The link between genes and cancer

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(Medical Xpress)—When people think about genes and their relationship to cancer, most probably think about a person's hereditary cancer risk, especially after Angelina Jolie's recent news about her inherited breast and ovarian cancer risk associated with the BRCA1 and BRCA2 gene abnormalities. But genetic counselors will tell you that only about 5 to 10 percent of cancers are caused by inherited genetic mutations.

Even though hereditary genetic mutations are relatively rare causes of cancer, genes still play a critical role in cancer development and

progression. Recently, a team of cancer researchers published a study in the journal *Nature* that found similarities in the genetic makeup of the most aggressive types of tumors.

So what exactly is the link between genes and cancer? For a better explanation, we asked cancer scientist Paul B. Fisher, Ph.D., to answer some questions about the connection between genes and cancer, and the implications of research like the Nature study on science and medicine. Fisher is the Thelma Newmeyer Corman Endowed Chair in Cancer Research and co-leader of the Cancer Molecular Genetics program at Virginia Commonwealth University Massey Cancer Center, chairman of the Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine in the VCU School of Medicine.

Q: How is the cancer-genes connection important? Why is understanding the underpinnings of this disease critical?

Genes are essential in defining what we are, who we are and, as we've come to learn, our disease states. However, before we go any further, it's important to understand what genetic mutations are and how they affect the physiological processes of cells.

In a lot of ways, genes act like a recipe to dictate how cells function and what traits they express. When a signal reaches the outside of a cell, whether from an environmental stimuli or a signal telling the cell to perform a normal biological function, it stimulates certain receptors on the outside of the cell. These receptors then cause biochemical changes within the cell, which are often carried out by proteins and enzymes responsible for initiating specific functions, such as telling the cell how and when to divide, dictating how the cell responds to stress, and, in cases of stem cells or embryonic cells, deciding what type of cell it

should become. Cells have various signaling pathways that carry out these responses, and genes ultimately control these pathways.

A mutation is simply a variation on what a gene normally does, and we are now seeing that certain genetic mutations are often responsible for some of the worst characteristics of cancer, such as its ability to grow and metastasize to other parts of the body. By understanding exactly how these genes become dysregulated and the effects of those mutations on normal cellular processes, we have a better chance at developing new treatments that target the underlying causes of cancer while having little to no negative effect on normal, healthy cells.

Q: Once you understand what a gene does, how do you use that knowledge to develop better treatments?

More recently, scientists in my field have suspected that cancers share certain common signatures and traits no matter where in the body they originate. The *Nature* study validated this assumption and leads to the hope that if genetic changes are similar between cancers, then therapies designed to target specific genes and molecular pathways could affect multiple types of cancer. It's as if we were looking for a needle in a haystack and finally found it, but now we need to figure out how to use the needle. My research is a good example.

We discovered one such "needle" in the form of melanoma differentiation associated gene-7 (mda-7), also known as interleukin (IL)-24. This gene was originally cloned in my laboratory when I was a scientist at Columbia University in New York, and I have continued this research at VCU. We have shown that this gene is not normally expressed in a variety of cancers including breast, prostate, colorectal, ovarian, pancreatic, brain and lung cancers, which is common for genes that suppress cancer. When forcibly expressed in these cancers, it

directly impacts two forms of cell suicide known as apoptosis and toxic autophagy, regulates the development of new blood vessels and plays a role in promoting cancer cell destruction by the immune system.

Our lab is developing several promising viral gene therapies utilizing the mda-7/IL-24 gene that have been shown to kill cancer cells at the original tumor site and also in distant metastases.

We are using engineered viruses (adenoviruses) that are modified to seek out and replicate only within cancer cells. When these adenoviruses infect the cancer cell, they deliver immune-modulating and toxic genes such as mda-7/IL-24. Current studies are also exploring the potential of directly delivering purified mda-7/IL-24 protein as a cancer therapeutic. Additionally, we are even pairing these strategies involving viruses, therapeutic proteins or chemotherapeutic agents with ultrasound-targeted microbubble destruction (UTMD) technology, which uses microscopic gas bubbles that can be combined with these therapies. The bubbles are treated with special molecules known as complement to place them under the immune system's radar and when injected into the bloodstream, researchers or physicians can, in principle, directly deliver the viruses (therapeutic proteins) to tumor sites (and their surrounding microenvironment) using ultrasound.

Alternatively, once you have identified and cloned a relevant gene, if it is a cancer-causing gene (referred to as an oncogene), you can develop small molecules, or drugs, that block it from working. This is the case with another gene originally cloned in my lab, mda-9/syntenin. We determined that this gene is directly responsible for metastasis in a variety of cancers, and we are currently using structural information about the protein, combined with large chemical libraries and a sophisticated approach called nuclear magnetic resonance (NMR), to identify small molecules that prevent this protein from interacting with other proteins required for its functioning as a pro-metastatic gene.

These approaches, combined with secondary medicinal chemistry to optimize the small molecule and develop it into a drug, will permit us to find those molecules that work best to inhibit the gene's function.

Q: How long before this type of therapy reaches the clinic?

It's important to note that there are few new therapies without basic laboratory research. Clinical trials are usually the last part of a long and arduous process that starts with an idea tested in a researcher's laboratory. Only after being proven many times through experiments involving cultured cells and increasingly complex animal models can a new therapy find its way to the clinic.

There has already been one successful phase 1 clinical trial testing a viral gene therapy involving mda-7/IL-24. It was shown to be safe when administered to patients with advanced cancers. My laboratory is performing experiments showing that these therapies are effective in animal models, and we are working with our partners in the clinic to initiate more phase 1 studies.

I'm hopeful that we will see a number of clinical trials initiated in this decade that test these types of targeted gene therapies. But it's important to note that science moves in slow, incremental ways. The Food and Drug Administration has an enormous job in trying to define what is going to be safe and what is going to potentially work. It may seem like an eternity, but it's important that we understand exactly how these drugs work within the human body before we move to widespread clinical use.

It is an exciting time to take part in cancer research, and hopefully people recognize how close we are getting to new and better therapies and why we need to support this type of research. Increased

governmental, industrial and private research support is essential to accelerate the progression of research from "lab to bedside" and to exploit the unique opportunities available through large-scale genomic analysis to develop effective targeted therapies for cancer and other diseases.

More information: www.nature.com/nature/journal/ … ull/nature12113.html

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