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Researchers at the University of Geneva have uncovered an epigenetic mechanism that prevents the activation of numerous genes, including those involved in the growth of breast cells

Our DNA is compacted into the cell nucleus thanks to its winding around proteins called nucleosomes. When a gene must be transcribed to produce proteins, the nucleosomes present must be temporarily ejected to enable the gene to be unwrapped. A team of biologists from the University of Geneva (UNIGE), Switzerland, studied the functioning of nucleosomes associated with genes activated by estrogens, which drive the growth of breast cells. They discovered that the stability of these nucleosomes, namely their tendency to be ejected, is determined by a biochemical modification on some of their components, called histones H2Bub1. The details of this new epigenetic mechanism - which modifies DNA without affecting the sequence - are published in the journal *Molecular Cell*.

Estrogens are responsible for the survival and proliferation of a certain type of breast cells, whether healthy or cancerous. The hormones act by binding to receptors called ERα, which activate various genes responsible for cell growth. 'These genes are generally wrapped around protein complexes called nucleosomes. The nucleosomes must be temporarily ejected so that genes can be deployed, allowing ERα to access them and activate their transcription', explains Didier Picard, professor at the Department of Cell Biology of the UNIGE Faculty of Science.

Modifying a molecule to stabilize the whole complex

The stability of nucleosomes, that is to say their propensity to be ejected, is primarily determined by biochemical changes on the proteins that compose them, called histones. 'These alterations, targeted and reversible, play a crucial role in the regulation of gene expression at the level of the whole genome. Indeed, the type of histone modification and the temporary composition of nucleosomes will determine their role as activators or repressors, as they affect access to genes. This allows a given gene to be expressed only at a given time', says Gregory Segala, researcher from the Geneva team and first author of the article.

The biologists have investigated the functioning of nucleosomes present in the region of DNA that binds ERα in human mammary cells. This highly dynamic region is subjected to strict controls governing the expression of estrogen-dependent genes, to prevent uncontrolled cell growth and proliferation. It is thus equip-

ped with distinct nucleosomes, composed of specific histones. The latter confer varying degrees of stability to the nucleosomes and influence their propensity to be ejected quickly, for a precise and fast adjustment of this control. 'We discovered the existence of stabilizing elements, called H2Bub1. This is a type of modified histone that, once incorporated into these nucleosomes, prevents their ejection', reveals Didier Picard. However, when certain signals increase sharply, H2Bub1 loses this modification, and the nucleosome, having become unstable again, is ejected: the gene unwinds and can bind ERα to be activated.

A widespread mode of epigenetic regulation

Histone modifications are described as epigenetic because they do not induce any change in the sequence of the DNA itself. Molecules added to or removed from histones, under the controlled action of an enzyme, act in fact as a signal, a kind of molecular switch capable of modulating the expression of a gene. The Geneva group demonstrates a repressor role for histone H2Bub1 in gene expression, which also extends to numerous genes that can be induced by specific factors, depending on the cells and the tissues in which they are located.

These guardians of nucleosome stability may be absent in certain conditions: 'A marked decrease in the amount of histones H2Bub1 was observed in breast cancer tissues compared to healthy ones. The mechanism controlling the expression of estrogen-dependent genes, which we uncovered, thus no longer exists in these cells', notes Gregory Segala.

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