SIMPLEX: a combinatorial multimolecular omics approach for systems biology

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Interconnected molecular networks are at the heart of signaling pathways that mediate adaptive plasticity of eukaryotic cells. To gain deeper insights into the underlying molecular mechanisms, a comprehensive and representative analysis demands a deep and parallel coverage of a broad spectrum of molecular species. Therefore, we introduce SIMPLEX (SImultaneous Metabolite, Protein, Lipid EXtraction procedure), a novel strategy for the quantitative investigation of lipids, metabolites and proteins. Compared to unimolecular workflows, SIMPLEX offers a fundamental turn in study design, since multiple molecular classes can be accessed in parallel from one sample with equal efficiency and reproducibility. Application of this method in mass spectrometry based workflows allowed the simultaneous quantification of 360 lipids, 75 metabolites and 3327 proteins from 10^6 cells. The versatility of this method is shown in a model system for adipogenesis - PPARG signaling in mesenchymal stem cells – where we explored with SIMPLEX cross-talk within and between all three molecular classes and identified novel potential molecular entry points for interventions, indicating that SIMPLEX provides a superior strategy compared to conventional workflows.