B·DEBATE International Center for Scientific Debate BARCELONA

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## Synopsis

# EPIGENETIC MECHANISMS IN HEALTH AND DISEASE

BARCELONA CONFERENCE ON EPIGENETICS AND CANCER (BCEC)

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# MECHANISMS OF EPIGENETICS: IN SICKNESS IN HEALTH

Genetic information is encoded in our DNA, which is metaphorically known as an instruction manual. However, this 'manual' is hard to interpret and the same instructions are used to create cells that are extremely different, like neurons and skin cells. In reality, it is more like **a choreography in which genes switch on and off depending on the time, circumstances and place.**

In this metaphor, beyond genetics, epigenetics would be directing the dancing. It encompasses a series of regulatory layers that use interconnected mechanisms to coordinate what each cell should do at any given time. We do not yet understand many of these mechanisms but they are so important that **alterations in the system can lead to numerous very serious problems**. Of all of these, one of the most widely studied is its relationship with **cancer** and epigenetic markers are already being used in some cases to refine diagnoses or guide therapy.

To discuss some of the latest, most important advances in this field, several top international experts met for a session of B·Debate, an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate. This is the fifth time this series of conferences on epigenetics has been held, helping put Barcelona in the spotlight in this booming field. In this occasion, the B·Debate was organized jointly with the Institute of Molecular Biology of Barcelona (CSIC) and the Institut d'Investigació contra la Leucèmia Josep Carreras (IJC), with the collaboration of the Institut de Recerca Biomèdica (IRB Barcelona), the Program 'Epigenetics and Cancer Biology (PEBC, IDIBELL) and the Center for Genomic Regulation (CRG).

## CONCLUSIONS

- Epigenetics is responsible for proper development of cells and tissue. Alterations in how it works are associated with serious diseases, including nearly all tumors.
- There is a very close connection between the most basic and applied research. The study of epigenetic mechanisms is yielding hints to possible treatments.
- Some of the applications of epigenetics to treat cancer include guiding certain therapies and classifying tumors of unknown origin.

- The genome is no longer seen as a linear instruction manual. To be read, its 3D structure is key and is one of the mechanisms of cell identity.

# 1. EPIGENETICS: FROM KNOWLEDGE TO APPLICATIONS

Although it is not always obvious, there is an intimate connection between the most basic research (that geared towards researching the most intimate mechanisms of cells) and applied research (which seeks more tangible, practical uses and, in the vast majority of cases, couldn't exist without the former). One example of this relationship emerged in the presentation given by Manel Esteller, director of the Cancer Epigenetics and Biology Program (PEBC) at IDIBELL Barcelona.

"**Epigenetics is responsible for different types of tissue developing from stem cells, and even for some cells returning to stem cells**," explained Esteller. But this basic function, *in health*, can be altered. It is so closely tied to cell division that changes in how it is regulated are part of nearly all tumor processes. "One of our lab's main goals is to have the results of our research help improve how cancer patients are managed," he said. His team has worked on a wide array of lines of research, all touching on various areas of epigenetics, in particular those associated with DNA methylation.

**In general terms, there are three types of epigenetic mechanisms: DNA methylation, histone modifications and non-coding RNA**, all of which interact and *play* amongst themselves. The first is when methyl groups are added to the DNA molecule, which tends to compact it and make it harder to read, inhibiting gene expression. Histones are the proteins that DNA coils around and, depending on the chemical markers added, they can also make it more compact or open, block or allow entry and reading. Non-coding RNA are truncated messengers. While RNA is the mediator between DNA and its final product, proteins, this type in particular does not create any proteins, it normally impedes others from doing so. It is, once again, an inhibiting agent.

"One of the fundamental pillars of cancer epigenetics," explained Esteller, "is that it can **inhibit tumor-suppressor genes**, generally through methylation gain. They are genes that aren't mutated, but hyper-methylated." Some of them can **also condition treatment**, like the MGMT gene, whose methylation is associated with the success of chemotherapy in gliomas, a type of brain tumor. "We've also seen that methylation of the

SLFN11 gene is associated with sensitivity to platinum-based therapies, which could be a step forward in personalized medicine," Esteller commented.

This type of methylation tends to occur in the vicinity of some genes, those called promoters, acting as a sort of lock that allows or impedes entry and reading. But it is much more complex than this. "We've seen that it can also happen in the enhancers." These switches or enhancers are located far from the genes, but **DNA has a 3D structure and, due to its spatial make-up, they can *get in there* and have a direct influence on expression**. "We've seen that a gene associated with Fanconi anemia and DNA repair (and therefore with many tumors) can be altered by the methylation of an enhancer," explained Esteller. "That's why we hadn't seen it in all these years."

One of the applications of DNA methylation already available in clinical practice is **classifying cancer of unknown primary site**. In 5% of patients, "physicians detect cancer that has already metastasized but can't find the primary origin." The prognosis in these cases is very bad, because there are not any clues as to the most effective treatment. In Esteller's lab, they have been able to identify origin based on methylation profiles quite precisely. Although they are still very serious cases, the **tool improves life expectancy and has already been approved for clinical use**.

These are some examples of applications from research. But many aspects of the most basic, intimate mechanisms of epigenetics are still not understood. A large part of the advances presented were associated with genome architecture and another key pillar: histones.

## 2. ARCHITECTURE AND HISTONES: A 3D POP-UP BOOK

More than an instruction manual, **DNA works like a three-dimensional pop-up book**. Constrained in the nucleus of cells, it is packaged with the help of histones, a type of protein it winds around. For some years now we have known that these histones can also undergo chemical alterations that condition DNA reading, but we are still far from understanding the code in full.

The group led by Carl Wu, professor at Johns Hopkins University in Baltimore, is unravelling some of these mysteries. For example, they have studied how the **histone H2A.Z is involved in both enhancers and promoters**, key areas of gene

regulation. It does this through a protein called SWR1, which intercedes in its exchange for other histones that previously occupied its spot. This journey and this exchange may be key factors in controlling gene expression.

The group led by Susan Gasser, director of the Friedrich Miescher Institute for Biomedical Research in Basil, Switzerland, uses worms called C. Elegans to study **how the multitude of repetitive elements** in our genome that don't give rise to proteins are controlled. Their work has established the importance of one type of methylation in type H3 histones (H3K9) for regulating and repressing transcription. Using animals in which this methylation is suppressed, they have proven that, in its absence, "there is a general deregulation and accumulation of DNA damage."

The work of Wendy Bickmore, professor at the MRC Human Genetics Unit in Edinburgh, has proven that the **spatial organization of chromosomes is also essential and that they have a preferred position inside the nucleus**. Although many histone modifications depend on what are known as polycomb complexes (groups of proteins that acts as a catalyst and coordinate reactions needed to add the various chemical groups), some of their effects are not directly contingent on these modifications, but on changes caused to the spatial set-up of the DNA. This is why these complexes are called "**the master weavers of the 3D genome**".

"**Something I was always interested in was knowing which mechanisms allow cells to maintain their identity**," confessed Amos Tanay, of the Department of Computer Science and Applied Mathematics at the Weizmann Institute in Israel. Cells divide, but somehow the daughters remember what they were before the division. "There are several mechanisms that explain this: one of them is the marks on the DNA that are passed along when the cell divides, like methylation. But there are others, like the **relationship with neighboring cells**, which helps form and maintain cell identity. And, even, the **organization of chromosomes inside the nucleus is important**." New 'single-cell' analysis techniques have allowed this group to study the architecture of the cell genome throughout its lifecycle, how it is organized into compartments and how different chromosomes come to relate to each other.

## 3. SOMEWHERE BETWEEN BASIC AND APPLIED

Many studies fall somewhere in between basic research and its possible applications. The group led by Eran Meshorer, researcher at the Hebrew University of Jerusalem in Israel, is studying normal stem cells, but their alterations are intimately linked to cancer so they

are always related. It not only seems they are the origin of many tumors, but also inside them "**there seems to be a hierarchical structure, where cancer stem cells *feed* the tumor**," commented Meshorer. In his lab, they have observed the crucial role played by one type of histones, encoded as H1.0, in controlling cell proliferation. "We've seen that expression of this type of histones is reduced in cancer stem cells and if we get them to express them again, they lose their cancerous properties." This observation seems to have clinical repercussions as well: "**When we classify patients according to H1.0 expression, it is associated with chance of survival in every type of tumor we look at**."

Another example was presented by Wendy Béguelin, researcher at Weill Cornell Medicine in New York. **During an immune response, B lymphocytes that produce antibodies multiply and divide in the lymph nodes**. EZH2, an enzyme that acts as a catalyst for a specific type of histones (H3K27me) and boosts cell flexibility to foster accelerated division, plays a key role in this process. Nevertheless, a mutation on this level predisposes people to developing tumors. This happens in 30% of patients with two specific types of lymphoma. And this is why **there are already EZH2 inhibitors being tested in clinical trials.**

But not all alterations are associated with cancer. Epigenetics is such a crucial part of cell function that **alterations in how it works may be behind diseases that have nothing to do with tumors, such as albinism**. This is "a genetic condition that may be caused by mutations on up to 20 different genes," explained Lluís Montoliu, professor at the National Center for Biotechnology in Madrid, who also highlighted that "**the biggest problem facing these individuals isn't the lack of pigment in their hair or skin, but their serious eyesight problems**."

Although much is known about the genetics of this condition, "**in 30% or 40% of cases, we can't make a proper diagnosis**." Meaning they do not have any of the known mutations. "We could contemplate it is because they are on other genes, but we think it is due to changes in elements that regulate the genes we already know," added Montoliu. And this seems to be the case. Before, given the structure of the genome, "it was very difficult to research these elements in the laboratory. For twenty years, we couldn't study them." But new technology today, especially that based on the CRISPR/Cas molecular scissors, has opened up a much simpler and more accessible path.