Kinase activity profiling identifies role of EPH & SRC in molecular subtyping of Colorectal Carcinoma

#1876

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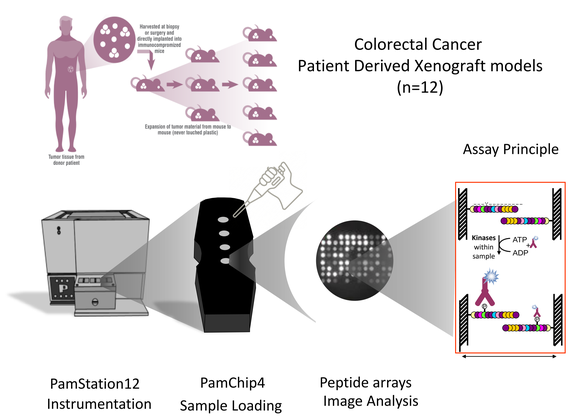
Introduction

Colorectal cancer (CRC) is heterogenous disease and is second leading cause of cancer death worldwide. Underlying molecular mechanisms for the observed heterogeneity are poorly understood.

Aim: To elucidate changes in cellular kinase signalling in CRC patient derived xenografts, to compare across the cohort for potential molecular signatures.

Whole kinome activity profiling assay: Activity of 380+ kinases was profiled in 12 CRC-patient derived xenograft models using PamGene's KinomePro technology. Frozen tissue samples were dissociated, and total protein was extracted as per standardised protocols. Tyrosine Kinase assay (PTK) and Serine/Threonine Kinase assay (STK) were run as per manufacturer's instructions.



Kinase activity profiling on PamChip® microarrays

PamGene's KinomePro technology

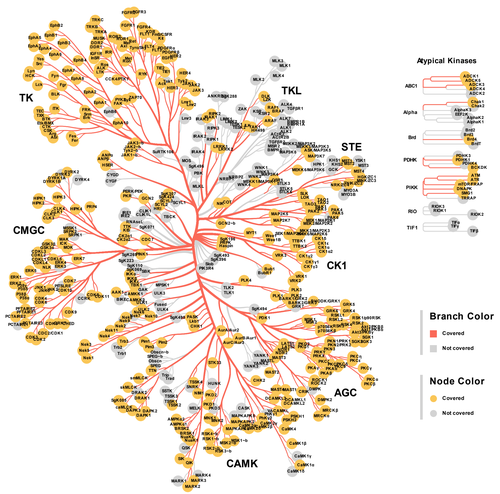
With the advanced PamChip® technology, we can simultaneously measure the activity of over 380 kinases, providing a comprehensive view of kinase signalling pathways in a wide range of cell types and tissues.

High-throughput Simultaneously analyze 380+ kinases.

Sensitive Only 0.5-5 µg total protein/ array

Sample Compatibility Primary cells, tissue samples, cultured cell lines, organoid or xenograft models.

End-to-end services Include sample prep, assay, data analysis, interpretation and reporting.

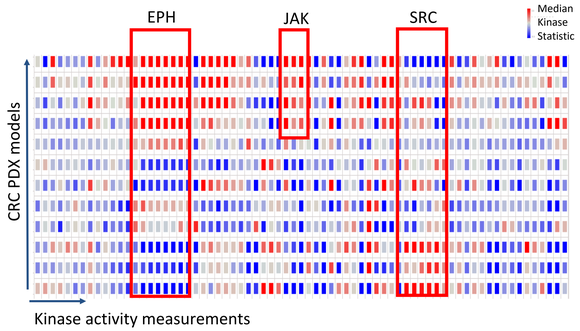


Kinases covered: by KinomePro

Kinase Activity Biomarker Discovery

Two molecular subtypes were identified based on EPH & SRC kinase activity.

EPH-high subgroup also showed high JAK activity. Conversely, EPH-low tumors showed high SRC activity. EPH/ephrin signaling is known to play an instrumental role in CRC carcinogenesis. Hence, heterogenous EPH activation as a potential biomarker is very promising.

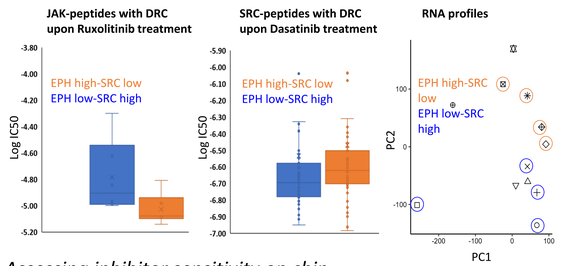


Molecular subtyping based on kinase activity

Kinase Inhibitor Profiling

Kinase Inhibitor IC50 determination: To validate the activity changes, a dose response curve of Ruxolitinib (JAK inhibitor) and Dasatinib (SRC inhibitor) was carried by spiking the inhibitors in tissue lysates during the kinase activity assay.

Assessment of inhibitor sensitivities showed good correlation with kinase activity status of these subgroups. IC50 of Ruxolitinib in EPH/JAK high group was higher than that of the low subgroup. RNA profiles of the cohorts were also distinct, indicative of differential molecular signalling.



Assessing inhibitor sensitivity on chip

Conclusions

Kinase activity profiling of Colorectal Cancer patient derived xenografts reveals EPH and SRC as markers for distinguishing subset of patients. Specific inhibitor profiling validates the observations. PamGene's KinomePro technology reveals a potential disease biomarker for molecular stratification of colorectal cancer patients.

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