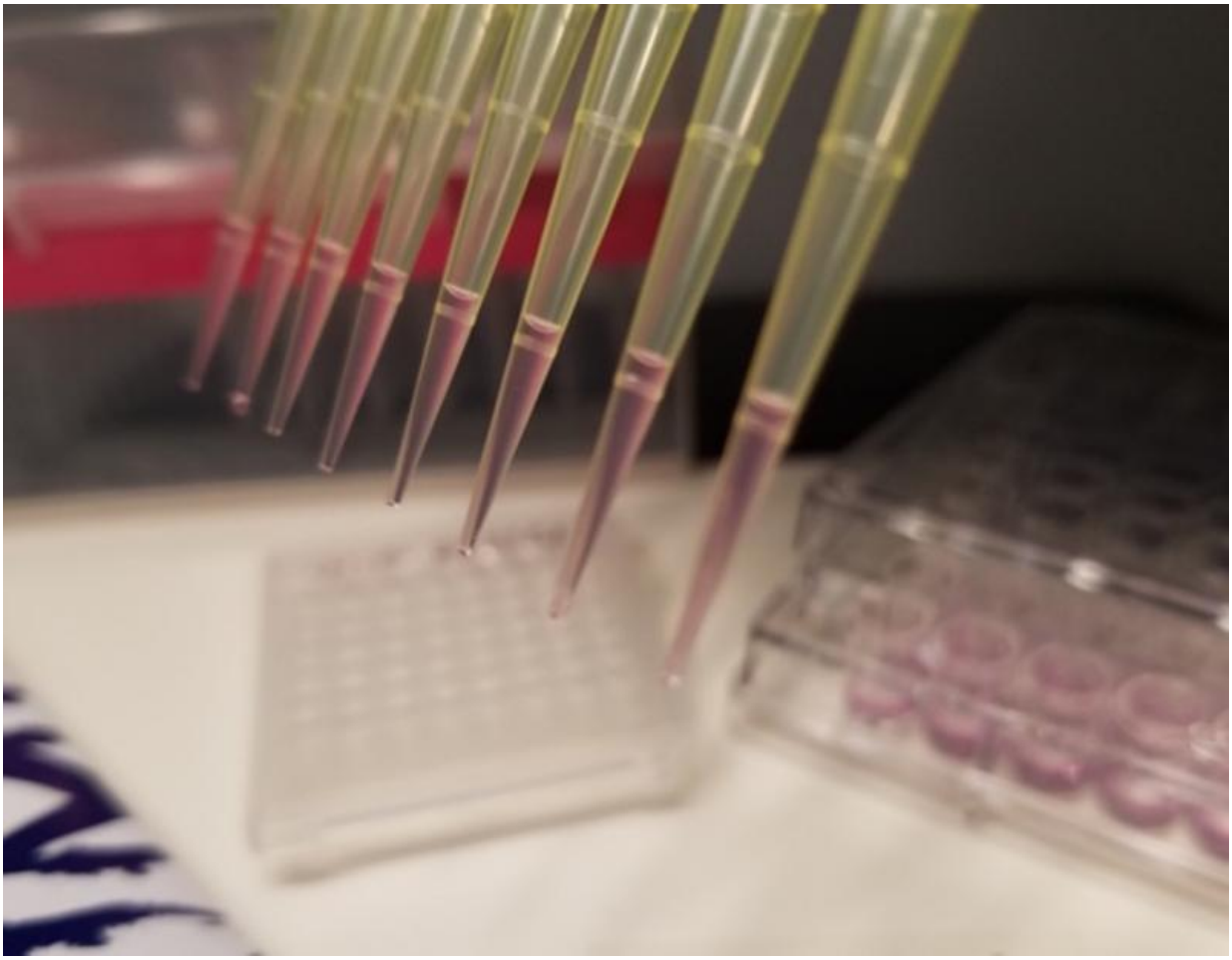
Can the study of epigenomics lead to personalized cancer treatment?

April 4 2017, by Fabian V. Filipp



Cancer precision targeting at the Systems Biology and Cancer Metabolism Laboratory. Credit: Systems Biology and Cancer Metabolism Laboratory. Credit: Fabian V. Filipp, Author provided

Molecular insight into our own DNA is now possible, a field called personal genomics. Such approaches can let us know when we might have cancer-causing alterations in our genes. Well-known examples are the melanoma oncogene BRAF kinase, the breast cancer gene BRCA1 and the prostate specific antigen PSA.

But there is more to cancer and other diseases than our genes. In addition to the DNA code, there is a hidden layer of regulation controlling the activity of genes – while not changing the DNA itself. This field, called epigenetics, is the study of how genes are regulated to express themselves, even though they rely on the same genetic information. A gene is still a gene, but it responds differently to many facets of its chemical environment.

For example, have you thought about why identical twins are different? How it is possible that the lifestyle of our grandparents can affect our lives today? Something beyond our DNA is at work. This is epigenetics.

The hidden layer responsible for fine-tuning alongside our DNA is called epigenomic regulation. Epigenomics is the field of quantifying epigenetic marks on a genome-wide scale, thereby capturing a snapshot of our epigenetic state.

Recently, the systems biology and cancer metabolism lab at UC Merced published discoveries about an epigenetic factor called Jumonji. This factor not only affects how an entire network of cancer genes behaves; it actually takes on the role of a cancer gene, bringing uncontrollable cell growth.

Epigenomics captures how gene activity is controlled

Already, doctors and others who diagnose diseases can, to some degree, use personal genomics tests that integrate our unique genetic makeup

into clinical decision-making. However, there is more to our genome than what such tests can reveal.

Epigenetics makes sense of chemical modifications that can switch genes on or off. Importantly, none of these modifications changes the DNA sequence. Alternatively, our own cells use epigenomic regulators to control the activity of genes. If the right chemistry is in place, the right gene products are expressed at the right time.

Environmental influences like nutrition or cigarette smoke as well as our own hormones have strong epigenetic impact and affect how active our genes are.

In a disease such as cancer, epigenomic regulators such as Jumonji are often mistuned, causing them to affect gene activity. One thing they may do is to fail to put the right chemical modifications on their target genes, which rely on many factors to switch their activity on or off. This can lead to altered metabolism, which promotes unlimited cellular growth. Once cells have unlimited ability to divide, a tumor forms.

The researchers found that Jumonji is overabundant in cancer cells and promotes uncontrolled division of cancer cells, which leads to unstoppable tumor growth. Jumonji takes the role of an epigenetic master regulator of cancer genes.

In addition, Jumonji teams up with hormone-dependent regulators that are responsible for treatment-resistant cancers.

Systems biologists can help to understand how we can overcome resistances. Systems biology opens possibilities to understand regulatory signals and circuits that govern our cells. If we are able to comprehend these signals, we can design drugs to break unwanted circuits and overcome resistances. Given its hidden, complex nature, epigenomics

benefits from a systems biology approach that lays open critical wiring of our cells.

Artistic illustration of an epigenomic handprint capturing regulation of a person beyond changes in DNA. In background research campus with art statue 'New Beginnings,' symbolizing hope for cure. Credit: Systems Biology and Cancer Metabolism Laboratory, Fabian V. Filipp

Toward personalized epigenomics

Epigenomics has a lot of promise for cancer treatments, but there are

still many more questions that we need to answer. What does the epigenome of a healthy person look? And how does the epigenome change as we age? How does the epigenome of a sick person differ? In the future, these important questions will be addressed by personalized epigenomics, which tries to extract information out of a comprehensive picture of a person's epigenome.

You may ask: Why can we not create a simple test that tells us if we have good genes but an unfavorable epigenome?

Our epigenome is highly dynamic. Epigenomic regulators are nonstop at work, including Jumonji, removing or adding chemical marks allowing for transient gene readouts while blocking it in the next minute.

Is it too early for consumers to think about personalized tests? Is the information still too cryptic or too unreliable to draw conclusions?

Personal gene tests for cancer exist. Hollywood actor Ben Stiller claims a simple genetic test for abnormally high levels of the prostate antigen saved his life.

Abnormally high levels of the prostate specific antigen in the blood can mean that a man has prostate cancer, but not always. That is why the test is not FDA-approved. And this test does not take epigenetic factors into account.

Cancer drugs against epigenomic factors promise hope

Drugs targeting the epigenomic machinery raise optimism as a viable direction of clinical research. Present-day clinical questions relevant to epigenetic research address which drug molecules modify the epigenome

and which specifically kill cancer cells. It is open whether epigenetics is on the good or on the bad side of cancer. Researchers found that epigenetics can even assist the cancer cells to manipulate our own immune system and to evade the drug targeting approaches.

According to recent genomic insights, researchers compare the delicate equilibrium to Yin and Yang, complementary forces that keep each other in check. If one force overtakes the systems, it is out of equilibrium. For the cells this means either unlimited growth, cancer or death. Without doubt, once we have a better understanding of epigenetic regulation, we can design drugs that counterregulate these factors.

This is beginning to happen with some cancers. Recent breakthroughs in melanoma research identified a genetic mutation of an epigenetic player. Cancer resistance to treatment is a major obstacle. However, epigenetic drugs, on their own or in combination with other drugs, can be a viable alternative.

The epigenetic drug used in the laboratory study stops the ability of cancer cells to hide from the immune system and makes the tumor vulnerable. For cancer patients with epigenetic activation, epigenetic drugs promise hope.

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