Capillary electrophoresis-mass spectrometry for micro-metabolomics: looking back and the next steps

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Gold statement
The utility of next-generation CE-MS approaches for mico-metabolomics is demonstrated, including highlighting next (technological) steps to make CE-MS a viable tool in this field.

Introduction
The analytical techniques commonly used in metabolomics often require relatively large amounts of biological material, in particular for sample preparation and injection. However, more and more biomedical questions are dealing with small sample amounts. For example, microfluidic 3D cell culture models are increasingly used to address biological questions. These microfluidic cell culture systems inherently deal with relatively low numbers of cells, i.e. typically in the range of hundreds to thousands of cells. To enable the study of material-restricted biomedical questions with metabolomics, i.e. micro-metabolomics, we have developed CE-MS methods for the efficient and sensitive profiling of polar ionogenic metabolites in small-volume biological samples over the past years. In this presentation we look back on these microscale analytical approaches, including highlighting aspects that still need to be addressed in order to make CE-MS a viable tool in this field.

Body
The use of sheathless CE-MS with nanoliter injection volumes resulted in sub-nanomolar detection limits for a wide range of polar metabolite classes, including amino acids, amines, nucleosides, organic acids, sugar phosphates and nucleotides, in both cell culture extracts and volume-restricted body fluids. A unique feature of the proposed sheathless CE-MS approach is that it allows the profiling of both basic (cationic) and acidic (anionic) metabolites using a single capillary/buffer combination by only switching the polarity of MS detection and of the electrophoretic separation voltage. For anionic metabolites, such as sugar phosphates, nucleotides and organic acids, detection limits in the low nanomolar range were obtained and structural isomers could be selectively analyzed without employing any derivatization. The CE-MS method could be effectively used for metabolic profiling of HepG2 cells when using a starting amount of 10,000 down to 500 cells only, which corresponded to the injection content of 5 HepG2 cells to less than one cell. Moreover, for selected endogenous metabolites a linear detector response was obtained when going from 10,000 to 500 HepG2 cells, indicating the strong potential of sheathless CE-MS for quantitative metabolomics studies intrinsically dealing with limited sample amounts.

Conclusion
Overall, the next-generation CE-MS approaches will allow metabolomics studies that have so far been lacking and it will open ways for a deeper understanding of biological processes in sample-limited cases.