BroadcastMed | Grand Rounds: The Promise of Epigenomics in Medical Research and Future Practice

RAUL URRUTIA: My name is Raul Urrutia. I represent the Translational Epigenomic Program of the Center for Individualized Medicine. And today, I will be talking about the promise of epigenomics in medical research and future practice. I have nothing to disclose, and our planning committee has nothing to disclose either.

Our objective is for students to learn about the definitions and the history of epigenetics and epigenomics, both the fundamental epigenetic and genomic mechanisms underlying the regulation of gene expression, DNA modification, chromatin dynamics, and how they contribute to inheritance, the role of epigenetics and epigenomics in human diseases, and the usefulness of epigenetics and epigenomics in diagnostics and therapeutics.

So please consider that we have been explaining the cycle of life, health, and disease and inheritance, primarily through the coding capacity of DNA. Science has celebrated the birth of genomics by publishing really high top-tier journals in funding. Why? Because it allows us to explain health and disease. The popular press has celebrated the birth of genomics. Medicine celebrates the birth of genomics because it allows us to explain human variation, disease mechanisms, allows us to develop very robust diagnostics, and we have the promise of gene therapy.

In our quest to conquer diseases and to honor our "patient first" commitment, we have strategically embraced new concepts and new methodologies from genomics-- remarkable. These new tools, no doubt, are advancing the mission of our three shields. However, we must consider a little or a big knowledge gap and that within humans or among humans and other organisms there are inherited variations which cannot be explained by the coding capacity of the DNA.

Look around nature. Consider, for instance, how remarkable different phenotypes like this butterfly from this caterpillar come about even having the same underlying DNA. If you were from outer space, you would think that these are two different organisms, and they have different DNA, but indeed they don't.

Consider human cells, for instance. We came from embryonic stem cells, and we can give rise to a large amount and variety of cell types with different morphologies. If you thought that these were unicellular organisms just like amoeba, then they would have like 40, 50, 100 different types of these organisms in ourselves. And indeed, they have the same genome.

Consider, please, time. We age. And while we age, the sequence of our genes seldom changes.

Consider, please, identity. Homozygotic twins-- we know that they have the same genetics. But many times they are different and so different that some of them develop diseases. We can find affected twins and unaffected member of that pair. The recent sequencing of the MS genome has shown that a small percentage of the problems in MS are explained by changes in the DNA code.

In other words, genomics cannot explain a large amount of mechanisms underlying the cycle of life and disease. We need to consider other concepts and other methodologies, and that's where epigenomics come to time.

So let me introduce a definition of epigenomics or epigenetics. It The term epigenetic was introduced first by Conrad Waddington in 1942 to explain those mechanisms, those changes in variations in phenotype, that occur independently of the DNA code. Please notice that this is 1942, and the DNA double helix was not published until 1952 or '53, so 10 years before it was introduced. I will show you-- one of our preferred definitions is the study of mechanisms that determine and propagate phenotypic variation above and beyond the DNA sequence. So epigenetic is above and beyond and compliments genetics.

Some things to consider-- epigenomics seeks to understand not the inheritance of this sequence of the genome but the regulation of the genome in an inherited manner. The regulatory mechanism for expressing the genome at the right level, at the right time, and the right place in order to give rise to particular phenotypes.

Epigenomics consider the mechanisms used to regulate the genome are inherited, just like genetics, so that their phenotype of individuals of the same species are maintained.

Epigenomics considers that alterations in mechanisms that regulate the genome are inherited as well, and these alterations inherited give rise to diseases independently of the DNA code, that environment has the capacity of modifying this regulatory mechanism code that environment can modify the epigenome. And if inherited, these modifications, independently of the DNA code, will influence a state of health and a state of diseases. That's the DNA give us the potential to be who we are, but epigenomics transformed this potential into the reality of who we are.

So we need to consider some mechanism, and we are learning as we go. Is there a code, just like the genetic code? Is there an epigenetic code? And I give you the take-home message, and we will expand from here. The epigenomic coding capacity relies on writing, reading, and erasing chemical marks-- and remember that key word, marks-- on DNA and the associated proteins. Now we know that DNA and associated proteins make what is called chromatin. So marks on chromatin are the mechanistic core of the epigenomic code.

Chromatin is in our cells to pack, to fold, and protect the DNA. And in doing so, I show you that they create a code, the epigenomic code. For instance, we have heterochromatin right here, which is a dense string-like fiber and keeps the gene silent. We also have euchromatin, which is a relaxed string-like fiber that keeps gene active. And there is a constant transition between euchromatin active gene expression and heterochromatin inactive gene expression. How does it come about?

Well, marks on the DNA and surrounding proteins-- for instance, histones-- are signaling to induce these transitions between the euchromatin, when the genes are on, and the heterochromatin, when the genes are off, as they can be in the cartoon. This is naked DNA. And this is the first euchromatic fiber. It's relaxed. The machinery that reads the genome can access this. There is epgenetic marking, in other words, the depositing of marks in DNA, such as DNA methylation, as you know, and in histones, such as histones marks, and those signal for the transition between the active euchromatin to the inactive heterochromatin.

So physiopathological and pathological stimuli chemically modified, in the form of marks, the genome and the epigenome. These marks are interpreted into a defined pattern of gene expression that will give rise to the inheritable phenotype.

So we must consider then something extremely important-- that the environment is able to impact on the epigenome and thereby impact our phenotype. The epigenome is regulated by environmental signal. One of the bases, and in fact, an important nascent basis of environment gene interaction. This happens at a whole organism level, or it can be also better explained in a cell. When a signal comes, an activator receptor goes through the cytoplasm, gets to the CPU, the brain of the cells, which is the nucleus, and then acts and marks either the DNA or histones. And there are those marks on chromatin that turn gene on and off-- right level, right place, at the right time to make the right organ and to keep homeostasis.

And very important-- DNA and histones marks are inherited. So this is one of the models out of several of the inheritance of the epigenomic marks. So what you can see is that replication fork-- how a single strand of DNA will give rise to two strands of DNA. Not only DNA is being replicated, but the marks that have been deposited before the DNA replication are reproduced again, reconstituted in each time on cell division, so that a cell, for instance, that gets transformed by those marks will give rise to cells that are transformed.

Consider, for instance, going from a fibroblast to [INAUDIBLE] something very important in regenerative medicine. What happened is I have put here the genes that are in the fibroblast and sequestering to heterochromatin in an silent state, you have neuronal genes. But if you are able to activate them, then these cells will be reprogrammed into neuronal cells just by the mere transition from heterochromatin to euchromatin. So fibroblast-specific genes have turned off, and not only one gene, not only two genes, but entire gene networks that bring the phenotype into being.

Now we said that at the core of these there are the marks, and I hope that when you go out, you start talking to each other about the marks because this is very important. But who regulates the marks? | there are enzymes that deposited these marks. You know very well for DNA methylases, there are writers, as we call them now. Not only they have to be deposited, but they have to be read. And these are read by a group of enzymes called the reader enzymes. And sometimes they have to be erased, such as in reprogramming, and that is achieved through the work of eraser enzymes. So we have the histone marks and DNA marks. The writers, the readers, and the erasers are at the core of the epigenomic code.

Let me give you an example on the role of epigenetic indices. Just like genetic alterations, epigenetic mechanisms can lead to the inherited aberrant silencing or activation of genes and thereby leading to diseases. There are many diseases that I could bring as an example. I will use a very simple example of cancer, where we sequester tumor suppressor genes into silent heterochromatin just by DNA methylation marks or histone marks or chromatin marks, and we turn them off to give rise to neoplasia.

So we go from having a gene that suppresses cancer, such as a tumor suppressor, and is in the active state [INAUDIBLE] euchromatin, and we experience it all the time to protect ourselves from cancer. And then we sequester it into inactive heterochromatin. And that is a remarkable step. Without that step, not even an oncogene can give rise to cancer. And this happened from this transition, as I said, from euchromatin to heterochromatin, which mediated by the marks that are deposited by the writers, interpreted by the readers, and sometimes then erased as needed by the erasers.

Diabetes, obesity, cardiovascular disease, endocrine disease, neurological diseases are increasing numbers of diseases that we can explain through epigenomics.

What about therapy then? Well, in contrast to genetic alteration, we have been working for the last 20 years--