Homocysteine and Epigenetics

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11.1 Epigenetics

When the DNA sequence of the gene was discovered as the carrier of all our traits, we could not imagine that there could be anything beyond; yet certain observations forced us to look beyond! Finally we realized that it is not the genetic make-up per se that defines an individual—it is how the genes are expressed that is the deciding factor. For almost a century now, scientists have been poking into the nooks and crannies of genes trying to decipher all the interactions and modulations that result in totally different expression of the same DNA sequence. The term "epigenetics" was introduced by Conrad H. Waddington in 1942 to describe "the interactions of genes with their environment that bring the phenotype into being". Waterland modified this description and stated that "epigenetics" is "mitotically and/or meiotically heritable and stable alterations in gene expression potential that are not caused by changes in DNA sequence".

Our DNA is made up of a string of purines and pyrimidines in a specific sequence which determines our traits. We now know that these sequences are made up of exons (which carry the code for a particular trait) and the introns (which are interspersed between the exons). It is stimuli to the *introns* that leads to expression of the *exons*. Even the stimuli are predetermined. When the stimulus changes, the expression of the gene (exon) is altered causing a difference in the final effect. If these altered stimuli are transient, they would lead to some change in the organism causing only a phenotypic modification which would not be inherited. However, when the stimuli are stable, they can be inherited, thus causing the same altered expression of the gene in the progeny as well! And this is *epigenetics.*

As you can well imagine, this changes our concept of genetic inheritance and adds an entirely new dimension to it.

Several epigenetic modifications have been identified which are stable. Of these, the most common are DNA methylation and histone modification. DNA methylation, the first recognized and most well-characterized epigenetic modification, is linked to transcriptional silencing and is important for gene regulation, development

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and tumorigenesis. Histones are the core protein around which the DNA is wrapped. Its modification can be in the form of acetylation as well as deacetylation, and its effects are, therefore, varied. To put it simply, methylation of certain DNA bases (typically the 5′ position of the cytosine ring) represses gene activity, and acetylation of histones enhances gene expression, whereas deacetylation suppresses it. But nothing in the human body, or any other living organism, is simple and straightforward as there are concomitant processes that affect each situation and each other differently—the end result is an expression of the sum effect.

DNA methylation is catalysed by DNA methyl transferase (DNMT). It occurs in normal cells where DNMT functions as a maintenance MT. This predominantly recognizes and methylates hemi-methylated cytosine-guanine repeat sequences. This pattern is transferred from parent strand to daughter strand and is thus inherited. Evidence indicates that absence of DNMTs can be lethal to the cell. Normally, genes have certain highly methylated repeat elements, including satellites (e.g. SAT2) and retrotransposons (e.g. LINEs). When there is a relative loss of methylation at these sites, it leads in genomic instability and oncogene activation. And global hypomethylation of DNA is the epigenetic hallmark of cancers, the number one killer in the world.

The purpose of giving this description at this juncture in this compilation is to emphasize that the one major methyl group donor which is involved in almost all one-carbon moiety reactions is SAM—*S*-adenosyl methionine—as shown in Fig. 1.1. Homocysteine is the precursor of methionine which is itself the precursor of SAM. When the circulating homocysteine increases, there is an upregulation of its metabolism resulting in increased concentrations of SAM and therefore, increased availability of methyl groups for epigenetic modification of the expression of genes.