Project title: Immunogenomics and PDX models for precision medicine on CRC

Precision Medicine on Colorectal Cancer

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Colorectal cancer (CRC) is a common yet potentially lethal disease. It has the highest incidence rate and the 3rd highest mortality among all cancers in Taiwan. A significant fraction of the patients might have reached the late stage of disease when they had the diagnosis. We have taken an immunogenomic approach to explore the possibility of identifying early diagnosis as well as treatment monitoring biomarker(s). By examining CDR3 sequence of B cell receptor in peripheral blood before treatment, we had observed that, among 32 cases, there were 15 common CDR3 sequences, which were shared by at least 3 cases. It is also found that CDR3 sequence repertoire varies among patients during treatment. Besides B cell receptor analysis, T cell receptor CDR3 sequences from 9 of the 32 cases were also found to have 15 common sequences, which were shared by at least 3 cases. These preliminary observations are encouraging in that it showed a potential of finding biomarkers for CRC diagnosis or treatment monitoring. For metastatic CRC (mCRC), treatment would rely on targeted therapy in combination with chemotherapy. Biological therapies for mCRC mainly target on EGFR and VEGF. However, any mutation occurred on the EGFR effectors would render anti-EGFR treatment ineffective. Screening for genomic variations is the pre-requisite for the success of a targeted therapy. The complex cancer-related alterations in the molecular networks, result in significant clinical heterogeneity among individual tumors and patients. To meet the needs, our study has recruited advanced cases of mCRC from two teaching hospitals and performed gene panels as well as whole-genome sequencing, identifying SNP, InDel, CNV, and other structural variations. From the sequence information, we looked for tumor-specific mutations to identify potential treatment targets and guide the selection of available medicines. We developed a platform, the Integrative ChemoResponse (ICR) assay, which combines “omics” analysis with chemoreponse assay in patient derived xenograft (PDX) mouse and the zebra fish model to help make clinical decision for advanced CRC cases. Additionally, we have studied the tumor heterogeneity in the PDX mouse system and investigated the clonal evolution caused by serial passage in the PDX in mice, and comparing responsive and resistant mice treated with regorafenib (Stivarga). To date, we have conducted the genomics, transcriptomics and proteomics analysis between these two groups, and the data should shed light on potential biomarkers for the selected medicine.