NUS Graduate School for Integrative Sciences and Engineering
Research Project Write-up

Title of Project : Genetic and genomic approaches to predicting drug response in advanced colorectal cancer patients.

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Short Description

Colorectal cancer is the commonest cancer in Singapore currently. Up to 80% of these patients will develop liver metastases but there is potential of cure through surgery with/without appropriate chemotherapy. In many colorectal-cancer-liver-only-metastases patients, neoadjuvant therapy is necessary to downsize the tumour before surgery is performed. The commonest chemotherapeutic regime is fluoropyrimidine/oxaliplatin combination. The response rate is however only ~60%. It is therefore important to be able to predict the responders from the non-responders prior to starting neoadjuvant chemotherapy so that those deemed borderline resectable are not made inoperable by a delay because of inappropriate chemotherapy regime.

Response to chemotherapy could be due to differential expression/activity of various drug-related genes as a result of differences in genetic profiles of the different individuals. Differential expression and polymorphisms in various drug response genes have been implicated in influencing the response to these drugs in the Western population. As different ethnic group respond differently to different drugs due to polymorphisms in the various drug response genes, it is important to examine polymorphisms of these genes in our local population and correlate the polymorphisms with fluoropyrimidine/oxaliplatin combination therapy for advanced colorectal cancer patients.

Genetic and genomic strategies will be used to predict drug response. Genetically, we will characterize the haplotype and linkage disequilibrium (LD) architecture of candidate fluoropyrimidine/oxaliplatin response genes in our local populations/Caucasians/African Americans and identify candidate functional polymorphisms. We will then correlate these functional polymorphisms with their gene expression and response to fluoropyrimidine/oxaliplatin combination.

Objectives

(1) In silico approaches to mine the HAPMAP and Perlegen databases for regions in the human genome that contains genes important for response to fluoropyrimidine and oxaliplatin drugs.
(2) Genotype selected drug response genes identified above in our 3 local populations (Chinese, Malays, Indians).
(3) Examine the haplotype and linkage disequilibrium profile of these regions using computational methods.
(4) Utilize computation methods to search for signatures of recent positive selection in these genes to identify potentially functional polymorphisms.
(5) Correlate these potentially functional polymorphisms with their gene expression and response to fluoropyrimidine/oxaliplatin combination.

References

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