Genomics, Biomarkers & New Approaches to Treatment

Cancer is a disease that occurs when the DNA of normal cells is changed or damaged, causing uncontrolled growth of affected cells. As such, a tumor is best understood as an overgrowth of cells. Typically, cells are programmed to serve their function and to avoid development of tumors. Normal cell behaviors—such as changing or differentiating, stopping growth, dying or self-destruction when damaged—protect against tumor formation. Unfortunately, damaged DNA can cause mistakes in these instructions, so that the cells no longer behave as they should. When this happens, cancer can develop.

Cancer genomics is a newer area of study for researchers seeking new treatment options for cancers of all types. Cancer genomics is the study of the DNA sequence in cancer cells versus normal cells. Because cancer cells have genetic alterations, they carry a different version of your DNA than healthy cells do.

DNA is a molecule that is found in every cell of an organism (a person, animal, plant, etc.) and carries genetic instructions for the development, functioning, growth and reproduction of that organism. DNA tells each cell how to behave and which proteins to produce. The information contained in the DNA, including any mutations or mistakes that might occur, is copied from one generation of cells to the next.

Cancer genomics also looks at gene expression to identify which genes and gene products (for example, proteins) are contributing to the growth of cancer. Gene expression, or activity, can be measured by the abundance of different RNA. RNA is a molecule that is present in all living cells and is essential for the coding, decoding, regulation and expression of genes. It acts as a messenger, carrying instructions from the DNA on how to make proteins. Proteins do a great variety of things within the body and can be understood as what makes each cell function. Some proteins assist the immune system in doing its work, some trigger or speed up chemical reactions, and others make up vital body structures like hair and skin. Genes can contribute to cancer growth by being too active, not active enough, or not active at all.

There are several types of genetic errors that can occur in cells that become cancer. These include DNA mutations, rearrangement of particular genes, gene deletion, or gene amplification (extra copies of a gene). These alterations can occur in a few ways: they can be inherited from your parents; caused by environmental exposure to things such as UV light, or cancer-causing substances like those in tobacco; or they can happen by accident during normal processes like cell division. The totality of genetic changes within an individual's genome are called *somatic* changes. These somatic changes and the resulting genetic abnormalities are believed to account for 95% of all cancer cases. So, understanding and being able to repair or eradicate these errors becomes key to successfully treating cancer.

The idea behind the study of cancer genomics is that, if we can understand what has gone wrong genetically to cause a particular cancer, then treatments can be developed to combat the DNA errors that are at fault. Essentially, we would treat the genetic errors, rather than using treatments like radiation and chemotherapy that broadly affect an entire region of the body, including healthy tissue and cells.

The current study of cancer genomics involves identifying molecules known as biomarkers. These molecules can tell us about things going on in the body that may be signs of underlying disease. Biomarkers could be DNA, gene mutations, gene rearrangements, missing genes, extra genes, proteins, enzymes, or hormones, for example. They are produced either by the cancer itself, or by other processes in the body, like an immune response to the cancer. Cancer biomarkers are useful in predicting how the cancer will progress and, consequently, your prognosis. Biomarkers are also currently being studied as a means of identifying which treatment a specific patient's cancer is likely to respond to.

If your doctor decides to examine the genomics of your particular cancer, he or she will take a sample of the tumor and send it to a lab for molecular profiling. The results will indicate which biomarkers are present and may offer clues as to which treatments are likely to be most effective, allowing for a more personalized treatment plan.

HNC Genomics

The study of head and neck cancer (HNC) genomics has, so far, revealed some useful findings that will serve as a foundation for future research. For example, we now know that HNCs associated with HPV and HNCs associated with tobacco use are molecularly distinct (different subtypes of HNC). So, what do we know so far?

HPV+ Head and Neck Cancers

- The human papillomavirus (HPV) carries cancer-causing genes called E6 and E7.
- When the HPV genome is integrated into a cell's genome during HPV infection, it causes errors in subsequent copies of the DNA, resulting in the partial or total loss of other genes. In the case of HPV, the virus's genome often causes a partial or total loss of genes E1 and E2, whose function is to regulate the activity of the cancer-causing genes E6 and E7. Essentially, with E1 and E2 removed or diminished in function, E6 and E7 can become active and eventually cause cancer.
- Researchers have discovered a surrogate (indirect) biomarker for HPV+ oropharyngeal (throat) cancer. The molecule is known as p16. In HPV+ squamous cell carcinoma of the head and neck (SCCHN), p16 is overexpressed as a result of the action of the HPV E7 protein. Consequently, if the presence of p16 is identified in a sample of tumor tissue, it is assumed that the cancer is HPV+. The presence of this biomarker is useful in determining the best course of treatment. If your cancer is identified as HPV+, it is more responsive to treatment and has a higher cure rate. This is great news for HPV+ patients.
- TP53, a gene that suppresses tumor growth, often exhibits a loss of function in HPV+ SCCHN, which prevents the p53 protein from performing its normal role of sensing and repairing DNA damage or inducing cell death due to DNA damage. In HPV+ cancer, the loss of function is due to the presence of the E6 gene/protein. When TP53 stops functioning, it allows damaged cells to continue growing and dividing, leading to tumor growth.
- Approximately 22% of HPV+ tumors have also been found to exhibit shortened or deleted TRAF3 genes, which help regulate immune response within the body. This may allow cancer to grow unchecked by the body's immune system.
- Approximately 19% of HPV+ tumors have extra copies of the E2F1 gene, which is involved in cell cycle regulation. An overabundance of E2F1 can lead to uncontrolled cell growth and cancer.
- Several studies suggest that, in HPV+ tumors, there is a higher prevalence of mutations that activate PIK3CA genes, which are important in cell growth, division, movement, and survival. Mutated PIK3CA has been shown to weaken signals that initiate cell death, and in this way, such mutations support the development of tumors.

HPV- Head and Neck Cancers:

- HNCs caused by tobacco typically show mutations that result in a loss of function in TP53, which prevents the p53 protein from performing its normal role of sensing and repairing DNA damage or inducing cell death due to DNA damage. These mutations occur in about 84% of HPV- tumors. Unlike in HPV+ tumors where p53 inactivation is caused by the presence of the E6 gene, in HPV- tumors the inactivation is caused by a mutation of the TP53 gene itself. When TP53 stops functioning, it allows damaged cells to continue growing and dividing, leading to tumor growth.
- 58% of HPV- tumors exhibit inactivation of the CDKN2A gene, which is a cell cycle inhibitor that prevents cells from dividing too quickly. Without proper functioning of this gene, cells may grow and divide too quickly, leading to development of tumors.
- HPV-negative tumors often carry extra copies of genes located at chromosomal sites 11q13 and 11q22. It is suspected that these extra copies promote the interaction of two other genes known as BIRC2 and FADD that work together to slow or prevent cell death. When cells do not die off as they should, cancer can develop.
- 12% of HPV- head and neck tumors showed extra copies of the EGFR gene, which promotes development of cancer.

Abnormalities Found in Both HPV+ and HPV- Cancers:

- One of the most commonly mutated genes in both HPV+ and HPV- head and neck cancer is PIK3CA. Mutated PIK3CA has been shown to weaken signals that initiate cell death, and in this way, such mutations support the development of tumors.

Precision Medicine / Targeted Therapies: The Good News and the Bad News

The study of cancer genomics has led to new treatment options for many types of cancer. These treatments are known as precision medicine or targeted therapy, and they combat the specific genetic or molecular changes present in a patient's cancer. Because they are treating only the cancer-causing genetic changes or molecular activities, such treatments are much less toxic to patients than traditional treatments like chemotherapy or radiation. Precision medicine is a high-priority focus area for head and neck cancer researchers.

Unfortunately, head and neck cancers have not seen the same success with precision medicine therapies as other types of cancer. While our understanding of the genomic factors at work in SCCHN have grown tremendously over the past several years, advancement in the treatments available for head and neck cancer have been limited to a single agent that targets EGFR (Cetuximab).

- **Cetuximab (Erbitux®):** This therapy targets the EGFR pathway, marking cancer cells for attack by the immune system. It is approved for subsets of patients with advanced head and neck cancer, including as a first-line therapy. Cetuximab is the only immune checkpoint inhibitor indicated for use in newly diagnosed patients, and it is only given in combination with chemotherapy or radiation.

Obstacles to the development of targeted therapies relate to the difficulty of targeting commonly mutated genes in SCCHN and to the large number of mutations found in these tumors. Head and neck cancer is a disease of long-term exposure—exposure to cancer-causing products, like tobacco or alcohol; exposure to viruses, like HPV or Epstein-Barr; or exposure to other environmental carcinogens. Lifelong exposures such as these mean that head and neck cancers often harbor a higher degree of genetic mutations than other types of cancer, and these mutations vary widely not just from one patient to the next, but very often within a single patient.

Because head and neck cancer tumors can be caused by so many different genetic errors, and because a single patient's cancer may exhibit multiple genetic anomalies acquired over a lifetime of exposures, these cancers have been notoriously difficult to treat. Because head and neck cancer is not a disease that lends itself well to "one-size-fits-most" treatment options, patients in the future will likely be treated with personalized therapy, or precision medicine, that is developed for their specific, individual cancers. Precision medicine for head and neck cancer will have to tackle the issue of tumors harboring multiple genetic mutations that may have varying susceptibility to available treatments. Depending on the mutations that are present in a particular cancer, some cells may be killed with one type of treatment, while other cells may be more resistant and require different therapy. Head and neck cancer is a complex disease, and there is much work to be done.

Immunotherapy

Until research into head and neck cancer precision medicine experiences new advances, the best option for patients, besides traditional chemotherapy, radiation and/or surgery, may lie in immunotherapy - treatments that activate the immune system to attack cancer cells. In recent years, the FDA has approved two immunotherapies (also called immune checkpoint inhibitors) to treat advanced, recurrent, or metastatic HNC. Checkpoint inhibitors block proteins on cancer cells that disguise them from the immune system, making them more visible to the immune system so it can attack the cancer cells.

Checkpoint inhibitor therapies that are currently available for head and neck cancer include:

- **Nivolumab (Opdivo®):** This therapy targets the PD-1/PD-L1 pathway, helping the immune system to recognize and kill cancer cells. It is approved for subsets of patients with advanced head and neck cancer.
- **Pembrolizumab (Keytruda®):** This therapy also targets the PD-1/PD-L1 pathway and is approved for subsets of patients with advanced head and neck cancer, including as a first-line therapy.

Clinical Trials

A number of clinical trials are examining immunotherapies and other potential treatments for SCCHN. To learn more about clinical trials, click here.

Resources

Immunotherapy Rack Card

This informational card, perfect for physicians' waiting rooms or exam rooms, lists questions patients cane ask their doctor on immunotherapy.

Questions to Ask Rack Cards

This informational card, perfect for physicians' waiting rooms or exam rooms, lists questions patients can ask their doctor before, during and after treatment.

Immunotherapy Patients Video

Our featured cancer survivors share how immunotherapy helped them with their battle against cancer.

Bayer Resources

Learn how genomic cancer testing can make an impact on your treatment journey and why you should ask your doctor about it.

BMS Videos – Garden Video

Learn more about immunotherapy and how it works through a garden analogy.

Mutations Matter

Learn how molecular profiling can molecular profiling can open the door to additional, personalized treatment options for cancer patients.

References

HEAD AND NECK CANCER ALLIANCE

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