Whole-exome sequencing in hepatocellular carcinoma

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Cancer is a disease of genetic alterations which cause cells to proliferate uncontrollably. Over the lifetime of an individual, his or her cells acquire somatic mutations that are different from the inherited, or germline, polymorphisms. In cancer, some of the somatic polymorphisms, the so-called cancer "drivers", lead to the proliferation of tumor cells. Understanding which particular mutations "drive" oncogenesis in each particular tumor is essential for developing efficient therapies that are targeted at the specific tumor – a task made particularly important due to the high toxicity and cost of chemotherapeutic drugs.

Next-generation sequencing is particularly well suited for uncovering the spectrum of somatic mutations in individual tumors. Whole-exome sequencing in particular is a practical approach to the discovery of novel mutations in clinical settings: mutations in coding regions are particularly important in pathogenesis and more easily interpretable than those non-coding regions, yet the exome occupies only a small fraction of the genome, keeping the sequencing cost manageable (1).

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and is the third largest contributor to cancer fatalities worldwide. Among the risk factors for HCC are hepatitis B and C, alcohol abuse, and exposure to carcinogens. To date, exome sequencing has been applied to HCC instances of various etiologies, mostly ones associated with the hepatitis infections (2-4).

In this study, we sequence the exomes of cancerous and normal liver tissue from five individuals with non-viral hepatocellular carcinoma who had their tumors removed at the N. N. Blokhin Cancer Research Center, and identify somatic mutations, short indels, and copy-number alterations in each tumor. Applying to these results computational methods for driver mutation predictions, we obtain candidate drivers for each tumor. We further map these mutations to signaling pathways in order to understand which pathways are affected. Finally, by looking at germline variants in normal tissue and applying to them computational methods for mutation impact prediction with a focus on known oncogenes, we look for the existence of inherited factors that might have predisposed each individual to cancer.

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