evropský sociální fond v ČR
EVROPSKÁ UNIE
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY
OP Vzdělávání pro konkurenceschopnost
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Název: Changes in the levels of metallothionein in organisms exposed to doxorubicin

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Datum: 14.3.2014

Reg.č.projektu: CZ.1.07/2.3.00/20.0148

Název projektu: Mezinárodní spolupráce v oblasti "in vivo" zobrazovacích technik

Metallothionein

MT is highly inducible in biological systems under stress such as the presence of heavy metals, starvation, heat, inflammation…

MT functions as a potent antioxidant has been demonstrated in both *in vitro* and *in vivo* studies.

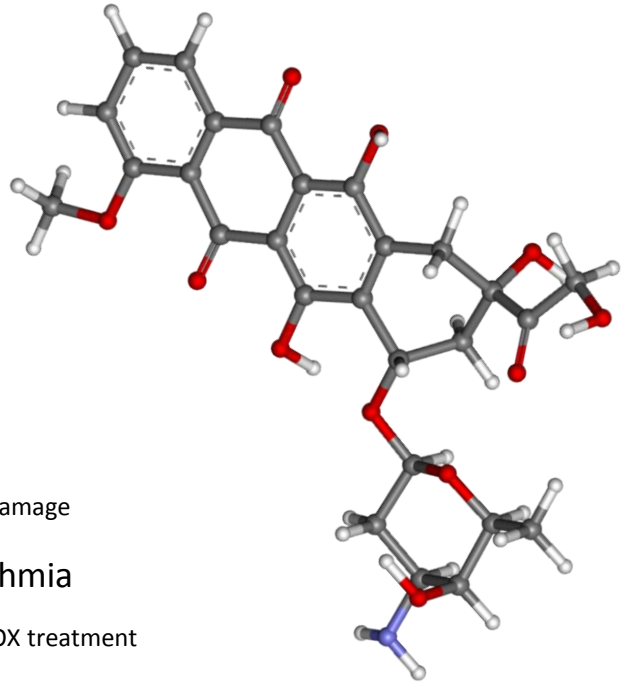
MT has been shown to scavenge hydroxyl radicals and to be more effective than GSH in preventing ROS-induced DNA degradation.

There is direct reaction of hydrogen peroxide with the sulfhydryl groups of MT.

The sulfhydryl groups in the MT are the preferential attacking targets of hydrogen peroxide compared with the other sulfhydryl residues from GSH and protein fractions.

Doxorubicin

Doxorubicin is a widely used and important chemotherapy agent though its application is limited by the incidence of cumulative cardiotoxicity.



3 types of DOX-induced cardiotoxicity:

1. Acute myocardial injury
   - most often in the form of arrhythmia
   - occurs immediately after a single dose of DOX
   - clinically manageable
2. Chronic cardiotoxicity
   - resulting in cardiomyopathy
   - more common and clinically most important form of damage
3. Late-onset ventricular dysfunction and arrhythmia
   - cardiomyopathy manifesting years to decades after DOX treatment

The chronic and late-onset cardiotoxicity is dose-related and produces significant morbidity and mortality.

The incidence dramatically increases at cumulative doses in excess of 550 mg/m^2 of body surface.

MT - DOX - heart

One of the proposed mechanisms for the cytotoxic effect of DOX is the production of reactive oxygen species during its intracellular metabolism.

In this context, many efforts have been made to increase myocardial antioxidant capacity as an approach to decrease the cardiotoxicity of DOX.

The heart is highly susceptible to oxygen radical injury because it contains considerably less protective mechanisms, such as glutathione, superoxide dismutase or catalase, than the other metabolic organs such as the liver or kidney.

Studies have been undertaken to explore whether MT can provide protection against DOX cardiotoxicity.

DOX toxicity was greatly suppressed in the heart of MT-overexpressing transgenic mice.

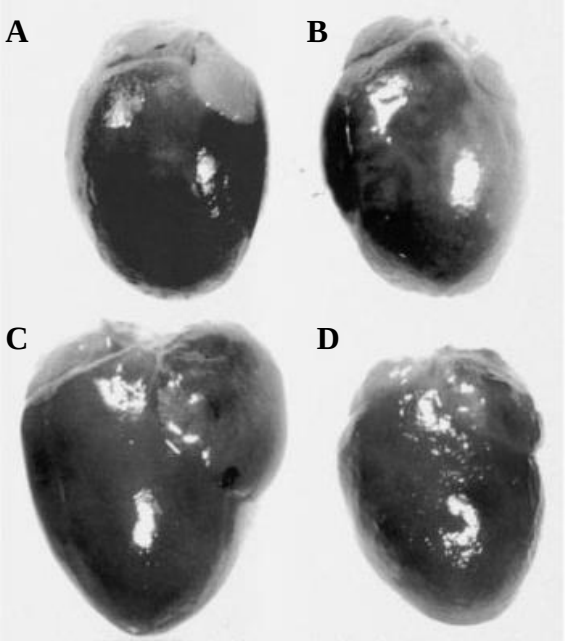
In these transgenic mice, MT was elevated only in the heart, not in the liver, kidneys, lungs, or skeletal muscles.

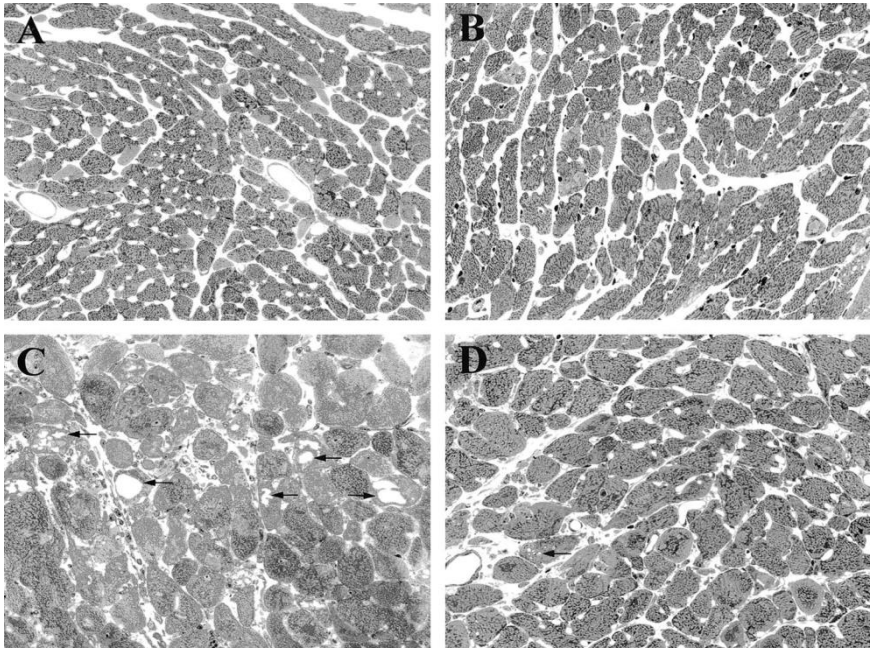
Other antioxidant components including GSH, GSH peroxidase, GSH reductase, catalase, and superoxide dismutase were not altered in the MT-overexpressing heart.

MT provided protection from DOX cardiotoxicity, including suppression of DOX-induced morphological changes.

Furthermore, MT prevents DOX-induced myocardial apoptosis through inhibition of DOX-activated proteinkinase and of DOX-induced mitochondrial cytochrome *c* release and caspase activation.

These cardiac protective effects of MT correlate with its inhibition of DOX-generated reactive oxygen species and lipid peroxidation.





		MT (mg/g tissue)
A	control Non-TG	5.3 ± 1.5
B	control TG	323.4 ± 13.7
C	DOX Non-TG	8.0 ± 2.4
D	DOX TG	273.8 ± 6.0

Mice hearts treated twice a week with 4 mg/kg for 7 weeks with saline/DOX.

MT vs. other thiols

Of all antioxidants found in cardiomyocytes, GSH is one of the most important antioxidants against ROS.

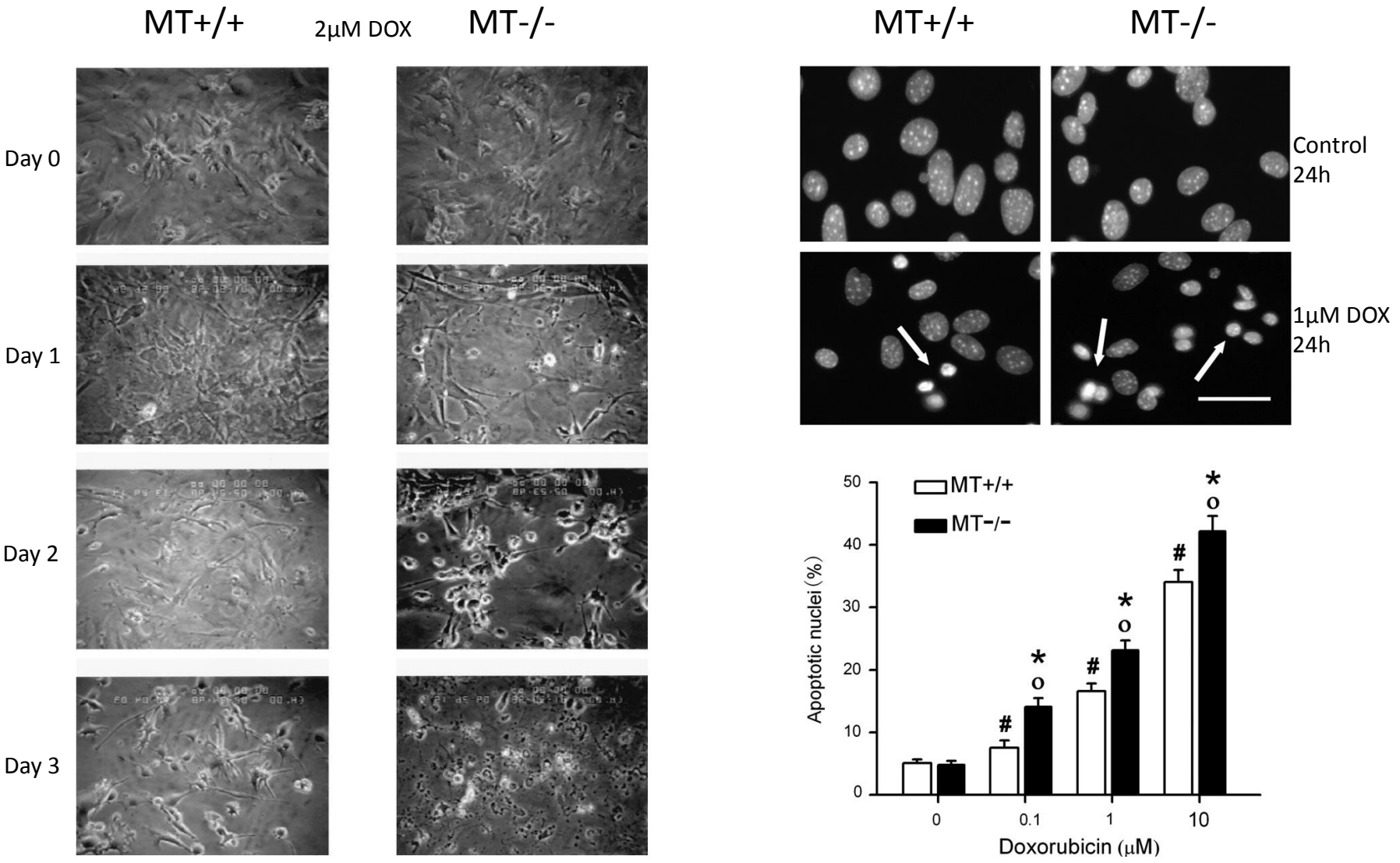
In vitro studies have shown that glutathione (GSH) and N-acetylcysteine (NAC), a precursor of GSH, can directly scavenge free radicals and reduce oxidant-induced cell damage and cell death.

NAC, GSH and MT almost completely inhibited DOX-induced increases of ROS production in MT+/+ cardiomyocytes, which may account for the eventual full protection against DOX-induced cell death.

However, both NAC and GSH can only partially protect against DOX-induced ROS production and cell death in MT-/- cardiomyocytes where MT-I/II is absent, indicating that these antioxidants cannot compensate the deficiency of MT in response to DOX-induced oxidative stress.

This finding particularly highlights the important role of MT as a cellular antioxidant in cardiomyocytes.

Therefore, exploring the protective effects of MT may provide a possible therapeutic strategy in prevention and/or treatment of DOX-induced cardiomyopathy.


MT+/+
2μM DOX
MT-/-
Day 0
Day 1
Day 2
Day 3
MT+/+
MT-/-
Control
24h
1μM DOX
24h
MT+/+
MT-/-
Apoptotic nuclei (%)
Doxorubicin (μM)
0
0.1
1
10
50
40
30
20
10
0
#
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MT - DOX - cancer

Patients who undergone post-surgical chemotherapy, those with low MT expression had a longer recurrence-free survival compared to their counterparts with high MT expression who experienced earlier relapses and emergence of treatment resistance.

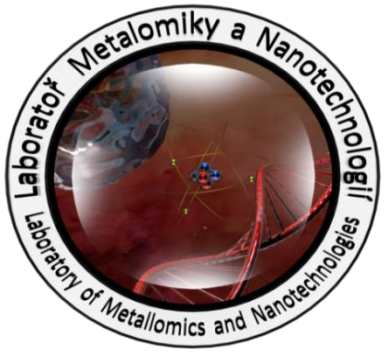
This supports findings relating MT over-expression to chemoresistance in breast carcinomas (MCF-7) as well oesophageal, ovarian, bladder, lung and prostate cancers (PC-3).

Cell cycle analysis revealed a corresponding increase in apoptosis in the MT down-regulated cells following doxorubicin exposure, showing that silencing the MT gene increased susceptibility to doxorubicin cytotoxicity.

If we identify the specific MT isoforms that can empower us with faster and more accurate predictions in terms of possible resistance and aggressive tumour profiles, then precise treatments can be tailored to such patients with greater speed and efficacy.

Furthermore, there is potential for MT to be developed as a molecular cancer target.

Acknowledgements



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Thank you for your attention!

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