Epigenetics Background

Definition

The term epigenetics was coined by Conrad Waddington in the 1940's. Waddington integrated the new knowledge about genes and genetics to embryology. The study of embryological growth and differentiation was commonly known as *Epigenesis*, a concept that was around since Aristotelian times. The integration of the concepts of *Epigenesis* and *Genetics* gave origin to the term *Epigenetics*. Waddington's goal with epigenetics was to provide insight into gene-environment interactions that influence development and embryology. Pioneering epigenetic experiments from Waddington on *Drosophila* demonstrated that a temperature shock from hours 17-23 after puparium formation produced cross veinless wings in flies. Flies with this phenotype were culled from the population and only those showing normal wings were used to carry on the line. After an expected initial reduction of the cross wingless phenotype in the population it surprisingly raised after generation 16. This phenotype was considered a 'genetic assimilation' and dealt with environmental exposures early in development with subsequent consequences on phenotypic inheritance.

The definition of epigenetics has evolved with greater clarity of the molecular mechanisms involved and a better understanding of genetic phenomena. The initial definition of Waddington focused on gene-environment interactions but had no molecular insights to consider. Holliday (1990) defined epigenetics as "the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms". His definition rescues the original Waddington's meaning of developmental biology, although does not differentiate between the action of what we currently know as epigenetic mechanisms and the action of genetic regulators of gene expression such as transcription factors. Another early definition, by Riggs and colleagues states that "The study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence". However, the term heritable is generally in reference to generational inheritance and not associated with growth of cells or tissues. Perhaps a more direct term would be mitotically stable. A more recent definition focuses on molecular elements that influence chromatin independent of DNA sequence. Bird defines epigenetics as "The structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states". Since there are a number of epigenetic elements that do not fit into this definition such as non-coding RNA and minor modifications of histones and DNA methylation of promoters, this definition appears not global enough to encompass all of epigenetics. Therefore, we propose a definition that is more global and encompasses all molecular elements and includes the use of the term Epi for around DNA. Epigenetics is defined as **"molecular factors and processes around DNA that regulate genome activity independent of DNA sequence and are mitotically stable."**

History

Table 2

History of Epigenetics

1940's	Conrad Waddington defined epigenetics as environment-gene interactions that induce developmental phenotypes
1975	Holliday and Pugh identify DNA methylation
1988	X-chromosome inactivation and DNA methylation
1990's	Imprinted genes, allelic expression and DNA methylation
1995	Histone modifications and chromatin structure
2000's	Small non-coding RNA's
2005	Epigenome mapping

Transgenerational

Transgenerational Phenotype Definition

The majority of the actions of environmental factors or toxicants involve direct exposures of somatic tissues that are important for the exposed individuals disease, but will not be transmitted to the next generation. In contrast, transgenerational phenotypes and toxicology by definition excludes direct exposure and must be transmitted through multiple generations. For example, exposure of a gestating female provides direct exposure of the F0 generation female, the F1 generation embryo, and the germ-line that will generate the F2 generation. Therefore, a phenotype in the F3 generation is required to have a transgenerational phenomenon or phenotype. The effects observed in the F0 and F1 generations are due to direct exposures, as well as that in the F2 generation germ-line. The ability of a direct exposure to influence multiple generations is defined as a multiple generation phenotype and not a transgenerational phenotype. In contrast, a transgenerational phenotype requires the absence of a direct exposure and transmission of the phenotype to minimally the F3 generation.