38,43].

5. Metallothionein as cancer biomarker

From numerous studies it is known, that expression of MT both on nucleic acids and protein level can be used as marker of tumour diseases [15,26,44,45]. Also methylation of MT promoters has been shown to be usable as a biomarker [34]. Increased level of MT in serum or full blood has been found in many cancer diseases and can be used as early stage biomarker [26,45,46]. Also changes in Zn isotopes in tumour tissues can be usable for detection of cancer. The authors hypothesize, that higher content of light isotopes in tumour tissue than in control tissues (both non tumour and healthy volunteers) is caused by preferential chelation of light isotopes by MT via SH groups [47].

6. Conclusion

MTs role is double-edged in carcinogenesis; in healthy cells with high MT content it has protective effects, while in healthy cells with low MT content, carcinogenesis via environmental factors occurs, on the other hand, at cancer-transformed cell the high MT content increases the tumour malignancy and chemotherapeutics resistance. Expression of MT both on nucleic acids and protein level can be used as marker of tumour diseases. Increased level of MT in serum or full blood has been found in many cancer diseases and can be used as early stage biomarker. To decrease tumour resistance, or on the other hand, to improve non-target cells tolerance to chemo-therapeutic multiple approaches are tested, including specific increasing or decreasing of MT expression based on specific compounds or targeted gene therapy, can be considered.

Acknowledgement

The financial support from League against cancer Prague (project 18257/2014-981) and CEITEC CZ.1.05/1.1.00/02.0068 is greatly acknowledged.

Conflicts of Interest

The authors declare no conflict of interest.

References


Wei, H.; Desouki, M.M.; Lin, S.; Xiao, D.; Franklin, R.B.; Feng, P. Differential expression


The article is freely distributed under license Creative Commons (BY-NC-ND). But you must include the author and the document can not be modified and used for commercial purposes.