Mass spectrometry: from imaging to metabolic networks

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Abstract

A deeper understanding of inter-tumor and intra-tumor heterogeneity is a critical factor for the advancement of next generation strategies against cancer. Under the hypothesis that heterogeneous progression of tumors is mirrored by their metabolic heterogeneity, detection of biochemical mechanisms responsible of the local metabolism becomes crucial.

We show that network analysis of co-localized ions from mass spectrometry imaging data provides a detailed spatio-temporal insight into the metabolic heterogeneity. Furthermore, module preservation analysis between colorectal cancer patients with and without metastatic recurrence suggests hypotheses on the nature of the different local metabolic pathways.

Materials & Methods

Weighted co-expression gene network analysis (WGCNA)1 was applied to detect the metabolic differences between two groups of patients (e.g. patients with and without metastatic relapse). A consensus network is defined using the signed adjacency matrix from MSI data of each sub-cohort patients’ MSI data. Afterwards, module detection is applied to the topological overlap matrix, in order to identify highly co-localized subsets of ions. Finally, modules with different network topologies between the two sub-cohort networks are detected using a module preservation analysis2,3 (based on a permutation test). A null hypothesis of modules independence from patients’ status is performed running N=100 times the entire analysis on coexpressed genes networks generated after shuffling the patients’ sub-cohort membership labels. A cohort of 32 colorectal cancer patients was tested for determining metabolic differences between patients with and without metastatic relapse (in a follow-up period of up to 5 years after the surgical removal). The tested cohort consisted of 8 patients with metastatic relapse and 24 patients without a metastatic relapse.

Results

WGCNA applied to DESI-MSH (negative ion mode) data from specimens collected at the center of the tumor revealed the presence of 6 ion modules in the metastatic-related network. The module preservation analysis revealed that one of the 4 tissue-related metabolic network modules was not preserved in the non-metastatic network. The presence of PGs and Arachidonic acid in the unpreserved module suggests that this module represents a local activity of phospholipase A2 related with an inflammatory response of the host. This is confirmed by the visualization of the associated spatial regions in the optical images of the H&E stained tissues. Free lipid droplets and macrophages were observed in those regions, suggesting a local inflammatory condition that has previously associated with an increased risk tumor infiltration5.

Conclusion

For the first time, we show that network analysis, in particular WGCNA, can be employed for exploratory analysis in mass spectrometry imaging data. The application of WGCNA efficiently reveals patterns of co-localized ions and their spatial distributions through their eigen-metabolite (analogous to the standard eigen-gene vectors). The assumption that co-localized ions represent the different metabolic pathways is exploited here to make hypothesis on the biochemical mechanisms associated with tumor heterogeneity. Furthermore, the module preservation analysis allows the identification of groups of co-localized ions in patients with metastatic recurrence that do not occur in the non-metastatic patients. This technique is used to identify hypotheses on the different local metabolism that can be associated with the different clinical outcome.

The presented method can be easily extended to datasets from other tissue types.

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References