2016 Human Proteome Organization Clinical Scientist Travel Grant

Cancer proteomics towards precision medicine by molecular targeting drug

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【Introduction and objectives】

Cancer is a genetically and clinically diverse disease, and treatments optimized for individual cancer patients have long been desired. The goal of precision medicine is a better clinical outcome based on stratified treatments harnessing the molecular background of cancer. This goal is now achievable owing to molecular targeted drugs. Cancer proteomics provides valuable information, which is otherwise unavailable. Several lines of evidence suggest that cancer proteomics has the potential to contribute to clinical practice.

【Methods】

To explore mechanisms of inherent resistance against molecular targeting by drugs and to identify the avenues for innovation in precision medicine, we investigated four levels of the proteome. Using a set of sarcoma cell lines showing differential responses to treatment with tyrosine kinase inhibitors, we investigated 1) the global protein expression profile by using mass spectrometry, 2) the expression of all tyrosine kinases by using antibody-based proteomics, 3) the activity of tyrosine kinases by using in-vitro kinase assay system, and 4) the quantity of secreted proteins by using antibody-conjugated bead technology. Moreover, we combined proteomic data with transcriptomic data obtained from our original mRNA expression database, which includes the DNA microarray data from more than 1000 sarcoma patients.

【Results and discussion】

We identified the proteome signature for resistance to treatment with tyrosine kinase inhibitors. The overexpression of six tyrosine kinases associated with the drug resistance was also observed. Interestingly, the overexpressed tyrosine kinases did not always provide apparent advantages to sarcoma cells, because gene silencing for only a limited type of tyrosine kinases was found to affect cell growth. Moreover, the quantity of tyrosine kinases did not always correlate with their activity, which probably explains the discordance between the expression level and the functional significance. Antibody-based proteomics identified unique proteins that were highly expressed in treatment-resistant sarcoma cells. Some of these proteins were expressed more after treatment with

tyrosine kinase inhibitors and were considered candidates for the prediction and monitoring of treatment effects. Finally, we validated our results using the global mRNA expression database. We initially confirmed the concordance between the protein and mRNA expression of the candidate genes and thereafter examined the mRNA expression across different types of sarcomas. The expression levels of the candidate genes differed among patient samples, reflecting the differential response to treatment with tyrosine kinase inhibitors.

【Conclusions】

By investigating the four levels of the proteome and by combining proteomic data with transcriptomic data, we came close to elucidating the molecular mechanisms of drug resistance. Our results strongly suggest the utility of cancer proteomics in precision medicine using molecular targeted drugs.

Personal information of Dr. Zhiwei Qiao

【Introduction】

I graduated from Inner Mongolia University of Science and Technology, Baotou Medical College, China in 2008. After graduation, I underwent a two-year resident program in the university hospital, and learned clinical practice as well as oncology. I found clinical practice so fascinating that I decided to devote myself to treating patients in the role of a surgeon. However, I realized the limitations of modern medicine in terms of the lack of a complete cure for cancer patients. I understood that basic research had the potential to innovate with regard to medical treatment. Indeed, many great medical discoveries in history were owing to doctors or scientists with medical background. Therefore, I changed my major to basic research, and went to Japan to learn front-end science in 2009. After finishing a four-year PhD course in the Akita University Medical School, I obtained a position as a regular researcher at the National Cancer Center Research Institute in 2015. The principal investigator of my laboratory, Prof. Tadashi Kondo, is a pioneering researcher in the field of cancer proteomics. He has been working in proteomics since 1992 and has introduced proteomic modalities to the National Cancer Center from 2001. I learned many unique aspects and the possibilities of cancer proteomics from him. Presently, I am engaged in the application of proteomics to rare cancer such as sarcomas and malignant brain tumors to discover innovative avenues for treatments.

【Brief description of my area of research】

I aim to discover the innovative avenues for development of novel medical treatments for cancer patients. After the advent of the Cancer Genome Project, several molecular targeted drugs were introduced in the oncology field, which has revolutionized cancer treatment. However, the contraindications and best applications of these drugs are subjects requiring urgent research. In this sense, I am interested in the re-localization of molecular targeted drugs, and therefore, I am developing predictive biomarkers. I think that rare cancers are unique and important subjects of study. Because of the relatively homogenous molecular background, certain rare cancers occasionally exhibit an unusually high response rate to treatment. In addition, because of low prevalence and small market size of rare cancers, the re-localization of molecular targeted drugs is a practical strategy for treatment, and re-localization is one of the most urgent research subjects in oncology. Moreover, as the National Cancer Center is the largest cancer hospital in Japan, frozen tissue samples from rare cancer patients are available for translational research. In addition, in the Prof. Kondo’s laboratory, unique patient-derived cancer models have been established and utilized for the development of novel therapy. Consequently, I have conducted proteomics-based research for rare cancers, to find innovative methods for the re-localization of molecular targeted drugs.

Using clinical samples, well-characterized cell lines, and patient-derived cancer models, I am investigating protein expression profiles. Presently, I use antibody-based and mass-spectrometry-based proteomics modalities. In addition to proteomics, bioinformatics is my favorite tool. I would like to join HPP in the field of biomarker development with these backgrounds. I believe that worldwide collaboration is mandatory to validate the results of cancer proteomics, because of the diversity found in cancers. It will be my pleasure to share my experience and research outcome with the members of HPP.

【Detailed plan of my research with proteomics modalities】

I have a regular position in the National Cancer Center Research Institute, and I wish to develop my career here. There are several unique proteomics modalities in my laboratory, including an expression profiling system using an antibody library, the equipment and technology for activity-based proteomics. My laboratory also has the large gel 2D-DIGE. Conventional proteomics modalities such as SILAC are also available. By using these modalities and by obtaining proteomic data, I intend to develop bioinformatics approaches and apply them to cancer proteomics. Presently, I have developed a data-mining system using R language and using our original custom database-compatible Connectivity Map. Bioinformatics is a widely used tool in cancer proteomics, where a large amount of data is routinely generated. By integrating multi-disciplinary data such as clinical, pathological, genetic, and proteomic data, I intend to discover the unique molecular signatures underlying important clinical observations. This idea may be common among researchers, but it is challenging to realize. In my laboratory, a unique collaboration among clinicians, pathologists, bioinformaticians, and researchers has been established for more than decade, and thus, I believe that I have a good chance of achieving this.

I have found that my medical background is useful in conducting cancer proteomic research. I follow the latest trends in the development of molecular targeted drugs for many types of malignancies by reading clinical papers and by attending clinical meetings. Knowledge about urgent clinical needs is necessary when we draft research proposals and plans. More than anything, my strong motivation from clinical practice helps me work hard. I hope to contribute towards easing the suffering faced by cancer patients by using cancer proteomics. This is the goal of my research, and I intend to devote all efforts to it.