Epigenetics

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Here Marilyn explains the significance of epigenetics for our understanding of gene regulation and programming of cell function.

All cells in the body have the same complement of 20,000 genes, yet different cells in the body have different characteristics depending on their specific function in the different tissues - such as nerve, muscle or gut. (There are about 100 different cell types in the body.) What makes the cells different from each other if they all have the same genes?

The answer is that different subpopulations of the cell's genes are programmed to be active or silent depending on requirements for cell function. First of all there will be genes programmed to be always active - the genes concerned with cell metabolism, growth, repair and division. These are the so-called housekeeping genes that will be active in all cells. Then there are the tissue-specific genes that are only active as required for specific function - neural genes are only active in nerve cells, muscle genes are only active in muscle cells, and so on. Specific genes for one type of cell are active (expressed) and other genes that are not needed are silenced. Generally, the activation and silencing of subpopulations of genes regulating tissue-specific cell function is laid down during development of the embryo and the foetus and is stably inherited at cell division throughout life. How are these different subpopulations of genes turned on or off in a stable and heritable (cell to cell) fashion?

The answer is epigenetic programming. The science of epigenetics is concerned with this heritable regulation of gene activity as the DNA is duplicated for cell division. The mechanism by which a gene is active or is silent depends on epigenetic modification(s) superimposed on the DNA of the gene. So far there are three ways known for this to occur -
First: a chemical modification of one of the DNA bases (methylation of the DNA base cytosine),
Second: chemical modifications of the proteins that support and wind the DNA in the chromosome (the histone proteins of the nucleosomes),
Third: the synthesis of specific regulatory messengers (mRNAs) that bind to their target genes.

These differing mechanisms associated with gene activation or silencing can act independently, or may be interdependent in that once one form of modification occurs to activate or silence a gene it will attract further modifications. In analogy with computers, we could consider the genome, the DNA in the chromosomes, as the hardware and the epigenetic programming (now called the epigenome) the software.

For several decades, interest in epigenetics was largely confined to its role in orchestrating the regulation of gene expression in the formation of different tissues and organs in the shaping up of the embryo and foetus during development. Then followed research concerned with dynamic epigenetic regulation of certain inducible genes which are turned on or off by the presence or absence of their inducing stimulus in the environment. More recently, in the last few decades, we have seen the development of the unexpected and important field of genomic imprinting.

Imprinting is the differential expression of certain genes depending on whether they are paternally-inherited (via the sperm) or maternally-inherited (via the egg). This means that certain DNA modifications influencing the potential of a gene to be expressed are able to pass through the germ line - through the egg and sperm - to the next generation. This is a highly significant discovery since a major objection to the possibility of Lamarckian inheritance (transgenerational inheritance of acquired characteristics) was the lack of a conceivable molecular mechanism. The demonstration of the possibility of passage of epigenetic modifications through the germ line means that the way we live our lives may influence the potential of the genes we pass to our offspring, and imbues upon us a certain longitudinal responsibility for future generations.

Now, in the last few years, several new and remarkable roles for epigenetic programming are appearing in the scientific literature. One is the 'conditioning' of the newborn genome to its physical, nutritional and psychological environment by epigenetic programming of gene expression. This epigenetic programming in early childhood will affect life-view, health and well being throughout life. A really important question here is whether this 'molecular conditioning' is reversible. Another new discovery is the highly dynamic role of epigenetic regulation of gene expression in the brain to regulate memory and behavioural conditioning, for example fear conditioning. And yet a third is the role of changing epigenetic programming in the determination of many lifestyle diseases, particularly mental illness and cancer. These lifestyle diseases, which now outnumber infectious disease, are programmed in our genes by the way we live our lives.

The epigenome may be seen as the interface between our genome (the genes we inherit) and our our environment (partly a matter of chance and partly what we make of it). The old idea of Nature (genes) versus Nurture (environment) is outdated and now replaced by a more realistic view of a continual interplay between the environment (inner and outer) and our genes through epigenetic programming, thus monitoring and changing our interactions with our environment, again changing environmental feedback to our genes, and so on. Our ever-changing epigenome constantly monitors our environment to determine who we are, our responses to external and internal stimuli, and the state of our health and well being.

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