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Plasticity & Epigenetics: The Basics

(This article is complementary material for Tutorials 1, 2 & 5)

Epigenetics

It’s currently one of the most exciting areas of neurohacking...so let’s catch up on the basics of the epigenome...

Quick summary:

- Epigenetics: the study of stable alterations in gene expression that arise during development and cell proliferation
- Epigenetic phenomena do NOT change the actual, primary genetic sequence
- Epigenetic phenomena are important because, together with promotor sequences and transcription factors, they modulate when and at what level genes are expressed
- The protein context of a cell can be understood as an epigenetic phenomenon.
- Examples include: DNA methylation, histone hypo-acetylation, chromatin modifications, X-inactivation, and imprinting.

Long Version:

Epigenetics, [literally "on genes”], refers to all modifications to genes other than changes in the DNA sequence itself.

Epigenetics is the study of changes in gene silencing or activation that occur without changes in the genes themselves. Many genes in the body are permanently turned on or off as part of normal development. But sometimes that process goes awry; turning off genes that should otherwise remain active, or turning genes on that cause harm. This field of study and its associated therapies aims to switch these genes on or off in a controlled way. It is a new and extremely promising approach to the treatment of aging, inherited diseases and cancer, not to mention neurohacking!

Our view of heredity has largely been written in the language of DNA, but recent discoveries in epigenetics show that how a cell “reads” those letters is critical. The idea of ‘good genes’ or ‘bad genes’ is suddenly secondary to the idea of turning genes on and off.

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, and different networks in the brain, 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.)

Imprinting

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.

"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.

Many imprinted genes regulate embryonic growth. Maternally-expressed imprinted genes (for which the copy from mom is always used) usually suppress excess growth, while paternally expressed genes usually enhance growth.

When Things Go Wrong

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 such as cancer 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.

Your Environment ‘Attunes’ You to Itself

There's also evidence that some imprinted genes play a role in behavior, particularly in nurturing and social situations, which is partly why this field of study is of such interest to neurohackers! Epigenetic alterations can be caused by environmental changes, such as diet, exercise and drugs, but also by exposure to other individuals in whom the genes are already active or redundant. This may involve subliminal communication via pheromones, but it brings home the point “You become more like whatever you are surrounded by” –[see neurohacking tutorials] and also goes a long way towards explaining ‘familial’ traits [characteristics shared by members of the same family that were not inherited genetically, or problems that have not been 'inherited' but initiated by familial modeling.]

Remember – most living organisms share an enormous amount of genetic coding information; the basic building blocks (proteins) of life are very similar, if not the same, across widely divergent species; what separates the humans from the amoebas –and often the healthy humans from the not-so-healthy- is gene regulation, when and how a gene is expressed.

Epigenetic factors are important in determining the phenotype of a given cell. For instance, the specific protein context of a cell plays an intrinsic role in the expression profile of the cell. Many genes require specific transcription factors for expression: if the transcription factor is present,

the gene is expressed, if the factor is not present, the gene is not expressed. Transcription factors also work to determine the level of gene expression – it is not necessarily a binary, on / off, system. Also, when a cell divides, its cytoplasm divides, donating its own particular cellular/protein context to its daughter cells. Each cell experiences an ongoing protein context that influences its own specific phenotype and functional profile.

Use It in the Right Way... or Lose It

Epigenetics will change the way the causes of disease are viewed, as well as the importance of lifestyles and social relationships.

Identical twins, for example, share the same DNA, but their epigenetic material may be different due to different environmental experiences. Moreover, whereas DNA variations are permanent, epigenetic changes are in a process of flux and generally accumulate over time. This may explain why some problems, such as bipolar disorder [BD], tend to manifest at ages 20–30 and 45-50, which coincides with major hormonal changes [which may substantially affect regulation of genes via their epigenetic modifications]. The dynamics of epigenetic changes may also account for the fluctuating course of BD; perhaps more so than static DNA variations.

But this is just the tip of the iceberg...Epigenetics explains the technical aspects of the Programming Hypothesis and Matrix Theory, via plasticity not only in neurons themselves, but also in the genes that enable or disable their growth and function. If environmental cues necessary for turning network development genes on are not forthcoming, such development cannot take place, and if environmental cues from “wrong input” are turning genes on that can cause dysfunction, the forthcoming epigenetics map will provide neurohackers with an “operators manual” for the brain and for intelligence itself. When that happens, will the pressure on humans to make lifestyle changes in favor of intelligence become public concern, or will the required societal changes prove too fundamental for humanity to implement? Scientific knowledge of the causes of obesity has done little to prevent its occurrence, but is this because of lack of public awareness or indifference? The same question must soon be asked about intelligence; when the causes of dysfunction are known, will anything be done about them?

Whatever the answer to this and other questions, at least those who do wish to pursue intelligence augmentation now have solid proof about why it works and how to achieve it. A list of the factors affecting intelligence growth or decline will inevitably emerge from the study of epigenetics. Serious neurohackers have of course had one for some time!

Drug Discovery, Therapy and Research

The fact that epigenetic anomalies can be reversed makes them inviting targets for a new generation of drugs. DNA methylation is the best-understood example of stable epigenetic phenomena.

DNA methylation turns off gene expression by establishing a silent chromatin state through the addition of a methyl-group to (predominately) the cytosine residue of a CpG dinucleotide. The addition of the methyl-group causes a physical change in the state of the chromatin that inhibits the expression of any genes in the methylated region. And, interestingly, this inhibitory chromatin state is passed on to daughter cells during cell division. Methylation patterns are specific and orchestrated during an organism's development, and are essential to an organism's vitality. For example, during embryonic development, the oocyte is demethlyated, then re-methylated during gastrulation; mutational loss of the enzymes that mediate this methylation process is fatal to the developing embryo; we cannot survive without methylation. Also, abnormal, post-gastrulation methylation has been implicated in various cancers and is seen in culture cell-lines. Further, DNA methylation is believed to be important in maintaining X-chromosome inactivation, which is a vital process that turns off one of the X-chromosomes in females and assures a proper balance of sex-linked gene transcripts.

Epigenetic modifications done on purpose 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. One of the main ways we can 'turn genes on or off' is by methylation. Methylation is chemical modification of one letter C (cytosine) of the four letters (A, G, C, and T) reiterated in our DNA. Adding a bulky methyl group to a C often blocks interaction with proteins required to activate gene expression, effectively silencing the methylated gene.

In mammals, methylation in regulatory regions next to genes generally silences genes. However, methylation across the body of a gene appears to correlate with higher expression.

Different cell types show different methylation patterns. DNA methylation in stem cells differs from that in a mature skin or nerve cell. Part of the makeover mature cells must undergo for therapeutic cloning purposes will likely involve remodeling methylation patterns to resemble those of stem cells.

Once a cell's DNA methylation pattern—be it normal or pathological—is established, methylated sites are faithfully inherited by daughter cells. The ability to take a high-resolution snapshot of what genes are methylated and which ones aren't during different developmental or disease states –possible now- might show how cells self-renew or growth control genes become de-regulated.

Methylation also silences transposons, so-called "jumping genes," which can wreak genomic havoc by hopping about the chromosomes. In the words of one researcher, undermethylated transposons "just go wild," suggesting that human biology keeps transposons in time-out by covering them with methyl groups.

Research

In a 2003 pilot study, Dr Petronis [head of the Krembil Family Epigenetics Laboratory at the University of Toronto] and his colleagues investigated the epigenetic gene modification in a section of the dopamine 2 receptor genes in two pairs of identical twins, one pair with both partners having schizophrenia and the other having only one partner with the illness. What they discovered was that the partner with schizophrenia from the mixed pair had more in common, epigenetically, with the other set of twins than his own unaffected twin.

Monozygotic twins exhibit numerous epigenetic differences

The National Human Genome Research Institute (NHGRI) has launched a public consortium known as ENCODE, for the Encyclopedia Of DNA Elements. Now that the human genome has been sequenced, ENCODE aims to develop technology to decipher what 30 million (1%) of those letters “spell” by identifying not only what genes they encode, but how epigenetic modifications switch genes off and on. Once that’s achieved, the effort will be scaled up to learn more about the dynamics of the whole human genome.