Fachhochschule Nordwestschweiz
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Molecular effects of silica nanoparticles in human liver cells

Masterthesis MAS Umwelttechnik und -management 2014

Background

Silica nanoparticles (SiO_2-NPs) are widely used in technical applications as well as in food industry. SiO_2-NPs are added to consumer products in order to confer desired physical properties such as ideal consistency of pastes or anticaking effects of powder products. Even though SiO_2-NPs are classified as riskless and are approved by the European Food Safety Authority (SiO_2 = E551), there has been increased concern about their potential adverse effects on human health.

The endoplasmic reticulum (ER) is an essential organelle in every eukaryotic cell. Disturbances within the cell can affect ER homeostasis, thus provoking the accumulation of unfolded and/or misfolded proteins within the ER. This cellular condition is known as ER stress. As a result of ER stress, the unfolded protein response (UPR) is initiated, which aims primarily at the reconstitution of cellular homeostasis. However, if ER stress persists and cells fail to restore homeostasis, the cellular responses switch from pro-survival to pro-apoptotic.

Christen et al. (2014) demonstrated that SiO_2-NPs induce endoplasmic reticulum stress in human liver cells. In addition, the activation of genes involved in inflammatory responses and genes down-stream of the mitogen activated protein kinases (MAPKs) was shown. The aim of this study was to analyse the effects of SiO_2-NPs in human liver cells in greater detail. Various genes related to pathways such as the UPR, MAPK signalling, apoptosis and inflammation were studied.

Results

After exposure of Huh7 cells to 0.05 mg/ml SiO_2-NPs for 24 h, UPR pathways were activated as significant inductions of the ER stress-related genes *XBP-1s*, *BIP, ATF4, DNAJB9* and *GADD34* were observed (Fig.1). Even though some of the MAPKs were down-regulated (data not shown), components of their signalling pathways such as *cJun*, *cFos*, *FRA1* and *c-myc* were significantly induced. This finding hints at interconnections between the UPR and MAPK signalling pathways downstream of the MAPKs.

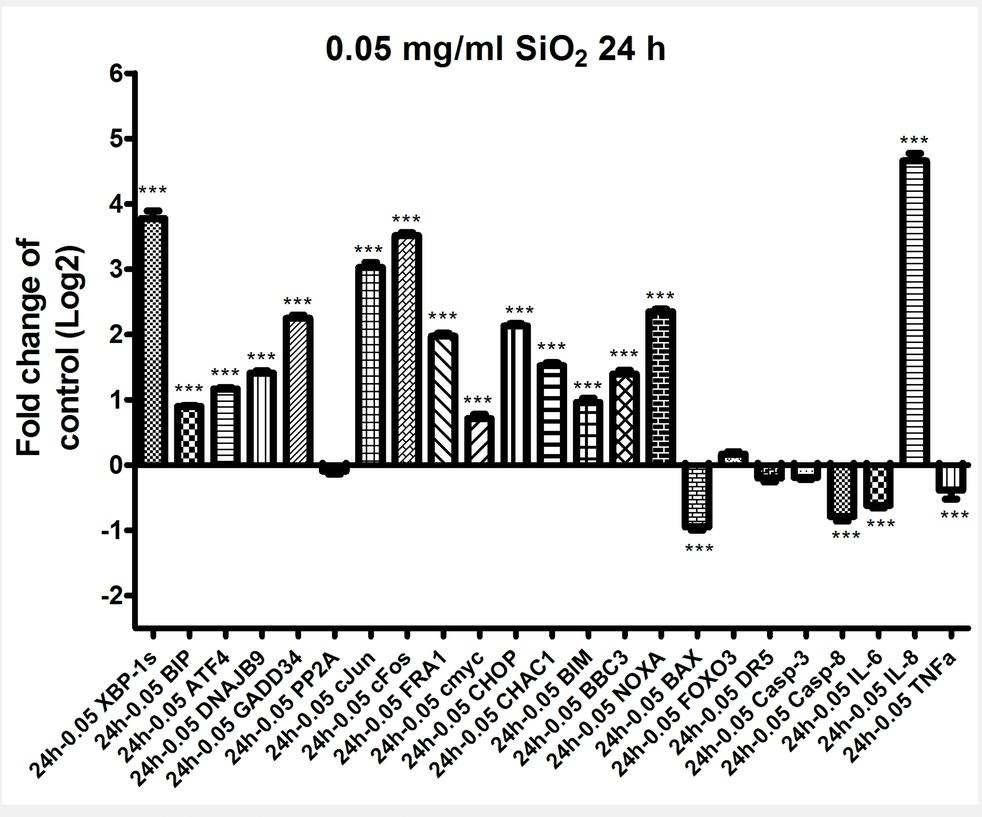

Fig. 1: Transcriptional changes of various genes in Huh7 cells after SiO_2 exposure. Significant differences to control cells with p-values ≤ 0.05 are marked with asterisks.

Pro-apoptotic genes were both up- and down-regulated. While *CHOP*, *CHAC1*, *BIM*, *BBC3/PUMA* and *NOXA* were significantly induced, the *BAX* and *Casp-3* genes were inhibited (Fig. 1). These results show that both pro-apoptotic and pro-survival genes are activated and that the final cellular response is the result of a complex signal analysis within the cell. *IL-6* and *IL-8*, both of them important players in inflammation, differed strongly in their transcriptional regulation. While *IL-6* was down-regulated, *IL-8* transcription was highly induced (Fig. 1). The expression of TNFα was extraordinary. In comparison to data obtained by Christen et al. (2014), TNFα expression was up-regulated in both control and treated cells (data not shown), resulting in a net down-regulation of TNFα in cells treated with SiO_2-NPs. This observation led to the conclusion that both control and treated cells were in an overall stressed condition. The diagram shown in Fig. 2 is an attempt to establish and illustrate interconnections between the genes analysed in this study. Genes whose transcript levels were either up- or down-regulated are highlighted in green and red, respectively.

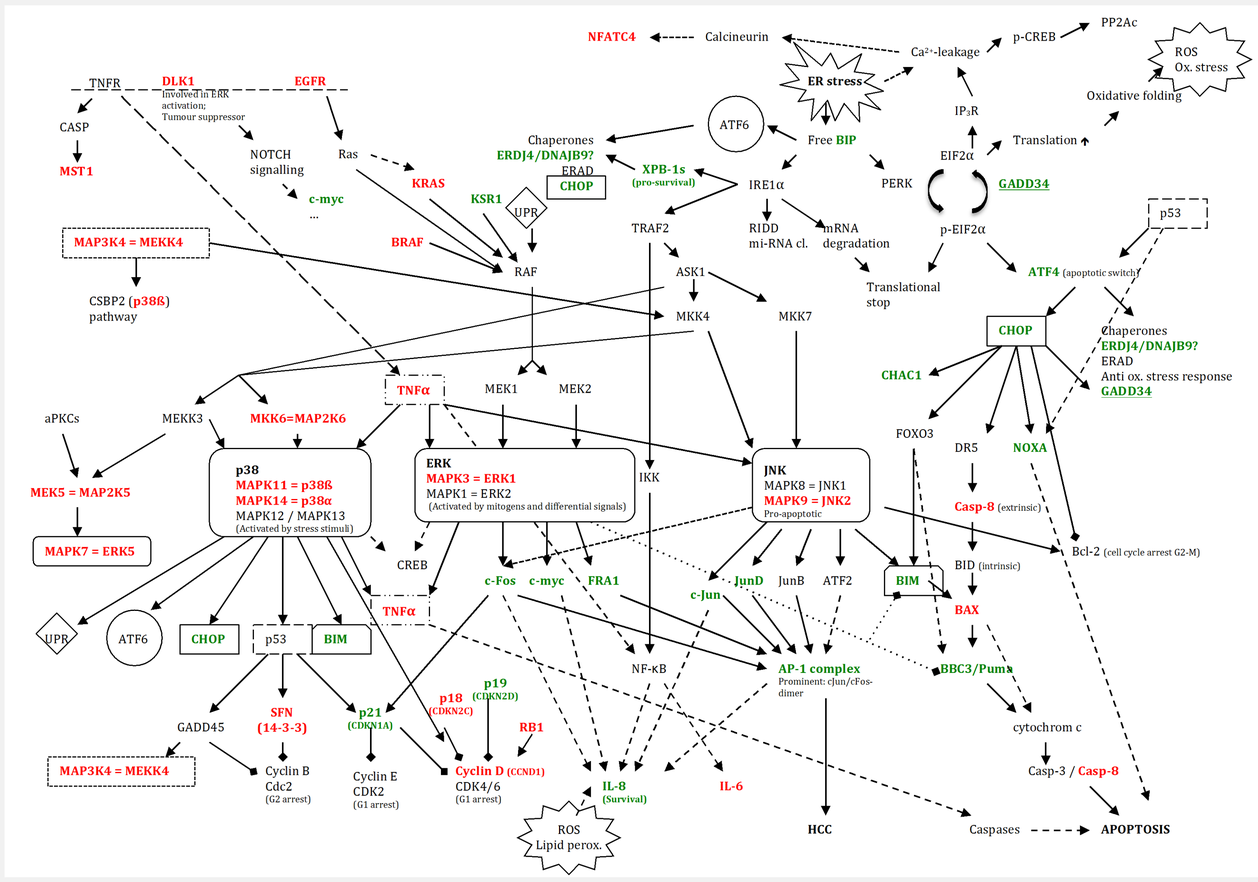

Fig. 2: Gene expression.

Conclusions

Treatment of Huh7 cells with 0.05 mg/ml SiO_2-NP leads to the initiation of the UPR stress response, the activation of components of the MAPK signalling pathways, changes in inflammation signalling pathways and alterations in the regulation of both pro-apoptotic and pro-survival genes.

Literature

Christen et al., (2014). Silica nanoparticles induce endoplasmatic reticulum stress response, oxidative stress and activate the mitogen-activated protein kinase (MAPK) signaling pathway. Toxicology Reports.

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