Lecture 2: BIMM-194 Notes:

https://bioboot.github.io/bimm194_W18/

Cancer Genomic Fundamentals

The increased availability of genome sequencing is having an enormous impact on the study and treatment of cancer. This is important because it is estimated that cancer will strike 40% of people at some point in their lifetime with frequently devastating effects. In this blog post we highlight how genomics has impacted our approach to cancer risk assessment, screening and prevention. We first review some of the underlying causes of cancer and major genes linked to cancer. We then focus on how genome sequencing has advanced cancer treatment and informed the development of new targeted therapy approaches.

Cancers involve multiple gene mutations

The vast majority of cancers are believed to have a **multigenic causation**. That is, they require mutations (*i.e.* genomic changes) in multiple different genes that affect cell growth and division (i.e. cell proliferation). These include mutations in genes that actively drive cell proliferation (so called **oncogenes**) as well as genes that normally constrain uncontrolled cell proliferation (so called **tumor suppressor genes**).

Normal cells have multiple compensatory mechanisms that help ensure the proper spatiotemporal control of cell proliferation and the elimination of abnormal cells before they become cancerous. The sequential accumulation of mutations during a persons lifetime may effectively 'wipe out' these compensatory mechanisms leading to neoplastic uncontrolled cell growth. Then as tumors continue to grow further mutations accumulate that may make the cancer more aggressive or more able to metastasize for example.

Many different mutation types may contribute to carcinogenesis - the initiation of caner formation. This includes both germline mutations, which we inherit from our parents, and somatic mutations, which occur spontaneously during our lifetime. Germline mutations are responsible for the cancers that run in families and often lead to a high predisposition for cancer. Somatic mutations may result from DNA damage (e.g. radiation or Sun exposure) and are not passed down from parent to child. Germline and somatic mutations may be single base changes, indels, and/or large structural variations.

A common mutation type in many cancers is so-called gene fusions. Gene fusions typically result from chromosome rearrangements that fuse a gene or its regulatory sequence to a proto-oncogene. This results in aberrant, continuous expression or activity of the oncogene protein product and uncontrolled cell proliferation. The first fusion gene to be implicated in cancer was the **BCR-ABL fusion**, which is a hallmark of chronic myeloid leukemia and occurs in more than 95% of cases. Several hundred different gene fusions have now been implicated in a variety of cancers.

There are many genes that, when mutated, can cause loss of control of cell proliferation and contribute to cancer. Examples of some genes commonly implicated in cancer are shown in **Table 1**.

Table 1. Examples of major oncogenes and tumor suppressor genes linked to cancer

Gene name	Biological Role	Cancer Types
Common oncogenes		
PI3K	Cell signaling	Many (e.g., colon, breast, brain, liver, stomach, lung)
BRAF	Cell signaling	Many (e.g., colon, breast, brain, liver, stomach, lung)
Ras family genes	Cell signaling	Many (e.g., breast, colon, ovarian, lung, pancreatic, leukemia)
HER2	Cell signaling	Breast
Common tumor suppressors		
APC	Cell signaling and adhesion; chromosome stability	Colorectal
SWI/SNF complex genes	Higher order DNA structure and gene expression	Many (e.g., ovarian, kidney, liver, melanoma)
TP53	DNA repair; cell death	Many (e.g., ovarian, colorectal, esophageal, head and neck, lung)

Genetic and genomic information can be used to tailor cancer treatment to the specific molecular characteristics of a tumor.

Although cancers have traditionally been described by their tissue of origin (e.g., breast cancer, lung cancer, or prostate cancer), in reality cancers of the same tissue may look and behave very differently depending on which mutations are present and which genes are expressed. This is known as the cancer's "**molecular signature".**

For example, breast cancer may be classified into various types based upon which proteins are expressed on tumor cell surfaces. Breast tumors that express human epidermal growth factor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR), or are triple negative (do not express HER2, ER, or PR) behave differently and have different prognoses. Tumors that are HER2 positive are treated with medications that bind to HER2 (e.g. trastuzumab, lapatinib) and inhibit its activity. ER and PR are hormone receptors, and ER/PR positive tumors are treated with antihormonal therapies (e.g. tamoxifen and aromatase inhibitors). Triple negative tumors have the poorest prognosis and are unlikely to respond to HER2-targeted therapies or antihormonal therapies. Such cancers are usually treated very aggressively with chemotherapy.

Targeted therapies
As more has been learned about the molecular signature of various cancer subtypes, therapies that are specifically targeted to those signatures have been developed. Conventional chemotherapy acts on all rapidly dividing cells and does not distinguish between cancer cells and normal cells. Chemotherapy may cause substantial side effects, because normal, rapidly dividing cells (e.g., those lining the stomach) are killed along with cancer cells. Radiation therapy is another general approach to eliminating rapidly dividing cells and has the advantage that it can be directed specifically at the tumor site; however, surrounding normal cells may still be affected. The normal cells that survive chemotherapy and radiation therapy may sometimes acquire harmful mutations that may cause them to become cancerous in the future. The new, targeted therapies attack tumor cells with greater precision and specificity than conventional chemotherapy approaches, and, therefore, can have enhanced antitumor effects and reduced associated side effects.

One notable example of the power of a targeted cancer therapy is imatinib (also known as Gleevec), which is very effective for treating Chronic Myelogenous Leukemia (CML). Imatinib specifically inhibits the BCR-ABL fusion protein that is constitutively activated in CML. Another targeted therapy, erlotinib, inhibits a receptor involved in cell growth control, the epidermal growth factor receptor (EGFR). EGFR is often mutated in many types of cancer, and erlotinib actually binds tighter and, therefore, is more inhibitory against those mutated forms of EGFR than against normal EGFR. Erlotinib is efficacious in the treatment of tumors that carry those mutated forms of EGFR.

Tailored treatment based upon results of molecular characterization of tumor cells is fairly common in oncology. The molecular characterization, however, is usually confined to those factors (aberrant proteins, mutated genes) that are typically associated with a given tumor type. Also, molecular characterization is usually limited to known prognostic factors and a handful of high-frequency “druggable targets,” that is, factors common in a given tumor type and for which targeted therapies exist. Rare but potentially “druggable” changes might be present but overlooked.

Genomics and cancer treatment
With the ability to sequence whole genomes and exomes, attention has turned to trying to understand the full spectrum of genetic mutations that underlie cancer. The genomes or exomes of tens of thousands of cancers have been sequenced yielding a number of important new insights into cancer biology.

- Every tumor is different and has a different genomic profile.

- Certain mutations are common in specific cancers. For example, many cancers have mutations in the tumor suppressor gene, TP53; many colon and ovarian cancers have mutations in the RAS pathway; and 40%–60% of melanomas have a very specific mutation in the BRAF proto-oncogene. Although the genetic basis of certain cancers was known prior to whole genome sequencing, our knowledge of the genes and biological pathways commonly mutated in many different types of cancers has been greatly expanded.

- Although there are many different types of cancer, the underlying molecular defects typically affect just a dozen or so processes or “**pathways**” often involved in cell growth and proliferation or in repair of DNA damage.

- it is very clear that cancers are best classified not only by tissue of origin (i.e., the conventional classification system), but also by their underlying molecular defects.

Although not yet a routine part of care, the potential for genomic analysis to help guide personalized treatment for cancer is generating considerable excitement. The hope is that drugs will no longer be used against cancer in situations where they have an extremely low probability of success, and, more importantly, targeting drivers of uncontrolled growth present in a given tumor in a timely manner will be highly effective with reduced side effects.

A new approach: What is immunotherapy?
Genomics is beginning to have an impact in an entirely new form of cancer treatment called "immunotherapy" in which a person's immune system is used to attack the cancer.

An important factor in developing cancer is the tumor's ability to evade the immune system. Typically, when a cell develops a cancer-causing mutation and becomes precancerous, the immune system recognizes that something has gone wrong with this particular cell leading to an immune response that eliminates the precancerous cells.

One trick cancer cells use to evade the immune system is to erect a "shield" around themselves that essentially stops the immune system from launching its attack on them. In some tumors, cancer cells begin massively overproducing signals that essentially tell the immune system, "Do not attack me!" One key signal is the PD-L1 protein. PD-L1 sits on the surface of the cancer cells and tells the immune cells not to attack. It does this by binding to a protein on the surface of the immune cells called PD-1.

Immunotherapy is a new major form of treatment that works by blocking the PD-L1/PD-1 shielding system that cancers use to turn off the immune response against them. After turning off those signals, the immune system is free to attack the tumor. Current immunotherapies usually block PD-1 (e.g. Nivolumab and Lambrolizumab), which essentially stops the "shut down" signal from the tumor to the immune system and allows the immune system to attack.

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How can genomics be used to harness the patient's own immune system to fight cancer?
Each person's cancer has a number of unique passenger mutations. These passenger mutations can be identified through genome sequencing. Analysis of gene expression patterns can be used to measure the expression of these mutations. Although these mutations are not technically causing the cancer, pieces of the mutated proteins they create (called "neoantigens") can be recognized by the immune system and targeted for attack. By "priming" (i.e., "vaccinating") the patient's immune system against passenger mutations in the tumor (using protein fragments carrying these cancer specific mutations), the immune response can be magnified, facilitating a stronger attack on the cancer cells.

Essentially, once neoantigens that are expressed are identified from genomics appraches, the patient can be vaccinated against those particular neoantigens, empowering the immune system to specifically attack the cancer cells.

DNA sequencing is at the heart of this approach, which requires identifying mutations unique to cancer cells (i.e. mutations in the cancer that are not present in the same patients healthy cells). With RNA sequencing used to determine whether these mutant proteins are expressed in the tumor. This information is then used together patients immune system HLA information (also from sequencing) to develop vaccines personally optimized for that patient.

Read more about the recent exciting advances in this field in this [Nature Outlook article from late Dec 2017](https://www.nature.com/articles/d41586-017-08706-3)

Can genomics help detect early cancer and monitor treatment effectiveness?

Many cancers, such as ovarian cancer and some kidney cancers, are typically only detected when they are relatively far advanced, because they may not be associated with noticeable symptoms in the earlier stages. One remarkable discovery in the past few years has been the finding that the DNA of solid tumor cells often can be found in the blood. This presumably occurs through the death of cancer cells whose contents are then released into the bloodstream. The discovery of this circulating tumor DNA (ctDNA) is important because it offers the possibility that a simple blood test might be used for detection of “silent” early cancers. Indeed, in a recent study designed to detect regions from 139 genes that frequently carry somatic mutations in non-small-cell lung carcinoma (NSCLC), ctDNA was detected in approximately 50% of patients with early (Stage I) NSCLC and in all of the patients with more advanced (Stage II–IV) NSCLC. This type of ctDNA assay is theoretically adaptable to many types of cancer, and it is likely that screening for ctDNA will become a standard component of cancer early detection in the future.

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