Proteomic segmentation of intratumour heterogeneity for identifying clinically relevant tumour subpopulations in gastrointestinal cancers

Rendicontazione

Informazioni relative al progetto

SITH

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Progetto chiuso

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Questo progetto è apparso in...

Final Report Summary - SITH (Proteomic segmentation of intratumour heterogeneity for identifying clinically relevant tumour subpopulations in gastrointestinal cancers)

An essential factor influencing the evolution of cancer and the clinical management of patients is intra-tumor molecular and phenotypic heterogeneity. The de novo identification of tumor subpopulations is a so far challenging task and requires an unlabeled and spatially resolved in situ read-out of the molecular information of the tumor.
Imaging mass spectrometry (IMS) combines mass spectrometry with microscopy of tissue sections, which enables the unlabeled imaging of different molecular classes (proteins, peptides, lipids, metabolites) in their histological context. Molecular distinct tumor subpopulations can be made visible by clustering the spatially resolved mass spectral data using multivariate statistical methods (segmentation of intra-tumor heterogeneity – SITH). Using IMS as central method, the SITH project has two main objectives: (A) the identification of tumor subpopulations that are linked to disease outcome of patients, and (B) the characterization of the molecular properties of these clinically relevant tumor subpopulations on a genetic, proteomic, and metabolic level.
Proteomic IMS data was gathered from samples of two different tumor types in order to study the effect of intra-tumor heterogeneity (ITH) on two different clinical endpoints:
• intestinal-type gastric cancer (n=63): effect of ITH on overall survival time of patients
• invasive ductal breast carcinoma (n=32): effect of ITH on the development of local lymph node metastases (pN0 vs. pN1)
By aligning mass spectral data and histology, IMS allows for a histology-guided extraction (virtual micro-dissection) of mass spectral profiles from user-defined regions of interest. Here, histologically homogeneous tumor areas were selected, thereby excluding any confounding effect on the detected heterogeneity due to the contribution of non-tumor cells or histologically distinguishable tumor cells.
Within the first project phase (aim A) a Matlab® based data processing and data analysis pipeline was developed. This pipeline involves first a data reduction through peak picking to enable a simultaneous segmentation of all samples and thereby the identification of subpopulations across the whole sample cohort. The segmentation was done using a multivariate consensus classification algorithm for IMS data (Jones et al. PLoS 2011, DOI: 10.1371/journal.pone.0024913).

This analysis revealed molecular heterogeneity between individual tumor samples, and also molecularly common tumor subpopulations across several samples, which are very likely based on general proteomic adaptations.
In order to determine the clinical importance of the common tumor subpopulations, the segmentation results were linked to the clinical data of the patients (overall survival or metastases). A tumor subpopulation was associated with the clinical data of a patient, if a tumor subpopulation was sufficiently present in a patient.This way the tumor subpopulations could be statistically compared to determine their clinical relevance:
• Gastric cancer: the analysis of the tumor subpopulations in the 63 intestinal-type gastric cancer patients revealed several of the regions to be statistically associated with a different overall survival. Especially the presence of one tumor subpopulation indicated a significantly unfavorable prognosis for the patient. Moreover, a proteomic similarity of this 'malicious' tumor subpopulation with a lymph node metastasis could be observed.
• Breast cancer: 32 primary breast cancer tissues were investigated for tumor subpopulations associated with the presence of regional lymph node metastasis. In comparison to the gastric cancer cohort, the breast cancer dataset exhibited less molecular heterogeneity, but still one subpopulation was found to be significantly associated with the presence of local metastases.
In the second phase of the SITH project, the aim was to determine the molecular properties of the clinically relevant subpopulations found in the gastric cancer results on a genetic, proteomic, and metabolic level. Analysis of the proteomic IMS data highlighted the importance of some proteins in the clinically most relevant tumor subpopulations: DEFA-1, an antimicrobial peptide, and histones and modifications of these. Metabolomic analysis of the very same tumor subpopulations using high-mass resolving IMS (MALDI-FT-ICR), showed not only reproducibility of the observed spatial heterogeneity on a metabolic level but also alterations in metabolic pathways between tumor subpopulations, including changes in purine, lactose, and glucose metabolisms. Gene expression analyses on macro-dissected material of these tumor subpopulations showed additional alterations in expression levels of genes involved in collagen degradation and formation, genome maintenance, and several signal pathways.
These results show the ability of this approach for understanding the underlying biological processes and changes of intra-tumor heterogeneity. Further studies will have to investigate the valorization potential of this knowledge in terms of novel targeted therapies against the tumor driving cells in gastric cancer. Ultimately, the procedure developed in the SITH project is generic (applicable to any kind of solid cancer that exhibits substantial heterogeneity) and opens novel options in cancer research, as it reveals microscopically indistinct tumor subpopulations that have an adverse impact on clinical outcome.
With intra-tumor heterogeneity being one of the factors that determine the clinical outcome of patients, the pipeline developed in this project can aid in deciphering intra-tumor heterogeneity and thereby accelerate the way we can treat and heal cancer.

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