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Zinc and metallothioneins in the cancer

ESSENTIAL ROLE OF ZINC

Zinc (Zn) belongs to trace elements of great significance in the growth and development of an organism. The principal working mechanism of this microelement is based on its participation in the structures of macromolecular compounds and activation of many enzymes involved in metabolic processes. In nature, over 300 zinc-dependent enzymes have been, identified. Zinc-enzymes represent all classes of enzymes and take part in the synthesis and decomposition of proteins, carbohydrates, fats and nucleic acids. Zinc plays a significant role in gene expression; it inducts enzymes participating in DNA synthesis both during the process of cell division and in cell differentiation. Moreover, zinc stabilizes the structure of DNA and RNA and influences their synthesis and decomposition. It also takes part in hormone regulation. It affects synthesis and excretion, and modulates the peripheral hormone activity (1,5,14).

Studies have shown that zinc plays an important role in gene expression (14). An essential part of gene expression and regulation is the binding of a regulatory protein to the recognition sequence of the appropiate gene. Many such proteins have in their structure a domain that binds to DNA. Miller et al. (13) reported that the Xenopus transcription factor IIIA (TFIIIA) contains small sequence units repeated in tandem, and they proposed that each unit is folded around a Zn atom to form separate structural domains. Similar units have been found in the amino acid sequence of other transcription factors, and a commonly used structure motif for DNA recognition has emerged conveniently called the zinc finger.

FUNCTIONS OF METALLOTHIONEINS IN THE ORGANISM

Metallothioneins (MTs) are a class of low molecular mass (6–7 kDa), cysteine-rich proteins which bind with high affinity d metal ions such as Zn(II), Cu(II), and Cu(I). One suggested role for MT lies in the handling of heavy metal ions in the maintenance of cellular homeostasis of essential trace metals, such as zinc and copper, and in the detoxification of physiologically harmful metals, such as Hg(II) and Cd(II) (2,4,6).

Metallothioneins have been isolated from a wide range of tissues, including liver, kidney, pancreas, and intestine. The an immunologic techniques for their detection have improved, metallothionein have been found in most other tissues, including brain, thymus, bone marrow, and reproductive organs. Detection by subcellula fractionation indicates that metallothioneins occur principally in the cytosol, but immuhistochemical studies have consistently revealed their presence also in nuclei. Although metallothioneins are mainly of intracellular origin, they also occur in small amounts in extracellular fluids such as plasma, bile, and urine (2).

The concentration of the protein in tissues is highly variable and is induced by many nutritional, physiological, and developmental factors (10). For example, concentrations are greatly decreased in tissues of zinc-deficient animals and are increased after imposition of many types of stress or metal administration. They are generally elevated during fetal development and vary dramatically among species.

The characteristic features of metallothioneins are their low molecular weight and their unusual amino acid composition: cysteine accounts for 30% of the residues and aromatic acids absent. Sequence studies have shown that the distribution of the cysteine residues along the polypeptide chain is fixed, regardless of the source or isoform of the protein (2,4).

Another main feature of metallothioneins is their high metal content, with 7 gram atoms of cadmium or zinc per mole or up to 12 gram atoms of copper per mole. This content is equivalent to one metal atom per three or two cysteine residues, respectively. The cadmium- and copper-induced metallothioneins usually contain also zinc as a secondary metal.

ZINC AND METALLOTHIONEINS IN THE CANCER

In the conducted experiments an increase of zinc content was found in the neoplastic tissue. The increase was perhaps caused by more rigorous demands of the neoplastic cell for zinc imposed by its more dynamic metabolism. An elevated zinc level is noted in many types of neoplastic tissue (11,12,16).

The examined neoplastic tissue also exhibited an elevated metallothionein level. An increased intracellular metallothionein expression was found in many human and animal neoplasms (9.17–19). MT synthesis induction is stimulated by such factors as metallic ions, free radicals, cytokines, lymphokines and stress (15). Experiments conducted on animals show an MT increase in the neoplastic tissue. However, MT synthesis induction was also present in a liver free from a neoplastic process. Also, the concentration of MT's in the plasma of the blood grew together with the MT concentration increase in the liver.

The mechanism that governs the induction of MT synthesis is not well known. Research shows that cytokines like interleukin 1, interleukin 6, tumour necrosis factor (TNF) or interferon may induce MT synthesis. It is not impossible that neoplastic cells can release cytokines into the bloodstream that induce MT synthesis both in a tumour and in a neoplasm-free liver. The existence of the interdependence between the neoplasm and MT induction in the liver is supported by the fact that after surgical removal of tumour proper values return (18).

In our studies (7) we found an increased level of zinc in breast cancer tissues, which may be justified considering their increased metabolism. In breast cancer tissues we also found and increased level of metallothioneins. Correlation coefficient of the studied parameters testify to strict interrelation between the level of zinc and the content of metallothioneins. It is very probable that zinc accumulated in the cell induces metallothionein synthesis. The presence of a regulating MRE (metal response element) sequence in the gene for metallothionein enables direct induction of MT synthesis by means of metals (15).

The experiments showed the function of matallothioneins as proteins taking part in the metabolism of metals that play an important role in the growth and development of the organism. In this case MT's are a reservoir of zinc ions. Metallothioneins equip newly synthesised apoproteins and regulatory molecules in zinc (20). This is a reason why zinc concentrates in the area of hyperplasia, where an active process of proliferation is under way (3,21).

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SUMMARY

Metallothioneins are intracellular macromolecules having a remarkable ability to bind metallic ions. These proteins bind metals indispensable for the organism as well as those which enter the organism incidentally as a result of environmental pollution (e.g. cadmium or lead). The elements which are vital for the organism, and for the homeostasis of which metallothioneins are responsible, are mainly zinc and copper. In the conducted experiments an increase of zinc and metallothioneins content was found in the neoplastic tissue. The increase

was perhaps caused by more rigorous demands of the neoplastic cell for zinc and metallothionein imposed by its more dynamic metabolism.

Cynk i metalotioneiny w raku

Metalotioneiny są białkami wewnątrzkomórkowymi, posiadającymi zdolność wiązania jonów metali. Białka te wiążą zarówno jony metali niezbędnych dla ustroju, jak i metale, które dostają się do organizmu w sposób przypadkowy w wyniku kontaktu ze skażonym środowiskiem. Metale niezbędne dla ustroju, za których homeostazę odpowiedzialne są między innymi metalotioneiny - to głównie cynk i miedź. Z danych literatur oraz badań własnych wynika, że stężenie cynku i metalotionein wzrasta w zmianach nowotworowych. Ten wzrost może wynikać ze wzmożonego metabolizmu komórek nowotworowych.