Assessment of health risks of red sludge exposition

Ph.D. thesis

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INTRODUCTION

Red mud or red sludge is a waste product of the Bayer process, the principal industrial means of refining bauxite in order to provide alumina as raw material for the production of aluminium. The red color originates from iron (III)oxide, the main component, which can make up to 60% of the mass of the red mud. In addition to iron, the other dominant particles include silica, unleached residual aluminium, and titanium oxide. The mud is highly alkaline with a pH ranging from 10 to 13. Red mud represent one of the biggest disposal problems of industry, usually it is stored in large open-air ponds.

In October 2010, approximately 1.5 million m^3 of red mud flooded Kolontár and other nearby locations in Hungary in the Ajka alumina plant accident, killing ten people and contaminating about 40 km^2 of land. The accident had deleterious ecological, physiological and financial effects. After the accident several studies examined the geochemical and toxicological properties of red mud. The team leading containment and the clean-up process tried to estimate the risk of health damage caused by the exposure. Heavy metal contamination of the soil exceeded the "B" contamination limit. Cytogenetical measurements performed in 17 victims who suffered chemical burns as well as in 35 people taking part in the clean-up. Compared to non-exposed controls, no significant difference was found, so genotoxic effect of red mud exposure was not proved in the examined individuals. Other examinations studied the mutagenic and cytotoxic effects of red mud. Based on the results of MTT and Ames tests no genotoxical and citotoxical effects were found.

However, red mud-induced alterations on gene expression and microRNA have not yet been examined. Environmental factors induce cascades of epigenetic and genomic regulatory mechanisms essential for survival and adaptation, while early-immediate responses mostly involve alterations in gene expression, and changes in the expression of microRNA playing a key role in the process of cell cycle, apoptosis and differentiation. This indicates that certain miRNA being in charge for the regulation of mRNA are suitable to predict and follow-up various environmental effects. In my work I aimed to examine the early changes in the expression of onco- and suppressor genes (c-myc, K-ras, p53, Bcl2) and microRNAs (miR-21, miR-27a, miR-93, miR-221) caused by the intraperitoneal administration of red mud.

AIMS

1. Examination of expression patterns of onco/suppressor genes:
   I aimed to investigate whether changes of onco/suppressor gene expression were detectable following experimental red sludge exposition.
2. Examination of targeted microRNA expression profile:
   I aimed to investigate whether there are changes of microRNA expression due to experimental red sludge exposition
3. I aimed to clear in view of the expression of onco/suppresor genes and micrRNA:
   - what health risk consequences can be drawn concerning red sludge exposition
   - how results relate to the outcome of other examinations in connection with the red sludge disaster
4. I aimed to clear what conclusions could be drawn concerning the adaptation of onco/suppresor genes and microRNA as early biomarkers based on the results.

MATERIALS AND METHODS

Sample

Red mud was collected exactly from the place, and on the day of the disaster, in the valley of Torna. The red mud was stored at a dark, temperated place, in hermetically closed containers. Before using it, we dried the mud over 24 h on 60°C, then the samples were diluted with distilled water to the required concentration.

Experimental testing system

Five groups of CBA/Ca (H-2K haplotype) male mice were used for the experiment. The animals were six weeks old (20±4 g) and were kept in isolated cages. The control group consumed the standard laboratory pellet and tap water ad libitum. Four groups of mice received a single intraperitoneal gavage of dried red mud, 25 mg/body weight dose, (0.5 mg/0.1 ml solved in distilled water). The control group was treated with distilled water. One, three, six and twenty-four hours after red mud injection mice were autopsied after cervical dislocation. The liver, lung, kidneys, spleen and lymph nodes of the animals were removed and 100-mg samples were obtained from each tissue of the respective groups.

Total RNS isolation

After homogenization of the organs, total cellular RNA was isolated using TRIZOL reagent (Invitrogen, Paisley, UK). The RNA quality was checked by denaturing gel-electrophoresis, and absorption measurement was performed at 260/280 nm (A260/A280 was over 1.8).

Examination of messenger RNA expression

Ten μg RNA were dot-blotted onto Hybond N+ nitrocellulose membrane (ECL kit, Amersham, Little Chalfont, UK) and hybridized with chemiluminescently labelled specific probes for cmyc, p53, bcl2 and Kras genes. Isolation of RNA, hybridization and detection were performed according to the manufacturer's instructions. The membranes were rehybridized with constitutively expressed beta-actin gene as a positive control. The chemiluminescent signals were detected on X-ray films, scanned into a computer and evaluated by Quantiscan 2.0 software (Biosoft, Cambridge, UK). Gene expression is reported as percentage relative to the level of the expression of β-actin control.

Examination of microRNA ecpression

The expression of the investigated miRNAs was determined by quantitative real-time polymerase chain reaction (PCR). Total RNA was exposed to RNAase-free DNAase and 2 μl was reverse transcribed into cDNA using Transcriptor First Strand cDNA Synthesis Kit (Roche, Berlin, Germany). PCR primers were designed using the primer finder database (www.applied-science.roche.com) and were synthesized by TIB Molbiol, ADR Logistics, (Roche Warehouse, Budapest, Hungary). Sequence specific primers:
miR-21 forward: 5'- GCTTATCAGACTGATGTTGACTG -3',
reverse: 5'- CAGCCCATCGACTGGTG-3';
miR-27a forward: 5'- GCAGGGCT TAGCTGCTTG-3',
reverse: 5'- GGCGGAACTTAGCCACTGT-3';
miR-93 forward: 5'-AAGTGCTGTTCGTGCAGGT-3',
reverse: 5'- CTCGGGAAGTGCTAGCTCA-3',
miR-221 forward: 5'-CCTG GCATACAATGTAGATTTCTG-3',
reverse: 5'-AAACCCAGCAG ACAATGTAGCT-3'.

The PCR was performed on a LightCycler 480 PCR system (Roche, Berlin, Germany). The PCR reaction mixture contained: 5 μl of template cDNS, 3 μl of H2O, 2 μl specific primer and 10 μl Master mix. The reaction mixtures were incubated in LightCycler 480 Multiwell Plate 96, for 5 min at 95˚C, followed by 55 three-step amplification cycles (95˚C for 10 s, 55˚C for 20 s, 72˚C for 15 s).

miRNA expressions were determined by absolute nucleic acid quantification with 480 Light Cycler software (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

The statistical calculation of differences in expression was performed using Statistical Program for Social Science 19.0 (SPSS) software (IBM, Armonk, NY, USA). Student's t-test was performed between control and treated groups, and p-values less than 0.05 were considered statistically significant.

RESULTS

Using quantitative real-time polymerase chain reaction the expression profile of apoptosis-regulatory onco- and tumor suppressor genes and miRNAs in vital organs of CBA/Ca mice were evaluated at 1-, 3-, 6- and 24-h time point following intraperitoneal injection of red sludge. Statistical significanses indicated with star signs.

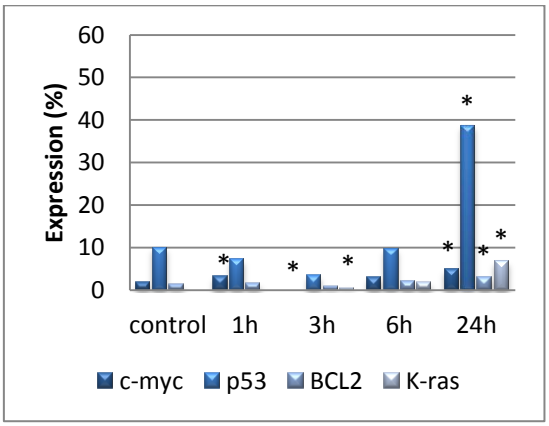

Figure 1. Onco- and tumor suppressor gene expressions in the liver

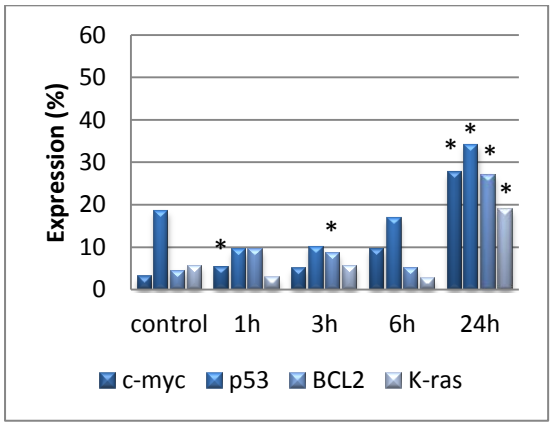

Figure 2. Onco- and tumor suppressor gene expressions in the spleen

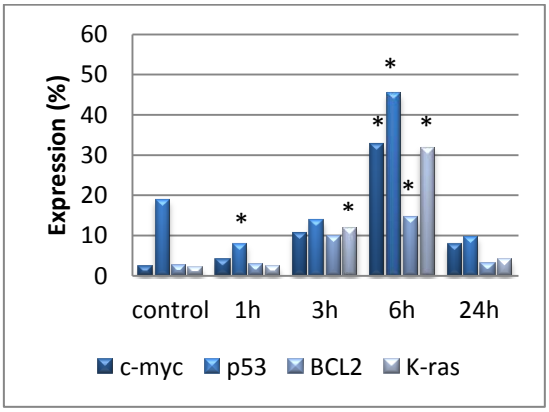

Figure 3. Onco- and tumor suppressor gene expressions in the lung

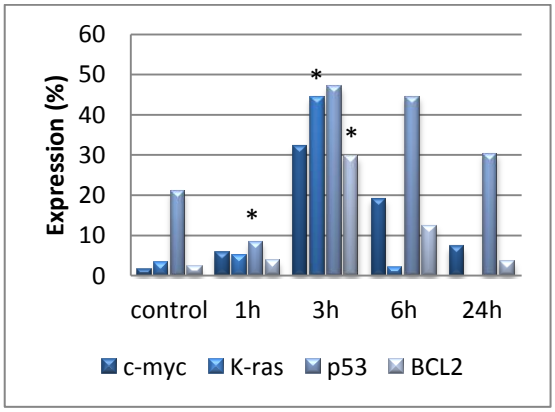

Figure 4. ábra: Onco- and tumor /suppressor gene expressions in the kidneys

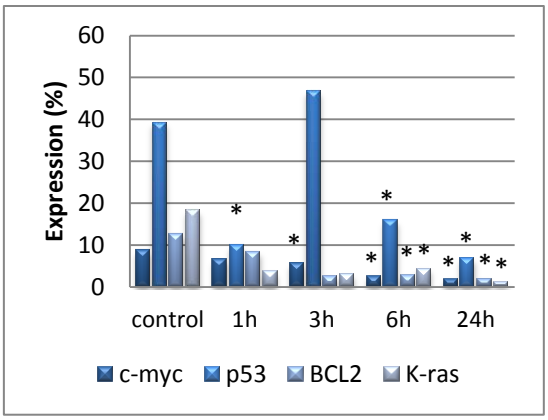

Figure 5. Onco- and tumor suppressor géne expressions in lymph nodes

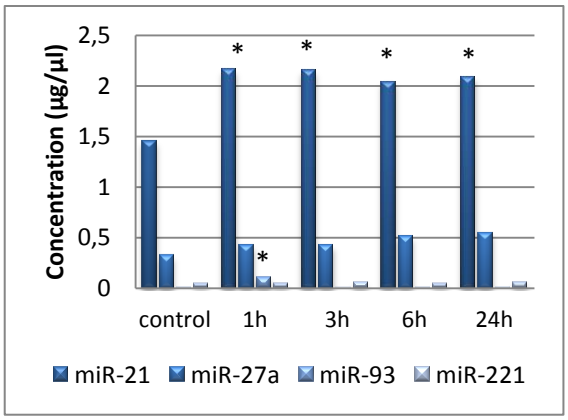

Figure 6. miRNA expressions in the liver

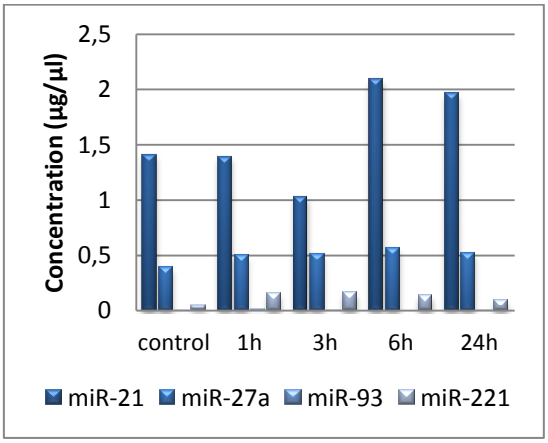

Figure 7. miRNA expressions in the spleen

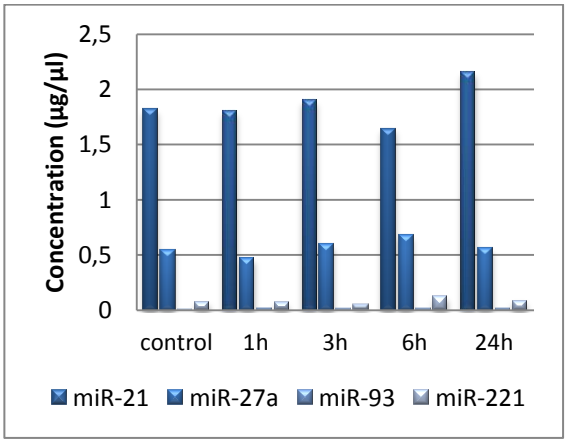

Figure 8. miRNA expressions in the lung

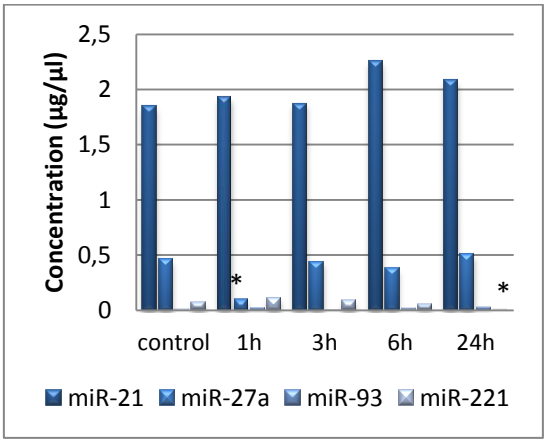

Figure 9. miRNA expressions in the kidneys

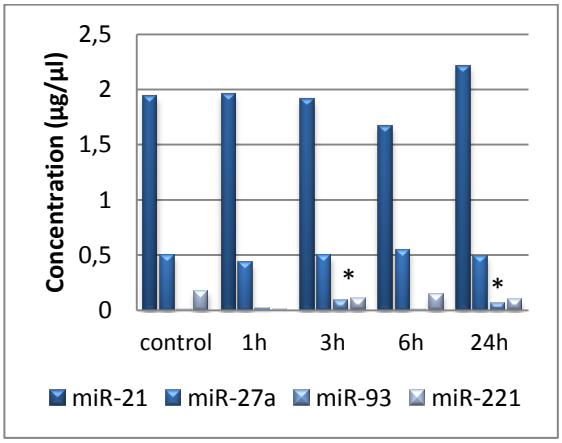

Figure 10. miRNA expressions in lymph nodes

One hour after the treatment we detected a significant upregulation of *c-Myc* in the liver and spleen (Figures 1,2), while there was a significant down-regulation in the expression of *p53* in the lung, kidneys and lymph nodes (Figures 3-5).

Considerably increased expression of *K-ras* gene was found in the liver, lungs and kidneys. 3 h after the injection of red sludge (Figures 1, 3 and 4). The expression of *Bcl2* gene showed upregulation in the spleen, lungs and kidneys at the 3-h time point (Figures 2-4). The expession of *c-myc* was decreased in the liver and lymph nodes at the specific time point (Figures 1 and 5). In the lungs, the expression levels of all investigated mRNAs were significantly elevated 6 h after the exposure with red sludge, while the lymph nodes showed decreased expression of the same mRNAs at the same time (Figures 3 and 5). We observed a significant up-regulation of the investigated mRNAs in the liver and spleen and their down-regulation in the lymph nodes 24 h after the treatment with red sludge (Figures 1, 2 and 5).

In the liver, miR-93 showed a significantly increased expression level relative to the control group at the 1-h time point (Figure 6), and miR-21 at 1-h, 3-h, 6-h, 24-h points. In the kidneys, we observed a marked decrease in the expression of miR-27a and miR-221 at the 1- and 24-h time point (Figure 9). A significant up-regulation of miR-93 was detected 3 hours and 24 h after the exposure in the lymph nodes (Figure 10).

DISCUSSION

The results of my studies prove the existence of early gene expression changes in mice after intraperitoneal administration of red mud. Intraperitoneal administration of red mud was proved to change the expression of several mRNAs and miRNAs that play a role in the processes of cell proliferation, differentiation, signal transduction and apoptosis.

The results raise the possibility of long-term deleterious health effects of red mud in humans. As our investigation was limited to the first 24 h after the administration of red sludge, it is not known wether the observed effect is permanent or temporary, thus the gene expression changes caused by red sludge require longer-term investigations with more genes. Chosing the appropriate target genes and adequate miRNA, mRNAand miRNA expressions may be promising biomarkers of carcinogen exposition. Their advantege is that they are not specific to a certain agent, and they can signal the carcinogenic effect of genotoxic and non-genotoxic exposures.

SUMMARY

1) short term animal tests confirmed that exposure to red mud causes significant changes in the expression of oncogenes and supressor genes.

2) short term animal tests confirmed that the exposure to red mud causes significant changes in the expression microRNA-s.

3) the changes of expressions manifestated within 24 hours.

4) results do not confirm supposed neutral health effects of red mud.

5) usefulness of traditional cytogenetical methods is limited for assessing possible health risks caused by red mud exposure.

6) The changes of expression of onco and supressor genes and microRNA-s are potentially useful biomarkers, which:

- can detect exposure to non genotoxical agents,
- can detect exposure within a short period,
- can follow up the acute changes caused by the exposure,
- can be isolated from the easily collectible samples,
- can be used for monitoRing the effects of mixed exposures.

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