Assessing the Safety of Nanomaterials by Genomic Approach Could Be Another Alternative

Meng *et al.*[1] presented an excellent overview on safety assessment of nanomaterials by predictive toxicological approach. We would also like to point out that identifying the genomic signature of nanomaterials could be another alternative, which has been overlooked. Despite toxicology studies that have identified the effects of nanomaterials on certain biological pathways, the genome-wide response to nanomaterial exposure remains largely unexplored under normal or basal conditions. Perhaps we can provide another piece of evidence why these nanowonders should not be "too small to overlook"[2] with our recent genomic study. Using whole-genome expression microarray analysis, we recently studied the transcriptional response of murine neuronal cells following exposure to a popular naked nano-oxide particle. We controlled the effect of particle size by using a larger diameter counterpart and its chemical properties by using other oxide particles. We found the nanonparticles induced chemical- and size-specific changes in the transcriptome and led to unique alteration of molecular signaling pathways. We believe systematic characterization of nanomaterial's "genomic signatures" through this evidence-based approach could provide better clues for designing tailored toxicology study and development of standard reference for nanomaterials.

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Reply to "Assessing the Safety of Nanomaterials by Genomic Approach Could Be Another Alternative"

We thank our colleagues, Drs. Lee, Chan, and Rennert, for their valued comments about our Perspective article[1] and for raising a valid point, namely, to consider the genomic signature of nanomaterials as a screening tool for predictive toxicological assessment of nanomaterials. We are in complete agreement and should point out that the hierarchical oxidative stress paradigm[2] to which we refer has emerged from proteome analysis[3] that was also confirmed by genome-wide microarray expression technology in endothelial cells.[4]

The recent emergence of "genomic signatures" using high-throughput gene expression technology has had many applications in the life sciences, including predicting the sensitivity to individual chemotherapeutic drugs,[5] elucidation of the human genomic response to avian influenza A infection,[6] monitoring of anthrax threats,[7] and so on. It is also very likely that, in the response to nanomaterials exhibiting potentially hazardous physicochemical properties, genomic footprints may emerge that could lead to the identification of nanomaterial hazard *in vitro* and *in vivo*. It will be necessary, however, to translate these footprints into a practical screening approach that can be used for the comparison of large batches of nanomaterials as well as to explain how the genome-wide response is linked to specific nanomaterial properties such as size, shape, and other factors.

While in our Perspective we list DNA and nucleic acid damage as potential platforms for developing nanomaterial hazard screening, there is little information as to how those injury effects may generate a genome-wide footprint. In the case of the hierarchical oxidative stress pathway, we have shown how a lower tier of oxidative stress is responsible for the transcriptional activation of phase 2 pathway genes *via* the master transcription factor, Nrf2, while at higher tiers of oxidative stress, the transcriptional activation of AP-1 and NF-κB sites in cytokine and chemokine promoters can be triggered through oxidative-stress-sensitive MAP kinase and NF-κB signaling cascades.[3,8,9] While evidence has been provided that the same signaling cascades can be activated by engineered nanomaterials, we do not yet know whether these might contribute to a genome-wide effect. It is interesting to note, however, that in the study of mononuclear cells from the blood of boilermakers exposed to welding fumes containing metal oxide nanoparticles (such as ZnO), genome-wide analysis elucidated an oxidative-stress footprint in association with increased expression of pro-inflammatory genes.[10−13] This response profiling was analogous to the biochemical demonstration of hierarchical oxidative stress responses in macrophages and bronchial epithelial cells, in which the activation of the IL-8 gene bore resemblance to the genomic response in the boilermakers.[14]

In summary, we agree with the assertion that genomic footprinting can be helpful in studying nanomaterial hazard and look forward to the communication of the results in neuronal cells by Lee *et al.*

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