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Integrating metabolic profiling into the toxicological assessment of nanomaterials: the case of silver nanoparticles

The interaction of nanomaterials with living cells and organisms is crucial to their biosafety and successful biomedical applications. Conventional toxicity assessments are typically based on single endpoints (e.g. cell viability, apoptosis, DNA damage) and can easily underestimate or overlook relevant effects. Hence, there is great need for new, sensitive methods which are able to detect subtle, unforeseen cellular responses to nanomaterials. Monitoring cell metabolism in response to nanomaterial exposure, using metabolomics, is a promising approach in this respect [1,2].

This work describes the metabolic signatures of silver nanoparticles (AgNPs) in cultured cells and in a mouse model, revealed by NMR metabolomics. The cell types studied (epidermis keratinocytes, liver cells and blood macrophages) showed changes in their metabolic composition even at sub-toxic AgNPs concentrations (Figure 1), reflecting reprogramming of energy producing pathways, upregulation of antioxidant protection, autophagic protein degradation, and/or membrane damage/remodeling. Such changes were dependent on the cell type and on the physicochemical properties of the nanoparticles tested. The *in vivo* study showed organ-specific, time-dependent metabolic changes in mice to which AgNPs were i.v. injected, at a dose not causing overt toxicity. Some changes (e.g. upregulation of glycogenesis and antioxidant defences in the liver, enhanced TCA cycle and ATP production in the heart) could play vital roles in protecting cells and mitigating toxic effects. These findings highlight the role of metabolism in governing cellular responses to nanoparticles and show that NMR metabolomics is exquisitely powerful for the untargeted screening and mechanistic understanding of nanomaterials biological effects.

References

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Figures

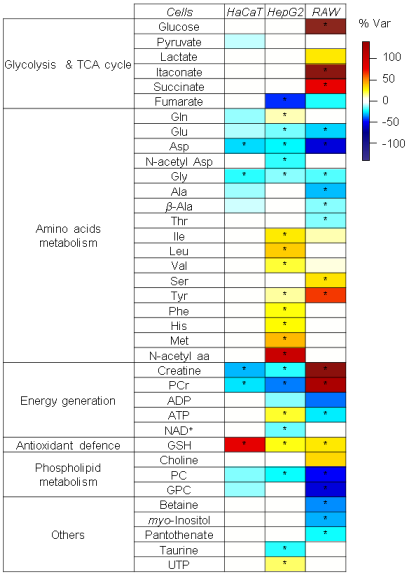

Figure 1: Main metabolic variations in HaCaT keratinocytes, HepG2 liver cells, and RAW 264.7 macrophages exposed to 30 nm AgNPs (24h at the IC_{20}), in relation to respective controls. * Statistically significant (p-value<0.05). Three letter code used for amino acids; PCr, phosphocreatine; ADP/ATP, adenosine di/triphosphate; NAD+, nicotinamide adenine dinucleotide; GSH, reduced glutathione; PC, phosphocholine; GPC, glycerophosphocholine; UTP, uridine triphosphate.