Development of a Pan-Cancer 15 Gene Expression Signature to Detect a Subgroup Driven by MAPK Signalling

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Background

• Unsupervised hierarchical clustering of gene expression data from 265 high grade serous ovarian cancer (HGSOC) tumours identified 3 molecular subgroups.
• These were characterised by upregulation of angiogenesis (Angio subgroup), immune (Immune subgroup) and both angiogenesis and immune (Angioimmune subgroup) genes, respectively.
• Further characterisation of the Angioimmune subgroup reveals it to be driven by MAPK pathway activation and is associated with an EMT (Epithelial to Mesenchymal Transition) like phenotype.
• The aim of this study was to develop a gene signature which could detect the MAPK/EMT subgroup across multiple cancer types.
• Using our datasets and publicly available gene expression datasets we have demonstrated that the MAPK/EMT subgroup (as defined by ‘EMT assay’) exists in other cancer types and is associated with poor prognosis.
• The EMT assay was validated in preclinical model systems.
• A positive result for the EMT assay is associated with higher sensitivity to drugs which target components of the MAPK and EMT pathways.

Identification of Molecular Subgroups of High Grade Serous Ovarian Cancer

A. Hierarchical clustering analysis of 356 FFPE treatment naïve HGSOC who were subsequently treated with platinum-based chemotherapy (carboplatin/cisplatin - 65%); 3 subgroups were identified: immune, angi and angiimmune.
B. Survival analysis of each identified molecular subgroup: immune subgroup is a poor prognosis subgroup and the angi and angiimmune subgroups are good prognosis subgroups in the context of GC. C. Replication of molecular subgroups in TCGA dataset. The angiimmune subgroup is associated with the TCGA immune subgroups. B. Survival analysis of molecular subgroups in TCGA dataset.

Conclusions

• A 15 gene signature has been developed from formalin fixed paraffin embedded samples to detect a molecular subgroup driven by MAPK/EMT signalling across multiple diseases.
• This assay predicts sensitivity to MEK inhibitors in pre-clinical cell line and mouse model systems.
• Further work aims to validate the EMT assay in clinical samples from patients treated with a MEK or EMT inhibitor.
• This assay may be helpful for clinical trial enrichment to select patients that are likely to benefit from MAPK or EMT targeted therapies.

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