Metabolic and signalling network map integration: application to cross-talk studies and omics data analysis in cancer

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The interplay between metabolic processes and signalling pathways remains poorly understood. Global, detailed and comprehensive reconstructions of human metabolism and signalling pathways exist in the form of molecular maps, but they have never been integrated together. We aim at filling in this gap by creating an integrated resource of both signalling and metabolic pathways allowing a visual exploration of multi-level omics data and study of cross-regulatory circuits between these processes in health and in disease.

We combined two comprehensive manually curated network maps. Atlas of Cancer Signalling Network (ACSN), containing mechanisms frequently implicated in cancer; and ReconMap 2.0, a comprehensive reconstruction of human metabolic network. We linked ACSN and ReconMap 2.0 maps via common players and represented the two maps as interconnected layers using the NaviCell platform for maps exploration. In addition, proteins catalysing metabolic reactions in ReconMap 2.0 were not previously visually represented on the map canvas. This precluded visualisation of omics data in the context of ReconMap 2.0. We suggested a solution for displaying protein nodes on the ReconMap 2.0 map in the vicinity of the corresponding reaction or process nodes. This permits multi-omics data visualisation in the context of both map layers. Exploration and shuttling between the two map layers is possible using Google Maps-like features of NaviCell. The integrated ACSN-ReconMap 2.0 resource is accessible online and allows data visualisation through various modes such as markers, heat maps, bar-plots, glyphs and map staining. The integrated resource was applied for comparison of immunoreactive and proliferative ovarian cancer subtypes using transcriptomic, copy number and mutation multi-omics data. A certain number of metabolic and signalling processes specifically deregulated in each of the ovarian cancer sub-types were identified.

As knowledge evolves and new omics data becomes more heterogeneous, gathering together existing domains of biology under common platforms is essential. We believe that an integrated ACSN-ReconMap 2.0 resource will help in understanding various disease mechanisms and discovery of new interactions at the intersection of cell signalling and metabolism. In addition, the successful integration of metabolic and signalling networks allows broader systems biology approach application for data interpretation and retrieval of intervention points to tackle simultaneously the key players coordinating signalling and metabolism in human diseases. The manuscript is available at BioRxiv (https://www.biorxiv.org/content/early/2018/03/03/274902).