Patient-derived cancer model for proteogenomics: Report by ICPC JAPAN team

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Abstract: Patient-derived cancer models play an important role in the basic study and translational research. They are indispensable for the functional significances of aberrant genes and proteins, and the response to novel anti-cancer drugs. Although many cell lines, organoids, and xenograftsh have been developed, and deposited in the public biobanking, we need to establish more patient-derived cancer models, considering the diversity and complexity of malignancies. The establishment of cancer models has been required especially for the rare cancers such as sarcomas. They are hardly available, probably because of the rarity of disease, hindering the basic and pre-clinical study in rare cancers. ICPC Japan team conducts the proteogenomics study in sarcomas. Sarcomas are the rare mesenchymal malignant tumors in bone and soft tissues, accounting for less than 1% of all malignancies. Sarcomas compose of more than 50 histological subtypes, which show the different clinical and pathological features with distinct molecular backgrounds. We generate the genome and proteome data of sarcomas, integrate them, trying to understand the molecular backgrounds of etiology, disease developlemt, and resistance against therapy. As a part of cancer proteogenomics, we established patient-derived sarcoma models, to study the functional significances of identified genes and proteins. Presently, we have established more than 40 patient-derived xenografts and 30 cell lines. We investigate the genetic mutations, enzyme activities, and effects of inhibitors in the developed cell lines. We found that the presence of kinase mutations does not guarantee the favorable response to the inhibitors against them, and the significant inhibitory effects were not always based on the genetic mutations. The association of the genetic mutations and the response to inhibitors may be the cancer dependent, and the examinations of kinase activity may solve the apparent discrepancies. In this sense, proteogenomics approach will generate intriguing and useful outcome for basic cancer research and clinical application.

Keywords: proteogenomics, sarcoma, mutation, activity, response to inhibitor