Proteogenomic approach to kinase regulation in osteosarcomas with different original sites: Report by ICPC JAPAN team

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Abstract: Aberrant regulations of kinase activity play a crucial role in the carcinogenesis and cancer progression. As therapeutic targets and biomarkers for companion diagnosis, the mutations in the activity domain of kinases are extensively investigated. In this study, we examined the utility of the multi-omics approach toward the comprehensive understanding of aberrant regulation of kinase. We investigated two types of osteosarcomas; one was originated from bone, and another from soft tissue. These two osteosarcomas exhibit the distinct clinical features, and we studied the mutations and activity of kinases, and the response to kinase inhibitors in their patient-derived cell lines. Mutation status of 27 kinases was examined by NCC Oncopanel, which is based on the next-generation sequencing technology. The activities of 100 kinases were monitored by the PamStation 12 platform, which is based on the in vitro kinase assay. In addition, the anti-proliferative effects of 30 FDA-approved kinase inhibitors were also examined in the cell lines. We found that the two types of osteosarcoma cells showed the remarkable differences in the activities of FGFRs1-4. Corresponding to the kinase activities, the inhibitors against them showed the considerable anti-proliferative effects. We found the mutations in PIK3CA in the osteosarcoma from soft tissue, and the amplification in EGFR in the osteosarcoma from bone. However, the inhibitors for the PI3K-AKT pathway or EGFR did not show the significant effects on their cell lines. Our result suggests that we need to investigate the kinase activities in addition to genetic mutations, to predict the effects of kinase inhibitors. The different status of kinase mutations, activities, and response to inhibitors should be considered in an integrative way. Overall, the multi-omics experiments and data integration will be a crucial approach to understand the mechanisms of cancer progression, and develop the novel therapy.

Keywords: osteosarcoma, kinase mutation, kinase activity, response to kinase inhibitor, osteosarcoma