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Epigenetics: A Lasting Impression?

SUMMARY

Epigenetics is the term that has been classically used to describe inheritable non-genetic factors that regulate genes. Although these factors were originally thought to act in a long time domain only, it is now clear that they can also be highly dynamic, changing over minutes. Transcription factors – including the glucocorticoid, oestrogen and androgen receptors – interact with these epigenetic mechanisms in a very dynamic manner to modify transcription of genes and consequently contribute to physiological processes, health and disease. Modern usage of the term epigenetics encompasses both longer term and transient changes and is relevant to multiple biological systems.

DNA in eukaryotic cells is in a complex with histone proteins to form chromatin. The histones H2A, H2B H3 and H4 form an octamer as a nucleosome. Epigenetic mechanisms alter chromatin structure through multiple mechanisms including histone variants such as H2A.Z, chromatin remodelling, DNA methylation and histone modifications such as acetylation (Ac), methylation (Me) and phosphorylation (P).

Molecular switches

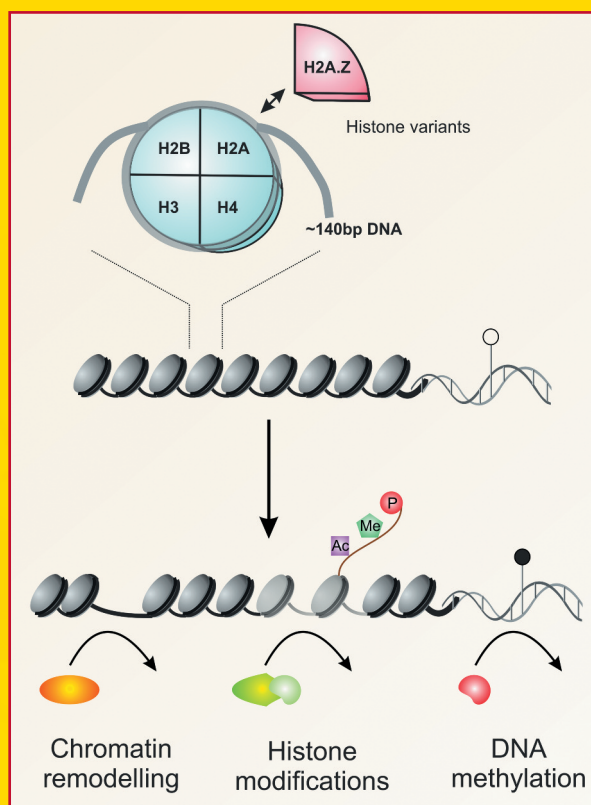
Despite the fact that each organism has one genome it is capable of encoding multiple biological functions and gives rise to complex organisms with hundreds of cells of diverse identities (phenotypes): cellular phenotypes arise from the selective expression of genes. DNA is organised into chromatin, a complex of DNA and histone proteins that make the nucleosome (see figure). Chromatin facilitates compaction of ~3 metres of human DNA into the 6 micrometres diameter cell nucleus. In addition to this property, chromatin also regulates gene transcription by *epigenetic* mechanisms. These epigenetic mechanisms are classically

mitotically and/or meiotically heritable changes in gene activity independent of DNA sequence. Epigenetic regulation therefore imparts a memory of transcriptional states through modification of histones, histone variants, chromatin remodelling by ATP-dependent complexes and DNA methylation (see figure). Cellular phenotypes transmitted in this mode include parental imprinting and X chromosome inactivation. The modern usage of epigenetics however also incorporates structural changes in chromatin that mark, signal and propagate transcription states that are often transient and dynamic. These epigenetic 'marks' result in changed access of transcription factors to DNA and thus switch the

availability of promoter sequences for activation or inhibition by the transcription factors that are critical for cellular activity.

Hormone signatures

The regulation of genes is mediated by transcription factors including the glucocorticoid, oestrogen and androgen hormone receptors. These nuclear receptors are a class of stimulus-inducible transcription factors that must overcome condensed chromatin to access and bind to DNA. In contrast to long-term epigenetic memory, hormone receptors have been shown to



promote rapid and transient epigenetic changes. This rapid and direct activity on gene transcription in response to hormone ligand makes steroid receptors ideal models for studying inducible changes in chromatin structure.

Histones can be chemically modified by acetylation, methylation and phosphorylation (see figure).

“Epigenetic regulation therefore imparts a memory...”

Receptor binding is known to alter the methylation and acetylation of histones at specific amino acid residues to modify chromatin accessibility. Hormone receptors mediate these events by recruiting other regulatory factors. These *cofactors* have enzymatic activity that catalyse the modification of histones. These histone modification signatures are therefore transient in nature, requiring the recruitment of histone methyltransferase and acetyltransferase enzymes by receptors. Receptors also recruit ATP-dependent chromatin remodelling complexes. These complexes enzymatically alter the contacts between DNA and histones to promote accessible chromatin and receptor binding. The alteration in chromatin structure is highly dynamic, paralleling transcriptional output mediated by receptors. These activities have been observed for numerous genes across the genome, including the circadian *period 1* gene, and the pituitary proopiomelanocortin (*POMC*) gene. In addition, receptors also induce the eviction of the H2 histone variant H2A.Z from nucleosomes, although the mechanisms and effect of this epigenetic phenomenon are not currently known.

While hormone receptors can recruit factors that regulate epigenetic functions, not all epigenetic marks are created equal. Certain epigenetic signatures are established during

early development and differentiation and do not alter upon the induction of transcription. The methylation of histone H3 on lysine 4 is an epigenetic mark of active genes and functional genomic sites. Conversely, methylated lysine 27 on H3 is associated with silent genes. These marks follow the classic definition of epigenetics, persisting over multiple cell divisions. Importantly, these epigenetic signatures are cell-specific, marking gene activity that defines cellular phenotype.

Altering a memory

The methylation of cytosine nucleotides contributes to imprinting, neuronal synaptic function, cell-specificity, autism and cancer. DNA methylation alters chromatin structure, impairing transcription factor binding and signalling inactive transcription. DNA methylation has long been considered a stable epigenetic memory, heritable across cell divisions and generations. These can have effects on behavioural responses known to involve receptor signalling, for example the regulation of stress by the glucocorticoid receptor. In rodents, pups which have suffered from maternal deprivation have methylated DNA near the transcription start site of the glucocorticoid receptor gene in the hippocampus, affecting behaviour. The glucocorticoid receptor gene is also methylated in humans with a history of child abuse. These findings suggest that early life environmental factors can epigenetically alter chromatin structure that persists into adulthood.

Recent evidence has altered our view of the stability of this epigenetic memory and suggests these changes are much more plastic and reversible. Oestrogen, vitamin D and parathyroid hormone receptor signalling studies have suggested that DNA methylation of genes can actually cycle through methylated and demethylated states. These observations indicate that a ‘stable’ epigenetic mark of gene activity can also be

modulated by transcription factors and dynamically respond to environmental signals.

The long and short

Although the classic definition of epigenetics is characterised by long-term memory of non-genetic factors on chromatin, modern usage of the term epigenetics embraces emerging evidence for dynamic epigenetic regulation. Epigenetic factors exert their effect on chromatin structure across various time scales, from minutes in receptor signalling to generations in imprinting. The dynamic character of epigenetics has implications in many systems, including the reprogramming of cells to stem cells, regulation of stress responses by glucocorticoids and the regulation of hormone-dependent cancers. The extensive and dynamic interaction between hormone receptors and epigenetic factors highlights epigenetic control as a major drug target in the treatment of numerous diseases, from depression to cancer.

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