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Oncogenomics of Mesothelioma in Humans

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Beginning in 1990, the Human Genome Project brought about a significant breakthrough in medical genetics and application of genetic knowledge in common diseases. It has revolutionized the traditional medical concept that genetics is involved only in extremely rare inherited diseases, to the new concept that genetic factors significantly contribute to the mechanism and progression of most diseases, as well as the response and side effects of the treatment. [1] Cancer is the best example to demonstrate the benefits of genetic knowledge. It is universally accepted that cancer is a genetic disorder that results in abnormal cell growth and invasiveness with the potential to spread to other parts of the body. Better understanding of cancer genetics leads to new types of cancer diagnostic tests and several novel drugs which are designed to target specific genetic abnormalities in cancer. Many patients who are suffering from various cancers, such as leukemia, breast cancer and lung cancer, are now having better treatment outcomes, longer life expectancy and suffering less adverse effects from treatment with those targeted therapies.

In addition to many discoveries on the genetic factors of more common diseases, innovation in molecular genetic technology also gives rise to revolutionary high throughput genome sequencing. From the era of capillary electrophoresis-based sequencing, it took 11 years and cost nearly $3 billion to complete the entire human genome sequence. The new technology, called "next generation sequencing (NGS)," makes large-scale genome sequencing possible. It currently takes less than two weeks and costs less than $2,000 to accomplish the sequencing of one human genome. The unprecedented throughput, speed and cost of sequencing enables researchers to investigate the genetic contribution of cancer and implement this NGS technology in real-world medical practice at a level never before possible.

Similar to the Human Genome Project, the United States National Institutes of Health together with several leading research institutes created the Cancer Genome Atlas in 2005 with the aim of achieving large-scale and comprehensive tumor genome sequencing of various cancers. We currently see widespread use of NGS in cancer research to discover genetic alterations in each cancer, to study disease mechanisms at the molecular level, to identify potential treatment targets, to predict the response to medical treatment and to use this technology to tailor the appropriate treatment for each patient.

Mesothelioma Tumor Genome

Mesothelioma is a cancer that arises from mesothelial cells. Though there are various affected organs, including the peritoneum and pericardium, pleural mesothelioma accounts for more than 90 percent of cases. It is a rare cancer with estimated incidence of about 10-20 cases per million. [2] Approximately 80 percent of pleural mesothelioma cases are associated with asbestos exposure. The disease carries a dismal prognosis since the majority of cases are diagnosed at advanced stages. The median overall survival ranges from 8 to 36 months. Current drug regimens are mostly ineffective. Thus, understanding the genetic alterations of mesothelioma is critical for successful development of diagnostic and therapeutic strategies.

The largest and most systematic investigation on mesothelioma tumor genetic alteration has been published recently. [3] The cohort consisted of 216 mesothelioma cases. The comprehensive study revealed several crucial findings on mesothelioma. The majority of the mutations (approximately 85 percent) were novel. None of the tumor samples carried germline variants in known cancer-associated genes. The average mutation burden was also low (24 +/- 11 protein-coding alterations per sample) unlike other solid tumors, especially tumors that were slow-growing and were associated with environmental exposure, such as lung cancer or colorectal cancer.

The mutation landscape of mesothelioma is more distinct than other cancers. Tumor suppressors *BAP1* and *NF2* were mutated in 23 percent and 19 percent of the samples, respectively. In contrast, *TP53* was mutated in only 8 percent. Other significant alteration includes autophagy kinase *ULK2*, a target of mammalian target of rapamycin (mTOR) negative regulation implicated in glioma development, which was mutated in 1.5 percent and *SETD2*, encoding a member of the SET domain family containing histone methyltransferase, which was mutated in 8 percent of the samples. Overall, the majority of altered genes found in mesothelioma are involved in four cell signaling pathways; the Hippo (*NF2*, *LATS1*, *MST1)*, mTOR *(ULK2*, *TSC1*, *TSC2)*, apoptosis (*TP53*, *CDKN2A*, *CDKN2B)*, and histone modification (*SETD2*, *SETDB1*, *SETD5*).

In conclusion, cancer arises from genetic dysfunction leading to out-of-control cell growth, causing tumor growth and spreading. Since each patient has a unique set of gene mutations driving cancer, there are multiple

targets in each patient that may need to be hit. This is where tumor profiling is useful.

Analyzing an individual patient's tumor is necessary to determine what combination of drugs will work best. With this approach also comes greater potential to decrease toxic side effects. Targeted drugs would give the ability to customize treatments for the patient. Further insight from mesothelioma genome and cellular pathways would enable physicians to move treatment from a broad-based approach – using radiation, surgery, and chemotherapy-to a more targeted technique in the future, which would that interfere with essential cell functions to kill cancer cells.

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