Recent Research Developments in Anti-Cancer Therapy

Editorial
Volume 5 Issue 2 - 2016

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Received: June 06, 2016 | **Published:** June 22, 2016

Editorial

In developing cancer, individuals differ in both their inherited tendency and exposure to the environment, a multi-event combination process. At the cellular level, mutations occasionally occur as the cells divide and, although not heritable by any offspring (somatic mutations); they can affect cell behavior sometimes causing more frequent growth and division. Normally, cell division responds to growth factors and stops when encountering growth inhibitory signals from surrounding cells. After a number of divisions, the cell dies and remains within the epithelium from which it is unable to migrate to other organs. To become cancerous, it would have to bypass these signals and accumulate new genetic mutations in a number of genes (3-7), the most frequent being a loss of function of the p53 protein (a tumor suppressor) or in the p5 pathway and/or a gain of function through mutations in the protein or in other oncogenes. It will then keep growing, escape from the epithelium and the primary tumor, cross the endothelium of a blood vessel, be transported by the blood stream and colonize a new organ(s) to give rise to metastases.

Research about cancer causes focuses on the following issues

a. What are the agents (e.g. viruses) and events (e.g. mutations) that cause or facilitate genetic changes in cells destined to become cancerous?

b. What is the precise nature of the genetic damage, and the genes that are affected by it? and

c. What are the consequences of those genetic changes on the biology of the cell, both in (a) generating the defining properties of a cancer cell, and (b) facilitating additional genetic events that lead to further progression of the cancer?

The vast majority of cancer cases are due to environmental risk factors, many of which (but not all) being controllable lifestyle choices and thus preventable. It has been suggested that more than 30% of cancer deaths could be prevented by avoiding risk factors including: tobacco, overweight, obesity, insufficient or/and inappropriate diet, physical inactivity, alcohol, transmitted infections, and air pollution. However, not all environmental causes are controllable such as naturally occurring background electromagnetic radiation. I will discuss these epigenetic/ecogenetic factors in a follow-up editorial. Here, I will describe four recent developments in cancer treatment, viz. immunotherapy using PD-1 inhibitors; immunotherapy using engineered T-cells; the DNA origami/trojan horse technique; and conversion of the binary form of the enzyme mnk-2 to overcome drug resistance.

Immunotherapy in general

Immunotherapy represents a paradigm shift in cancer treatment in that it targets the immune system, not the cancer itself. In 2013, the Science magazine declared it as that year's breakthrough! Nonetheless, today's immunotherapies do not help everyone (e.g., the odds remain long for patients with metastatic cancer) and biomarkers that might offer answers remain to be designed as well as experimenting with ways to make therapies more potent.

In clinical trials, new immune system-boosting cancer drugs have saved lives in seemingly untreatable melanoma or lung cancer cases, but the drugs seem useless against colon cancer. Nonetheless, even cancers impervious to the new drugs (3%- 4%) could be treated if those malignancies have the right error-riddled DNA signature.

Immunotherapy using PD-1 inhibitors

Tumor cells hide from T-cells by activating PD-1 receptors on the surface of the immune system's T- cells and can attack them if the receptors are blocked by PD-1 inhibitors. There are two new types of drugs (including pembrolizumab [Keytruda]) to harness the immune system, keeping tumors at bay for years. In clinical trials, they generally have worked in less than half the cases, and work best on tumors with lots of mutations. Advanced cancers seem more likely to respond if they have so-called mismatch repair mutations, which explains why the best outcomes have been for the heavy mutation tumors of lung cancer and melanoma. The hypothesis is that some of these mutations may alter genes to code for abnormal (or foreign) proteins or antigens so that the more of them, the more antigens to launch an attack from T-cells unleashed by a PD-1 inhibitor.

Clinical trials conducted by Profs. Dung Le, Luis Diaz and their colleagues at The Johns Hopkins University in Baltimore, Maryland and by Dr. Jedd Wolchok at the Memorial Sloan Kettering Cancer Center in New York City, New York found that mutations in mismatch repair genes can lead to cancer-promoting mutations and would respond to PD-1 inhibitors. In the case of few mutations, one implication is that the tumors might respond better to PD-1 inhibitors if they first receive radiation or chemotherapy that create new mutations.

Immunotherapy using engineered T-cells

Combining gene therapy, synthetic biology and cell biology, engineering T-cells involves the following steps: (a) Extracting

from the blood T-cells known to respond best to a given disease; (b) implanting them with new genes using a custom-built virus; (c) creating cells that target a molecule (CD19) found on surfaces of few cancers; and (d) returning to the body the modified cells where their new DNA gives them a fresh set of targets to attack. The technique can be refined by overcoming the treatment's toxic effects that may occur in most advanced cancers. Here, a runaway reaction (called a cytokine storm) can be fatal so the dose is brought down to its lowest to reduce this immune system's overreaction.

In acute lymphoblastic lymphoma (ALL), there was complete remission in 93% of the 31 cases treated in a clinical trial, an unprecedented result. Unfortunately, this approach is difficult to expand to other cancers because priming a T-cell attack requires precise coordinates lest it locks onto and destroys something else in the body.

Unfortunately, besides CD19, we know of no other chemical target that is specific to cancer alone. Prof. Kole Roybal and his colleagues at the University of California, San Francisco have therefore proposed a modified technique in which cells are tweaked to attack when they sense not one but two different target chemicals. The idea is that whereas neither target may be unique, the combination might be, allowing the immune system to be unleashed on tumors whilst sparing healthy tissue.

Engineered T-cells (and perhaps also B-cells, another part of the immune system) might be used to treat a wide range of diseases besides cancer, including HIV, immune deficiencies, and autoimmune disorders. The idea of boosting the body's own defenses is elegant and appealing. Further, once their task completed, the engineered cells remain in the body, offering protection against recurrence or re-infection for years to come.

The DNA origami/trojan horse technique

In the original origami technique of Byrd, Castro and Lucas, to foil drug resistance in solid tumors, a cancer drug is packaged in a capsule made of folded-up DNA. In acute myeloid leukemia (AML), resistance develops against the drug daunorubicin. Specifically, when molecules of daunorubicin enter an AML cell, the cell recognizes them and pumps them back out through openings in the cell wall.

Researchers at The Ohio State University found that daunoribicin-resistant AML cells effectively absorb drug molecules when these are hidden inside tiny rod-shaped capsules made of DNA. They used this observation to refine the origami technique into what they dubbed the "Trojan horse" technique. They used the genome of a common bacteriophage and synthetic strands that were designed to fold up its DNA. This DNA capsule simply holds a shape and doesn't encode any proteins or do any of the normal DNA functions. Potentially, the technique should work on most any form of drug-resistant cancer.

Conversion of binary form of enzyme mnk-2 to overcome drug resistance

Cancer cells can become resistant to many types of chemotherapeutic treatment, and this so much so that many medical oncologists are unsure as to whether a given patient may benefit from any particular drug. In a breakthrough discovery, Prof. Karni and his team at the Hebrew University Medical Center, Jerusalem, Israel, have identified a process in which cancer cells become resistant to certain drugs, leading to a reliable outcome prediction. They found that breast, lung and colon cancer cells change the structure of the enzyme mnk-2, which is involved in the transmission of information from the environment/body into the cell. This enzyme is binary with a "normal" form that inhibits cancer development and an "abnormal" form that promotes it. The balance between these two forms will determine whether the cancer is arrested or promoted. To overcome drug resistance, Karni et al further developed molecules that can convert the abnormal to the normal form of mnk-2. The underlying mechanism elucidates how cancer cells eliminate the anti-cancer form and provides a means to reverse it. This research could lead to the development of a new biomarker for testing patient sensitivity to specific drugs. A diagnostic test for this marker is being investigated.

In spite of the technical elegance and encouraging findings of the above approaches, much remains to be done in the laboratory and in clinical trials before being able to routinely translate the results to humans.

Citation: Fymat AL (2016) Recent Research Developments in Anti-Cancer Therapy. J Cancer Prev Curr Res 5(2): 00155. DOI: 10.15406/jcpcr.2016.05.00155