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Backgrounder: Epigenetics and Imprinted Genes

There is far more to genetics than the sequence of building blocks in the DNA molecules that make up our genes and chromosomes. The "more" is known as **epigenetics.**

What is epigenetics?
Epigenetics, literally "on" genes, refers to all modifications to genes other than changes in the DNA sequence itself. Epigenetic modifications include addition of molecules, like methyl groups, to the DNA backbone. Adding these groups changes the appearance and structure of DNA, altering how a gene can interact with important interpreting (transcribing) molecules in the cell's nucleus.

How do epigenetic modifications affect genes?
Genes carry the blueprints to make proteins in the cell. The DNA sequence of a gene is transcribed into RNA, which is then translated into the sequence of a protein. Every cell in the body has the same genetic information; what makes cells, tissues and organs different is that different sets of genes are turned on or expressed.

Because they change how genes can interact with the cell's transcribing machinery, epigenetic modifications, or "marks," generally turn genes on or off, allowing or preventing the gene from being used to make a protein. On the other hand, mutations and bigger changes in the DNA sequence (like insertions or deletions) change not only the sequence of the DNA and RNA, but may affect the sequence of the protein as well. (Mutations in the sequence can prevent a gene from being recognized, amounting to its being turned off, but only if the mutations affect specific regions of the DNA.)

There are different kinds of epigenetic "marks," chemical additions to the genetic sequence. The addition of methyl groups to the DNA backbone is used on some genes to distinguish the gene copy inherited from the father and that inherited from the mother. In this situation, known as "imprinting," the marks both distinguish the gene copies and tell the cell which copy to use to make proteins.

What is "imprinting?"
"Imprinted genes" don't rely on traditional laws of Mendelian genetics, which describe the inheritance of traits as either dominant or recessive. In Mendelian genetics, both parental copies are equally likely to contribute to the outcome. The impact of an imprinted gene copy, however, depends only on which parent it was inherited from. For some imprinted genes, the cell only uses the copy from the

mother to make proteins, and for others only that from the father.

Imprinting in genetics is not new, but it is gaining visibility as it is linked to more diseases and conditions that affect humans. Centuries ago, mule breeders in Iraq noted that crossing a male horse and a female donkey created a different animal than breeding a female horse and a male donkey. In the modern scientific era, however, the initial evidence for parent-of-origin effects in genetics didn't appear until the mid 1950s or so.

Then, in the mid 1980s, scientists studying mice discovered that inheritance of genetic material from both a male and a female parent was required for normal development. The experiments also revealed that the resulting abnormalities changed depending on whether the inherited genetic material was all male in origin or all female.

Around the same time, others discovered that the effects of some transgenes in mice differed when they were passed from the male or female parent. The first naturally occurring example of an imprinted gene was the discovery of imprinting in the IGF-2 gene in mice in 1991, and currently about 50 imprinted genes have been identified in mice and humans.

Why should it matter which parent donated the gene copy?
Why imprinting evolved in animals is unclear, but one hypothesis is that imprinting represents a genetic "battle of the sexes," since many imprinted genes regulate embryonic growth. Maternally-expressed imprinted genes (for which the copy from mom is always used) usually suppress growth, while paternally expressed genes usually enhance growth.

The "battle of the sexes" hypothesis is partly based on studies in animals that suggest growth-promoting imprinted genes help ensure the continuation of the father's genes, a particularly important issue for species in which more than one male can contribute to a single litter of offspring. The mother, however, is more interested in maintaining her own health, biologically speaking, and hence her genes "fight" the paternal genes and limit the size of the embryo or fetus.

What role does imprinting play in disease?
Because of their growth-related aspects, imprinted genes likely play a major role in the development of cancer and other conditions in which cell and tissue growth are abnormal. Imprinted genes in which the copy from the mother is turned on (maternally expressed) usually suppress growth, while paternally expressed genes usually stimulate growth (see above).

In cancer, some tumor suppressor genes are actually maternally expressed genes that are mistakenly turned off, preventing the growth-limiting protein from being made. Likewise, many oncogenes -- growth-promoting genes -- are paternally expressed genes for which a single dose of the protein is just right for normal cell proliferation. However, if the maternal copy of the oncogene loses its epigenetic marks and is turned on as well, uncontrolled cell growth can result.

In the collection of birth defects known as Beckwith-Wiedemann syndrome (BWS),

abnormal epigenetics leads to abnormal growth of tissues, overgrowth of abdominal organs, low blood sugar at birth and cancers. Similiarly, in the imprinting disorder Prader-Willi syndrome, abnormal epigenetics causes short stature and mental retardation as well as other syndromic features.

There's also evidence in mice that some imprinted genes may play a role in behavior, particularly in nurturing and social situations.

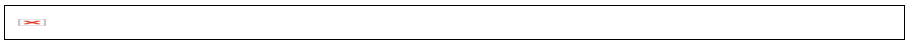
How does imprinting get messed up?
Just as mutations in the sequence of DNA can be acquired as a cell copies its DNA, changes in a cell's epigenetics can be acquired as well, although how those errors occur isn't as well understood. Scientists do know that epigenetic alterations can be caused by environmental changes, such as the laboratory conditions used for growing cells, but the details are murky.

For example, researchers are still trying to understand the process by which cells maintain or change their gene's imprinting marks. In sperm and egg, for instance, imprinted gene copies have to be re-imprinted. Imagine one copy of a paternally imprinted gene passed from a father to his daughter (the copy is paternally inherited and will be "on") and then to her child (it's now a maternally inherited copy and will be "off").

Many scientists believe that "incorrect" epigenetic changes to tumor suppressor genes and oncogenes are some of the first steps in cancer initiation. Determining when and how imprinting marks get re-written during egg and sperm development is crucial in figuring out whether imprinting abnormalities could be corrected in cancer.

What's next for imprinting research?
As more is learned about what role abnormal imprinting plays in biology and disease, it's important to continue learning about exactly how imprinting works. What marks distinguish maternal and paternal gene copies, and are they the same for all imprinted genes? How and when during conception or formation of sperm and egg are the tell-tale marks changed? Can epigenetics be manipulated to return normal control to cells in tumors?

To find answers to these and other questions, imprinting in early stage embryos will need to be studied. Hopkins researchers recently created a mouse model in which the paternal and maternal gene copies are easily distinguished in order to help answer these questions. The true test will be one day evaluating the questions in humans, although such experiments are not currently permitted.



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