

# Glosario fraseológico de genomic imprinting

*Maria Verónica Saladrigas*

Servicio de Traducción, Novartis Pharma AG,  
Basilea (Suiza)

## acetylation

### acetilación

En los genes sellados también se observan cambios en la cromatina y modificaciones más específicas, como la acetilación de histonas<sup>1</sup>.

## androgenote (*androgenetic zygote*) → gynogenote cigoto androgénico, androgenoto

Removing a maternally derived pronucleus and replacing it with a paternally derived pronucleus results in a genotypically identical zygote that has received all of its genetic information from the father (an androgenote)<sup>2</sup>.

## antisense RNA, aRNA (*complementary RNA*) → sense RNA

### ARN antimensajero, ARN complementario

An RNA sequence that is complementary to all or part of a functional mRNA molecule, to which it binds, blocking its translation<sup>3</sup>.

**Nota:** los ARN complementarios pueden ser sintéticos o naturales. Cuando son sintéticos suelen llamarse *micRNA*, por *messenger-RNA-interfering complementary RNA*<sup>4</sup>, una molécula de ARN monocatenario de secuencia parcial o totalmente complementaria a un ARN transcripto natural. Los naturales suelen desempeñar una función reguladora disminuyendo la expresión del ARNm correspondiente.

## antisense strand (*non-coding strand, anticoding strand, template strand, complementary strand, minus strand, transcribing strand*) → sense strand

### hebra no codificadora

The DNA strand that forms the template for both the transcribed mRNA and the coding DNA strand<sup>4</sup>.

**Nota:** de todos los sinónimos aquí recogidos, la JCBN (Joint Commission on Biochemical Nomenclature) y la NC-IUB (Nomenclature Commission of the International Union of Biochemistry and Molecular Biology) prefieren la voz *non-coding strand* (hebra no codificadora) para designar la hebra de secuencia complementaria al ARN (mensajero, ribosómico, de transferencia), es decir, la que sirve de plantilla para la síntesis de ARN. Éste es idéntico en secuencia a la hebra codificadora o *sense strand* (salvo que en el ARN el uracilo reemplaza a la timina)<sup>4,5,6</sup>.

## chromatin boundary (*chromatin insulator*)

### aislador de la cromatina

These results raised the possibility that, under normal circumstances, this region might act as an *insulator* or *chromatin boundary element*, shielding the maternal Igf2 promoters from the H19 enhancers<sup>7</sup>.

## chromatin insulator → chromatin boundary

### aislador de la cromatina

## conditioned

### acondicionado

Para explicar sus resultados, McGrath y Solter aventuraron la hipótesis de que el genoma materno o paterno es acondicionado (*conditioned*) o modificado (*altered*) durante la gametogénesis y que ese ‘acondicionamiento’ es totalmente reversible<sup>1</sup>.

## core DMRs → primary DMRs

## CpG islands

### islas de CpG

Sequence regions where there is high density of CpG residues are termed CpG islands, and are loosely defined as being sequences of 200-plus base pairs with a G+C content of greater than 50% and CpG/GpC ratio of > 0.6 (Gardiner-Garden and Frommer, 1987)<sup>8</sup>.

## cytotrophoblastic cells → hydatidiform mole

### células citotrofoblásticas

## de novo methyltransferase

### metiltransferasa de novo

*De novo* methyltransferases are believed to be responsible for establishing methylation patterns in unmethylated DNA<sup>9</sup>.

## deacetylase → histone deacetylase

### desacetilasa

## demethylase

### desmetilasa

The role of demethylases, capable of removing d<sup>m</sup>C residues, is still not well characterized but may be involved in modifying methylation patterns in nondividing cells<sup>9</sup>.

## dermoid (*benign ovarian teratoma*)

### quiste dermoide<sup>10</sup>

Dermoids, on the other hand, are maternally derived diploids with no paternal genome component, possibly resulting from an unfertilized oocyte. These cysts, called *benign ovarian teratomas*, show disorganized fetal structures often including teeth, hair and bone tissues, supporting the fact that the maternal genome is essential for fetal development but incapable of supporting the development of embryos to term<sup>11</sup>.

### **differentially methylated regions, DMRs**

#### **regiones de metilación diferencial**

Los genes sellados de las células somáticas contienen una o más regiones de metilación diferencial (*DMRs*, *differentially methylated regions*), de modo que uno de los alelos es metilado en ese determinado sitio o región y el otro no<sup>1</sup>.

#### **direct repeats**

#### **repeticiones directas, secuencias repetidas de nucleótidos en idéntica orientación**

Two or more stretches of DNA within a single molecule which have the same nucleotide sequence in the same orientation. Direct repeats may be either adjacent to one another or far apart on the same molecule. For example TATTA...TATTA

ATAAT...ATAAT<sup>3</sup>

**Nota:** se denominan asimismo *tandem repeats* cuando son adyacentes; en este caso pueden traducirse por «repeticiones directas adyacentes».

#### **DNA demethylation**

#### **desmetilación del ADN**

Este proceso puede ser revertido mediante histona-acetiltransferasas (*histone acetyltransferases*) y desmetilación del ADN (*DNA demethylation*)<sup>1</sup>.

#### **downstream → upstream**

#### **en el extremo 3'**

The paternally expressed *Igf-2* gene lies immediately downstream from *Ins-2*<sup>12</sup>.

In molecular biology, the stretch of nucleotides of DNA that lie in the 3' direction from the site of initiation of transcription, which is designated as +1 (remembering the convention that the sequence of a DNA molecule is written from the 5' end to the 3' end). Downstream nucleotides are marked with plus signs, e.g., +2, +10. Also, to the 3' side of a particular gene or sequence of nucleotides<sup>3,13</sup>.

#### **enhancer**

#### **potenciador de la transcripción**

A 50-150 bp sequence of DNA that increases the rate of transcription of coding sequences. It may be located at various distances and in either orientation upstream from, downstream from or within a structural gene. The site binds cellular transcription factors, including steroid-receptor complexes<sup>3,13</sup>.

#### **enhancer competition model**

#### **modelo de la competencia por potenciadores**

Se conocen por lo menos cuatro modelos de sellado genómico: 1) El modelo de la competencia de los ARN mensajero (*sense*) y complementario (*antisense*) por la expresión aleloespecífica del gen *Igf2r* en el cromosoma 17 del ratón; 2) el modelo de la competencia por

potenciadores (*enhancer competition model*) de los genes *Igf2* y *H19* murinos y humanos; 3) el modelo del centro de sellado bipartito, con varios genes sellados en la región del síndrome de Prader-Willi/Angelman (PWS-AS); y 4) el modelo de impresión inversa específica de promotor del locus *Gnas* en múridos y humanos<sup>1</sup>.

#### **enucleated oocyte**

#### **ovocito desnucleado**

Cloning of various mammalian organisms has been achieved recently using donor nuclei from differentiated cells. Gene expression and, presumably, epigenetic modifications need to be reprogrammed when the somatic nuclei are introduced into the enucleated oocyte<sup>14</sup>.

#### **epigenetic**

#### **epigenético**

The adjective *epigenetic* has been used to describe many types of biological processes, but with the evolution of epigenetics into a subdiscipline of molecular biology, its meaning has become quite focused. Although the term is sometimes used more broadly, epigenetic effects are usually taken to encompass changes in the genetic material –the genomic DNA and chromatin– that alter gene expression in a manner that is heritable during somatic cell divisions (and sometimes even in germline transmission), but that is non mutational and therefore fundamentally reversible<sup>15</sup>.

Descriptive of control phenomena superimposed upon DNA-sequence based phenomena, such as genetic imprinting, tissue-specific development, etc.<sup>13</sup>

#### **epigenetic inheritance**

#### **herencia epigenética**

Imprinting is a special type of epigenetic inheritance that is passed through the gene line into somatic tissues of the progeny and is parent-specific<sup>16</sup>.

Both genetic and epigenetic mechanisms can be inherited, although the patterns of genetic inheritance are much better understood than epigenetic inheritance<sup>17</sup>.

#### **epigenetic phenomena**

#### **fenómenos epigenéticos**

The epigenetic phenomena that are known to influence, regulate, or correspond to the expression (or inactivity) of imprinted genes include genomic methylation, replication-timing, and trans-acting factors that recognize specific parental DNA sequences or chromatin structures<sup>16</sup>.

#### **epigenetics**

#### **epigenética**

The term *epigenetics* has been used in two somewhat different senses. The original definition was that of C. H. Waddington (Principles of Embryology. London: Allen and Unwin; 1956) who defined *epigenetics* as all those

'interactions of genes with their environment that bring the phenotype into being'. Today, however, the term is most often used to denote all those somatically heritable changes in gene expression that do not involve changes in DNA sequence<sup>18</sup>.

Specifically, these changes consist of variations of the DNA methylation patterns that overlay the primary structure of the genome, and, logically, the study of this field has been termed *epigenetics*, the prefix *epi-* meaning *upon*, or *in addition to*<sup>8</sup>.

### **epigenome**

#### **epigenoma**

A set of what may be hundreds of genes whose function is determined by [genetic] imprinting<sup>19</sup>.

### **epigenomics**

#### **epigenómica**

An approach that views these [imprinting, metabolic networks, genetic hierarchies in embryonic development, and epigenetic mechanisms of gene activation in cancer] and other complex phenotypes from the genomic level down, rather than from the genetic level up, can provide powerful insights into the functional interrelationships of genes in health and disease<sup>20</sup>.

### **epigenotype**

#### **epigenotípo**

*epigenotype*: Genomic methylation pattern<sup>21</sup>. The proposed IC in 15p11.2 is defined by relatively small deletions that have the effect of freezing the epigenotype on the chromosome on which they occur as either maternal or paternal<sup>22</sup>.

### **epimutation (epigenetic alteration, epigenetic error, epigenetic modification, epigenetic mutation)**

#### **epimutación**

[...] just as mutations alter DNA, epimutations alter DNA methylation or chromatin patterns. Epimutations in imprinted genes can lead either to biallelic expression (*loss of imprinting*) or to biallelic silencing. How frequent these alterations are either in the germ line or during somatic development is not known. Epimutations that are not likely to have been caused by underlying DNA mutations have been observed in several disease situations, including Wilms tumour (*H19* methylation), BWS (*H19* methylation, *kvDMR1* demethylation), and PWS/AS (*SNURF-SNRPN* methylation/demethylation)<sup>14</sup>.

### **erasable imprint**

#### **sello deleble**

Although imprinted genes remember their origins, an imprint is erasable because a particular allele may be maternally inherited in one generation but paternally inherited in the next<sup>21</sup>.

### **erasure**

#### **eliminación**

Eliminación (*erasure*), impresión (*establishment*) y mantenimiento (*maintenance*) del sello gamético en un centro de sellado (*IC, imprinting centre*) en las células germinativas (*germ cells*) y durante el desarrollo embrionario<sup>1</sup>.

### **establishment → erasure**

#### **impresión**

### **gain of imprinting → loss of imprinting**

#### **ganancia de sellado, sellado adquirido**

*Gain of imprinting* i.e. loss of *IGF2* expression from one (Li et al., 1997) allele has also been reported in meningiomas (Muller et al., 2000); the meninges usually do not show *IGF2* imprinting<sup>23</sup>.

The second type of LOI [*loss of imprinting*] mutation in BWS shows biallelic *IGF2* associated with loss of expression of the maternal *H19* gene. By analogy with the mouse, this phenotype would be more usefully described as *gain of imprinting*, because the patient has, in effect, two imprinted chromosomes<sup>24</sup>.

### **gamete imprinting → genomic imprinting**

#### **gametic mark (gametic imprint, epigenetic mark, primary imprint, imprinting signal, gamete-specific epigenetic modification, imprint mark, germline methylation imprint)**

#### **sello gamético**

The *H19* DMR seems to carry a *germline methylation imprint* in the sense that the sperm copy is methylated, the oocyte copy is not, and these methylation patterns are inherited through all stages of development (Olek and Walter, 1997; Tremblay et al., 1997), except in germ cells where they are switched as appropriate<sup>25</sup>.

### **gene knockout → knockout gene**

#### **desactivación génica**

### **gene targeting**

#### **dianización génica, modificación de un gen por recombinación homóloga**

Another line of evidence was provided from a gene-targeting experiment with which two endoderm-specific enhancers located at the 3' region of *H19* were destroyed (Leighton et al. 1995)<sup>26</sup>.

*Nota*: en la *modificación de un gen por recombinación homóloga (gene targeting)*<sup>27</sup>, se anula la expresión de un gen al insertarle una secuencia de ADN exógena, o reemplazarlo por otro<sup>13,27</sup>. Si en francés se acuñó el neologismo *ciblage génique* para traducir la voz *gene targeting*, en español, para evitar el circunloquio, podríamos seguir el modelo francés y hacer lo propio a partir de diana (*cible*), dianización (*ciblage*).

### **genetic conflict hypothesis hipótesis del conflicto génico**

[...] se han propuesto varias teorías para explicar su origen, pero ninguna acierta a explicar todos los matices del fenómeno. Una de ellas sostiene que el sellado genómico evolucionó a partir de un mecanismo de autodefensa de los procariotas; la segunda afirma que surgió debido a la necesidad de restringir el excesivo crecimiento de la placenta en las hembras de los mamíferos. La tercera, y quizás más popular, es la «hipótesis del conflicto génico» (*Haig conflict hypothesis o genetic conflict hypothesis*)<sup>1</sup>.

**genetic imprinting → genomic imprinting**

**genomic imprinting** (*genome imprint, parental imprinting, genetic imprinting, gametic imprinting, imprinting*)

#### **sellado genómico**

Genomic imprinting is an epigenetic chromosomal modification in the germ line that leads to preferential expression of one of the two parental alleles in a parent-of-origin-specific manner<sup>28</sup>.

**germ cells → erasure**

células germinativas, células reproductoras

**gynogenote** (*gynogenetic zygote*) → **androgenote**  
**cigoto ginogénico, ginogenoto**

Removal of a paternally derived pronucleus and replacement by a maternally derived pronucleus results in a diploid zygote that is identical in genotype to fertilized zygotes of similar crosses, the only difference being that all of its genetic information has been maternally derived (a gynogenote)<sup>2</sup>.

**Haig conflict hypothesis → genetic conflict hypothesis**

**histone acetyltransferase → DNA demethylation**  
**histona-acetiltransferasa**

Este proceso puede ser invertido mediante histona-acetiltransferasas (*histone acetyltransferases*) y desmetilación del ADN (*DNA demethylation*)<sup>1</sup>.

**histone deacetylase**  
**histona-desacetilasa**

Estas proteínas podrían inhibir las interacciones con los factores de transcripción necesarios para que el gen se exprese; además, podrían atraer hacia sí otros elementos –por ejemplo, histona-desacetilasas (*histone deacetylases*)– que, al eliminar los grupos acetilos de las histonas, inducirían la compresión de los nucleosomas imposibilitando la transcripción (figura 4)<sup>1</sup>.  
[...] with other proteins including histone deacetylases

which remove acetyl groups from histones and contribute to gene silencing<sup>9</sup>.

**hydatidiform mole** (*hydatid mole, vesicular mole, cystic mole, complete mole*)

#### **mola hidatiforme**

Las molas hidatiformes son placas anormales, fruto de la fecundación de un óvulo sin núcleo por un espermatozoide (*spermatozoon*) o, más raramente, por dos espermatozoides. En este tipo de placenta, el gen *H19* se expresa de forma bialélica en las células citotrofoblasticas (*cytotrophoblastic cells*) que debieran expresar el ARN de *H19* sólo a partir del alelo materno, lo cual se ha interpretado como otro ejemplo de «pérdida de sellado»<sup>1</sup>.

**Igf2**

**Igf2, gen del factor de crecimiento seudoinsulínico II murino**

We will follow the usual convention of naming mouse genes in lower-case italics (for example, *Igf2*), human genes in upper-case italics (*IGF2*), and their protein products in upper-case roman script (IGF-II)<sup>29</sup>.

**IGF2 → Igf2**

**IGF2, gen del factor de crecimiento seudoinsulínico II humano**

**IGF-II → Igf2**

**IGF-II, factor de crecimiento seudoinsulínico II**

**imprint → gametic mark**  
**sello**

**imprinted expression**  
**expresión sellada**

The expression of an allele on UPD chromosomes of such persons has been thought to be suppressed (imprinted)<sup>30</sup>.

**imprinted gene**

#### **gen sellado**

For a number of imprinted genes, the imprint appears to silence gene expression, and in working parlance the *imprinted allele* is often identified with silent one. Strictly speaking (and for the purposes of this series), the imprinted allele should be understood to be the allele that has undergone an active epigenetic modification during gametogenesis, whether that modification ultimately causes transcription of a given gene to be activated or suppressed<sup>15</sup>.

**imprinting (imprintor) → imprintor mutation**  
**sellador, impresor del sello**

Researchers are now focusing their efforts on identifying the *trans-acting* modifiers of imprinting –(i.e., *imprintor* genes), understanding the role of DNA conformation and

chromatin structure surrounding imprinted loci (i.e., *cis*-elements) and on determining the role of imprinting in development (establishment of the imprint) and human disease<sup>31</sup>.

### **imprinting → genomic imprinting**

#### **imprinting centres (ICs, imprinting control sequences, imprinting control elements, cis-acting imprinting control centres)**

##### **centros de sellado**

By definition, the IC coordinate three activities: the establishment of imprint marks, the maintenance of these imprint marks throughout development, and the implementation of the preferential expression from a specific parental allele (for review, see Ben-Porath and Cedar 2000)<sup>28</sup>.

Gametic methylation of IC elements located far away from the promoter region can induce methylation/demethylation of the promoter CpG islands, thus allowing *working from a distance*. IC methylation acting in *cis* and *trans* can coordinate sense/antisense transcripts through direct promoter methylation, chromatin remodelling (e.g., by recruiting histone deacetylase), or acting on a chromosomal boundary with enhancer blocking activity<sup>28</sup>.

ICs can be defined as complex *cis*-acting elements which exist in two alternative structural forms. Switching takes place during gametogenesis where the maternal allele is set up in one conformation whereas the paternal allele adopts the alternate structure. Once established, each of these structures is maintained through fertilization and embryonic development and then, following implantation, acts as a type of regional organizer which can set up imprinted patterns of methylation, chromatin structure and gene expression<sup>32</sup>.

### **imprinting element**

#### **diana de sellado**

We have earlier proposed that CG rich sequences resembling CpG islands, which are associated with many imprinted genes and often subject to parental-specific methylation, could act as a common imprinting element.

### **imprinting mutation → epimutation**

#### **mutación de sellado**

Thus, a hypothesis was proposed: there must be an imprinting center (IC) in this cryptic deletion extent by which abnormal methylation patterns appear. This kind of abnormality is called *imprinting mutation* (Buiting et al., 1995); namely, by a mutation of the IC, the paternal chromosome shows the maternal methylation pattern in PWS, making both alleles silent, and vice versa in AS (Fig. 6)<sup>26</sup>.

### **imprinting polymorphism**

#### **polimorfismo de sellado, sellado polimórfico**

The human Wilms tumor gene, WTI, shows an imprinting polymorphism in the placenta, i.e., there are two populations, one with maternal monoallelic expression and the other with biallelic expression (Jinno et al., 1994)<sup>33</sup>.

### **imprinting status**

#### **estado sellado, nivel de expresión**

The exact role of UBE3A and GABRB3 in the syndrome and their imprinting status are under investigation.

### **imprintor mutation (imprinter mutation)**

#### **→ imprinter, imprinting centres**

#### **mutación en el sellador, mutación en el centro de sellado**

Imprintor mutations can be transmitted silently on paternal chromosomes –because these are demethylated– but reveal themselves on transmission through a female (leading to AS)<sup>34</sup>.

**Nota:** Norio Niikawa nomina *imprintor* al centro de sellado (*imprinting centre*). Para otros autores los *imprinters* o *imprintors* son elementos que actúan en *trans*. Los centros de sellado pueden actuar tanto en *cis* como en *trans*.

### **imprint-recognition gene**

#### **gen avistasellos**

### **knock-out gene → knock-out mouse**

#### **gen desactivado**

### **knock-out mouse → gene knockout**

#### **ratón con desactivación génica**

The precise function of the conserved elements within the DMR will be revealed by site-directed mutagenesis combined with gene knockout in mice<sup>35</sup>.

### **loop**

#### **bucle**

El modelo más verosímil de interacción del promotor con los potenciadores es el del «bucle» (*loop*) de ADN: el ADN se pliega para acercarse al promotor que debe activar salvando distancias considerables (100 000 pb)<sup>1</sup>.

### **loss of imprinting, LOI (relaxation of imprinting) →**

#### **gain of imprinting**

#### **pérdida de sellado, sellado deficiente**

Through an expression study of mRNA, it was shown that Igf2 is paternally and monoallelically expressed in normal individuals, but loses its imprinting (*loss of imprinting*, LOI) in a part of neuronal tissues during mid-fetal life, leading to show biallelic expression<sup>26</sup>.

[...] some diseases have been associated with *relaxation* of imprinting, such that both alleles are expressed<sup>9</sup>.

The term that we coined for this novel epigenetic alteration in cancer was *Loss of imprinting* or LOI, which simply means ‘loss of the normal parental-origin-specific pattern of differential allele expression of an imprinted gene’. Thus, LOI could involve activation of the normally silent allele (as seen in IGF2) or silencing of the normally expressed allele. LOI also need not require absolute erasure of an imprinting mark<sup>36</sup>.

**Nota:** según la definición de Feinberg, la *pérdida de sellado* puede conducir a la expresión o al silenciamiento de los dos alelos de un gen.

**loss of imprinting mutation** → *loss of imprinting*  
mutación por pérdida de sellado

**lyonization (chromosome-X inactivation)**  
inactivación del cromosoma X

Most of the second X in females undergoes lyonization and this is largely a random event<sup>37</sup>.

**maintenance** → erasure  
mantenimiento

**maintenance methyltransferase** → *de novo*  
methyltransferase  
metiltransferasa de mantenimiento

In contrast, maintenance methyltransferases preferentially recognize hemimethylated DNA and are responsible for maintaining methylation patterns through mitosis.

**maternal imprinting (paternal expression)**  
→ *maternally imprinted, paternally expressed gene*  
sellado materno (expresión paterna)

**maternally imprinted, paternally expressed gene**  
gen de expresión paterna, con sellado materno

Por ejemplo, el gen del factor de crecimiento seudoinuslínico II, *Igf2*, presenta sellado materno y expresión paterna (*maternally imprinted, paternally expressed gene*): se sella –silencia– el alelo materno. El gen de su receptor *Igf2r*, y el gen *H19*, por el contrario, presentan sellado paterno y expresión materna (*paternally imprinted, maternally expressed gene*): se sella –silencia– el alelo paterno<sup>1</sup>.

**methylation imprint** (*imprinted methylation*)  
→ *gametic mark*  
sello metílico

**methylcytosine binding proteins, MeCP2**  
proteínas de unión a metilcitosinas

La segunda se basa en la existencia de una familia de proteínas nucleares específicas, las proteínas de unión a metilcitosinas (*methylcytosine binding proteins, MeCP2*), que reconocen y se unen a las secuencias metiladas del ADN (d<sup>m</sup>CpG)<sup>1</sup>.

**nuclear transplantation technique** (*pronuclear karyoplast transplantation technique*)

→ *pronuclear karyoplast*

**técnica del trasplante de pronúcleos**

En 1984, varios grupos de investigadores llevaron a cabo una serie de experimentos, entre los que destaca el de McGrath y Solter, quienes, aplicando su «técnica de trasplante de pronúcleos» a embriones unicelulares murinos, evidenciaron que el crecimiento y desarrollo normal de un embrión de mamífero requería la presencia indefectible del genoma de la madre y del padre<sup>1</sup>.

**nullallelic expression status**

**expresión nulialélica, expresión nula**

The expression status of an imprinted gene as biallelic or nullallelic in Dnmt-/- embryos provides clues as to how methylation might act to produce monoallelic expression in the normal situation<sup>38</sup>.

**oncodevelopmental genes (oncofetal genes)**  
genes oncofetales

Los genes que se expresan durante la embriogénesis, mermando su expresión a medida que se desarrollan los tejidos, y se vuelven a expresar en diversas neoplasias, se denominan ‘oncofetales’ (*oncofetal genes, onco-developmental genes*). El gen *H19*, tan conservado en la naturaleza, pertenecería a esta categoría<sup>1</sup>.

**opening of the chromatin**  
relajación de la cromatina

En la región ampliada debajo de los cromosomas destacan los cambios epigenéticos aleloespecíficos, como la condensación de los nucleosomas por desacetilación y metilación (alelo 1), y la relajación (*opening*) de la cromatina mediante acetilación y desmetilación (alelo 2)<sup>1</sup>.

**paramutable** → *paramutation*  
**paramutable**

**paramutagenic** → *paramutation*  
paramutágeno

**paramutant** → *paramutation*  
paramutante

**paramutation**  
paramutación

*Paramutation* is defined as homology-dependent silencing of one allele by another in specific heterozygotes (Chandler et al., this issue): Alleles that induce silencing, such as *R-stippled* (*R-st*), are called *paramutagenic*; those that are sensitive to silencing, such as *R-r:std*, are *paramutable*. The altered form of *R-r:std* is called *paramutant* and is denoted *R-r:std'*. Paramutation results in a progressive increase in cytosine methylation of paramutable alleles with a

decrease in anthocyanin production in the maize aleurone (Kermicle and Alleman, 1990; Walker, 1998)<sup>39</sup>.

**parental imprinting** → *genomic imprinting*

**parentally imprinted gene** → *parental imprinting*  
gen sellado

**parent-of-origin-specific effects**

**efectos específicos de origen parental**

No obstante, existen organismos sin la actividad metiltransferasa en los que se mantienen grados estables de activación y represión génica y en los que también se observan efectos específicos de origen parental (*parent-of-origin-specific effects*)<sup>41</sup>.

**paternal imprinting (maternal expression)**

→ *maternal imprinting (paternal expression)*  
**sellado paterno (expresión materna)**

**paternally imprinted, maternally expressed gene**  
→ *maternally imprinted, paternally expressed gene*

**primary DMRs (core DMRs)** → *differentially methylated regions, DMRs; secondary DMRs*

**DMR primarias, regiones principales de metilación diferencial**

Los genes sellados de las células somáticas contienen una o más regiones de metilación diferencial (*DMRs, differentially methylated regions*), de modo que uno de los alelos es metilado en ese determinado sitio o región y el otro no<sup>26,34</sup>. Cuando estas regiones coinciden con los centros de sellado gamético (*IC*) se denominan «regiones principales de metilación diferencial» (*primary DMRs o core DMRs*)<sup>41</sup>.

**pronuclear karyoplast (membrane-bound pronuclei)**

**carioplasto pronuclear, pronúcleos rodeados de membrana**

The pipette, which now contained the membrane-bound pronuclei (pronuclear karyoplast), was moved to a second drop containing Sendai virus inactivated with β-propiolactone (2000 to 3000 hemagglutinating units per milliliter) [...]<sup>40</sup>.

**reciprocally imprinted gene (oppositely imprinted gene, inversely imprinted gene)**

**genes sellados de forma recíproca**

The genes are located only 90 kb apart in the same transcriptional orientation, but are reciprocally imprinted: *Igf2* is paternally expressed while *H19* is maternally expressed.

[...] el centro de sellado IC1 afecta a la expresión de dos conocidos genes sellados (*imprinted*), *H19* y *Igf2*, de forma

recíproca o complementaria: en el *H19* solo se expresa el alelo materno (señalado con rojo), mientras que en el *Igf2*, solo se expresa el alelo paterno (señalado con celeste)<sup>41</sup>.

**restriction landmark genome scanning method, RLGS**

**método de exploración genómica por sitios de restricción**

The strategy known as RLGS –for *restriction landmark genome scanning*– for example, uses methylation-sensitive enzymes to identify imprinted genes from genomic DNA<sup>41</sup>.

Briefly, genomic DNA is isolated and digested with a restriction enzyme to create landmark sites. One cleavage end is radioactively labeled, then the DNA is fractionated on a 0.8% capillary agarose gel. After fractionation, DNA still embedded in the gel is digested with another restriction enzyme, then the agarose gel is fused with a standard 5% polyacrylamide gel and the DNA is separated in a second-dimension. The gel is dried and subjected to autoradiography. The RLGS method visualizes the physical status of the entire genome, and different samples can be compared with one another easily. The *Arabidopsis thaliana* DNA hypomethylation mutant, *ddm1*, results in a variety of developmental abnormalities, such as changes in flower organ identity, increase in stamen number, change in response to light, and delay in flowering initiation. Each phenotype had stochastic onset, but once induced, it is heritable. Using a systematic approach with the RLGS method, we seek genes suppressed by methylation that may account for *ddm1*-induced phenotypes. Precise and genome-wide information about methylation will clarify the role of epigenetic factors in various biological issues. This result and the scanning system can be transferred to other plant species such as agricultural crops and trees<sup>42</sup>.

**reversible epigenetic imprinting signal** → *gametic mark*

**sello epigenético reversible**

**RNA interference, RNAi**

**interferencia por ARN**

In *C elegans*, injected dsRNA is an effective gene silencer on its own –a phenomenon known as RNA interference (RNAi)<sup>17</sup>.

**secondary DMRs** → *differentially methylated regions (DMRs); primary DMRs*

**DMR secundarias, regiones secundarias de metilación diferencial**

Las regiones de metilación diferencial que se observan tras la fecundación, o después de la metilación *de novo* en los primeros estadios posteriores a la implantación del

embrión, son regiones secundarias de metilación diferencial (*secondary DMRs*)<sup>1</sup>.

#### **sense RNA → antisense RNA**

#### **ARN mensajero, ARN transcripto primario**

El modelo de la competencia de los ARN mensajero (*sense*) y complementario (*antisense*) por la expresión aleloespecífica del gen *Igf2r* en el cromosoma 17 del ratón<sup>1</sup>. **Nota:** puede ser tanto el ARNm como el ARN transcripto primario<sup>11</sup> idéntico en secuencia a la hebra codificadora del ADN (*sense strand*), que se traduce en proteína.

#### **sense strand (coding strand, antitemplate strand, codogenic strand, nontranscribing strand, plus strand) → antisense strand**

#### **hebra codificadora**

The DNA strand with the same sequence as the transcribed mRNA (given U in RNA and T in DNA) and containing the linear array of codons which interact with anticodons of tRNA during translation to give the primary sequence of a protein. Compare with anticoding strand<sup>4</sup>.

**Nota:** de todos los sinónimos aquí recogidos, la JCBN (Joint Commission on Biochemical Nomenclature) y la NC-IUB (Nomenclature Commission of the International Union of Biochemistry and Molecular Biology) dan preferencia a la voz *coding strand* (hebra codificadora) para designar la hebra de secuencia idéntica al ARN (mensajero, ribosómico, de transferencia).

#### **silencer → silencing**

#### **silenciador**

#### **silencing**

#### **silenciamiento**

Silencing refers to the general inactivation of gene expression in a discrete region of the genome due to the combined action of regulatory sites on the DNA, known as *silencers*, and the proteins that act through these sites. Genetic and molecular experiments indicate that, at its most fundamental level, silencing involves the assembly of the silenced regions into a specialized chromatin structure that blocks the interaction of RNA polymerase, or virtually any other sequence-specific DNA-binding protein, with its cognate sequence<sup>43</sup>.

#### **stochastic expression hypothesis**

#### **hipótesis de expresión estocástica**

Los autores, en su «hipótesis de expresión estocástica» (*stochastic expression hypothesis*), presumen que la expresión monoalélica de los locos autosómicos sellados fue en un principio aleatoria, pero que posteriormente se volvió estable, coordinada y dependiente de la ubicación de esos alelos en un cromosoma paterno o materno dado, con la evolución de secuencias reguladoras análogas al gen *XIST*, que regula la inactivación del cromosoma X<sup>1</sup>.

#### **subtraction hybridization method (subtractive hybridization)**

#### **método de hibridación sustrativa**

[...] another approach, a screening strategy using the subtraction hybridization method, made it possible to isolate two novel paternally expressed genes<sup>26</sup>.

#### **ubiquitin-protein ligase**

#### **ubiquitina-proteína-ligasa**

El producto génico responsable de este trastorno aparentemente unigénico es UBE3A (figura 1), una ubiquitina-proteína-ligasa (*ubiquitin-protein ligase*) que actúa en la vía de degradación proteosómica de las proteínas marcadas con ubiquitina (*ubiquitin-proteosome proteolytic pathway*)<sup>1</sup>.

#### **ubiquitin-proteosome proteolytic pathway → ubiquitin-protein ligase**

#### **vía de degradación proteosómica de las proteínas marcadas con ubiquitina**

#### **uniparental disomy, UDP**

#### **disomía uniparental**

UPD is defined as an event where both of the homologous chromosomes are derived from one parent<sup>30</sup>. The nomenclature for describing a particular form of UPD is *upd*, followed by the number of chromosome involved in parentheses, followed by *mat* for maternal or *pat* for paternal origin of the disomy. Thus, disomy for maternal chromosomes 7 is designated as *upd(7)mat*<sup>21</sup>.

#### **unswitched allele**

#### **alelo no convertido**

Las microdelecciones en el centro de sellado respectivo (*imprinting mutations*) impiden el restablecimiento de los sellos conforme al sexo del individuo durante la gametogénesis. Por este motivo, en los varones portadores de este tipo de mutaciones, el epigenotipo materno del cromosoma 15 heredado de la madre no puede transformarse en epigenotipo paterno en las células germinativas (se habla entonces de un «fallo en la conversión del epigenotipo», por falta de eliminación del sello materno o de fijación del paterno). Si este alelo «no convertido» (*unswitched allele*) se transmite a los hijos, éstos heredarán dos cromosomas con epigenotipo materno: el «no convertido» del padre y el tipo materno de la madre. En estos casos, el síndrome de Prader-Willi se produce por una falta de contribución «paterna» de los genes regulados por el centro de sellado, en otras palabras, por una «disomía materna de tipo funcional» al heredar los niños un cromosoma 15 paterno con el característico sellado materno<sup>1</sup>.

#### **upstream → downstream**

#### **en el extremo 5'**

En ciertas ocasiones, la enfermedad también se manifiesta

por microdelecciones en el centro de sellado bipartito situado en el extremo 5' (*upstream*) del gen *SNRPN*, que abarca el promotor y el primer exón de dicho gen (se conocen en esta región dos centros de sellado: uno es responsable del sellado paterno, y el otro, del materno; las microdelecciones, en este caso, ocurren en el primero de ellos)<sup>1</sup>.

### ***zinc finger protein***

#### **proteína con dedos de zinc**

Que *H19* o *Igf2* puedan valerse de los mismos potenciadores depende de la presencia de un aislador de la cromatina, CTCF, una proteína que utiliza sus (once) dedos de zinc (*zinc finger protein*) para unirse al centro de sellado<sup>1</sup>. ■

### **Bibliografía**

1. Saladrigas MV. Monografía: Genomic Imprinting. Panace@ 2001, 2 (5): 57-72.
2. Sapienza C, Hall J. Chapter 7. Genetic Imprinting in Human Disease <<http://bioneer.kaist.ac.kr/labs/molgenet/lectures/AG/imprinting/ch7.html>> (14 sep. 2000).
3. Zaid A, Hughes HG, Porceddu E, Nicholas F. Glossary of Biotechnology and Genetic Engineering. Food and Agriculture Organization. <<http://www.fao.org/DOCREP/003/X3910E/X3910E00.HTM>> (11 sep. 2001).
4. Oxford Dictionary of Biochemistry and Molecular Biology. Revised edition. Nueva York: Oxford University Press Inc.; 2000.
5. The University of Edinburgh. School of Biology. Glossary of Genetics. <<http://helios.bto.ed.ac.uk/bto/glossary/ab.htm>> (3 jul. 2001).
6. International Union of Biochemistry and Molecular Biology IUPAC-IUBMB Joint Commission on Biochemical Nomenclature and Nomenclature Committee of IUBMB. Designation of the two strands of DNA, coding and non-coding (Compendium p. 334) <<http://www.chem.qmw.ac.uk/iupac/bibliog/jcbn.html>> (12 feb. 2001).
7. Reik W, Murrell A. Genomic imprinting: silence across the border. Nature 2000; 405: 408-409.
8. Malik K, Brown KW. Epigenetic gene deregulation in cancer. Br J Cancer 2000; 83: 1583-1588.
9. Richardson B, Yung R. Role of DNA methylation in the regulation of cell function. J Lab Clin Med 1999; 134: 333-340.
10. Foto de un quiste dermoide en The University of Kansas Medical Center, <[http://www.kumc.edu/instruction/medicine/pathology/ed/ch\\_18/c18\\_dermoid\\_gross.html](http://www.kumc.edu/instruction/medicine/pathology/ed/ch_18/c18_dermoid_gross.html)> (27 mar. 2001).
11. Coskun-Ari FF. Genomic imprinting: a specialized form of gene regulation. Turk J Biol 2000; 24: 241-252.
12. Leighton PA, Saam JR, Ingram RS, Tilghman SM. Genomic imprinting in mice: its function and mechanism. Biol Reprod 1996; 54: 273-278.
13. Glick D. Glossary of Biochemistry and Molecular Biology. Revised edition. Londres: Portland Press Ltd.; 1997.
14. Reik W, Walter J. Genomic imprinting: parental influence on the genome. Nat Genet 2001; 2: 21-32.
15. Tycko B, Ashkenas J. Epigenetics and its role in disease. J Clin Invest 2000; 105: 245-246.
16. Rogan PK. Genomic Imprinting. Genetics in Practice. <<http://www.pgh.auhs.edu/genetics/brochure/agh/news/oct96/imprinting.html>> (14 sep. 2000).
17. Ortner M. Epigenetics: Silencing the Gene. Technology & Strategy. Drug & Market Development. Septiembre 2000.
18. Wilkins AS. Epigenetics. Ciba Foundation Symposium, 24-26 jun. 1997. <<http://www.bioessays.demon.co.uk/1997/bio1318.htm>> (14 feb. 2001).
19. Post Gazette News Bar Harbor, Maine genetics seminar, 26 jul. 2000. <<http://www.post-gazette.com/healthscience/20000726heredity1.asp>> (18 abr. 2001).
20. Beck B, Olek A, Walter J. From genomics to epigenomics. Nature Biotechnology 1999; 17: 1144. Citado en: Epigenomics GmbH, Germany - Company profile. <<http://www.epigenomics.com/profile/default.htm>> (18 abr. 2001).
21. Van Leeuwen I MM. Department of Theoretical Biology, Vrije Universiteit Amsterdam. Oncology glossary, en línea: <<http://www.bio.vu.nl/thb/users/ingeborg/Terms.html>> (27 sep. 2001)
22. Lindgren V. Genomic imprinting in disorders of growth. Endocrinol Metab Clin North Am 1996, 25: 503-521.
23. Schofield PN, Joyce JA, Lam WK, Grandjean V, Ferguson-Smith A, Reik W et al. Genomic imprinting and cancer: new paradigms in the genetics of neoplasia. Toxicol Lett 2001; 120: 151-160.
24. Pfeifer K. Mechanisms of genomic imprinting. Am J Hum Genet 2000; 67: 777-787.
25. Reik W, Constancia M, Dean W, Davies K, Bowden L, Murrell A et al. Igf2 imprinting in development and disease. Int J Dev Biol 2000; 44: 145-150.
26. Niikawa N. Genomic imprinting relevant to genetic diseases. Southeast Asian J Trop Med Public Health 1997; 28 (Supl. 3): 46-57.
27. Lacadena JR. Genética General – Conceptos fundamentales. Madrid: Editorial Síntesis, 1999.

28. Vu TH, Hoffman AR. Comparative genomics sheds light on mechanisms of genomic imprinting. *Genome Res* 2000; 10: 1660-1663.
29. Preece MA, Moore GE. Genomic imprinting, uniparental disomy and foetal growth. *Trends Endocrinol Metab* 2000; 11: 270-275.
30. Human Genome Research and Society. Proceedings of the Second International Bioethics Seminar. Fukui, Japan. 20-21 March, 1992. Fujiki N, Macer DRJ (Eds.). Christchurch: Eubios Ethics Institute; 1992. p. 56-63.
31. Martin CC. Genomic Imprinting. Department of Anatomy and Neurobiology. University of Ottawa. Ontario. Canadá. <<http://bioneer.kaist.ac.kr/labs/molgenet/lectures/AG/imprinting/browser.html>> (2 mar. 2001).
32. Ben-Porath I, Cedar H. Imprinting: focusing on the center. *Curr Opin Genet Dev* 2000; 10: 550-554.
33. Niikawa N. Genomic imprinting and its relevance to genetic diseases. *Jpn J Human Genet* 1996; 41: 351-361.
34. Reik R, Walter J. Imprinting mechanisms in mammals. *Curr Opin Genet Dev* 1998; 8: 154-164.
35. Sasaki H, Ishihara K, Kato R. Mechanisms of Igf2/H19 imprinting: DNA methylation, chromatin and long-distance gene regulation. *J Biochem* 2000; 127: 711-715.
36. Feinberg AP. DNA methylation, genomic imprinting and cancer. En: Jones PA, Vog PK (eds.). DNA methylation and cancer. Current Topics in Microbiology and Immunology 249. Berlin: Springer-Verlag; 2000.
37. Gilchrist D., Glerum DM, Wevrick R. Deconstructing Mendel: new paradigms in genetic mechanisms. *Clin Invest Med* 2000; 23: 188-198.
38. Mann JR, Szabo PE, Reed MR, Singer-Sam J. Methylated DNA sequences in genomic imprinting. *Crit Rev Eukaryot Gene Expr* 2000; 10: 241-257.
39. Alleman M, Doctor J. Genomic imprinting in plants: observations and evolutionary implications. *Plant Mol Biol* 2000; 43: 147-161.
40. Mc Grath J, Solter D. Nuclear transplantation in the mouse embryo by microsurgery and cell fusion. *Science* 1983; 220: 1300-1302.
41. Neumann B, Barlow DP. Multiple roles for DNA methylation in gametic imprinting. *Curr Opin Genet Dev* 1996; 6: 159-163.
42. Komatsu S. National Institute of Agrobiological Sciences. Department of Molecular Genetics. Laboratory of Epigenetics. <[http://ss.abraffrc.go.jp/organization/MolecularGenetics/0509/index\\_e.html](http://ss.abraffrc.go.jp/organization/MolecularGenetics/0509/index_e.html)> (24 abr. 2001).
43. Fox CA, Rine J. Influences of the cell cycle on silencing. *Curr Opin Cell Biol* 1996; 8: 354-357.

## En una palabra

### *Agony*

F. A. Navarro

En cierta ocasión leí un informe médico en inglés sobre un accidente de tráfico. Cuando la UVI móvil llegó al lugar de los hechos, sobre el asfalto yacía aún el único herido de consideración. Y el médico describía su situación con estas palabras: *The wounded man was in agony*. La mayoría de los lectores de habla hispana, incluso con buenos conocimientos de inglés, no pueden evitar un escalofrío de espanto ante este dictamen del médico. ¡Agonizando, pobre hombre!, seguramente no podrá hacerse ya nada.

Por eso, si seguimos leyendo el informe, nos sorprende enterarnos de que, tan sólo un par de horas después, el paciente salía tan campante por la puerta de urgencias del hospital, con el brazo en cabestrillo, para dirigirse a su casa.

El problema radica, como algún lector habrá ya imaginado —sobre todo después de haber leído el título de esta columna—, en el distinto significado que tienen las palabras “agonía” y *agony*. Nuestra agonía, que señala la proximidad de la muerte, corresponde al inglés *last agony* o *death agony*. Pero si en inglés hablan de *agony* a secas, hacen referencia a un dolor muy intenso o a una angustia extrema. En nuestro ejemplo, el herido, que no tenía más que una luxación de hombro (afeción ciertamente muy dolorosa, pero de escasa gravedad), lo que estaba era retorciéndose de dolor, pero no, ¡por Dios!, agonizando.

Reproducido con autorización de *El Trujamán* del Centro Virtual Cervantes (<http://cvc.cervantes.es/trujaman/>)