Advancements in high content analysis and application to toxicology

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Mammalian cell-image based assays also referred to as high content analysis (HCA) assays are powerful approaches for analyzing the fundamental toxicological effects of compounds on cell physiology. Thanks to HCA, early toxicology studies can now decipher subtle effect of drugs on internal organelles and measure differences in damaged cell functions by different compounds.

Several challenges still limit HCA as a solution to compound risk assessment during early stage drug discovery. These include a high variability in cell phenotypic behavior and a restricted number of available analytical and statistical tools for quantifying images with multifactorial information (morphology, co-localization, …). Above all, the success of HCA suffers from the lack of physiologically relevant cell systems for toxicology.

One progressive technology that can positively impact HCA at several levels across the workflow (cell physiology, imaging, image analysis) is the use of micropatterns that reduce cell variability to background "noise" levels. By providing stable and directed micro-environmental cues, micropatterns can help towards cell polarization and maintenance of higher order cell differentiated functions, including metabolism of drugs. Other benefits of micropatterns for screening include fewer cells needing to be analyzed in order to generate statistically meaningful data, leading to easier scale-down, higher throughput and an increased opportunity for the use of rare cells.

Here we show how micropatterns offer promise for a range of new analysis strategies applicable to toxicology studies, both for individual cells and cell groups. Thus:

i) generation of normalized renal proximal tubes and hepatocyte cell groups on micropatterns holds hope for providing functionally relevant toxicology models that are compatible with the constraints of HCA,

ii) a novel image analysis algorithm allows an unbiased comparison of fluorescent signals based on probabilistic density maps generated from single micropatterned cells, providing a truly quantitative approach to cytotoxicity profiling and the detection of subtle changes possibly linked to downstream effects *in vivo*