ENCYCLOPEDIA
on Early Childhood
Development

Biology of the Epigenome

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November 2017

Introduction

The new scientific field of behavioural or social epigenetics is poised to revolutionize our understanding of human development. We describe the biology of the epigenome and recent findings on epigenetic processes that affect gene expression as early as the embryonic stage of human development.

Subject

DNA lies deep within the nuclei of cells, like books on a library shelf waiting to be opened, read and transcribed to reveal the instructions used to make the substances of life our bodies require.[1] The word ‘epigenetics’ consists of the word ‘genetics’ and the Greek root epi, which means upon or over. There are a number of different types of epigenetic mechanisms. These include DNA methylation, histone modification and the regulation of gene expression by small RNA molecules that do not code for proteins (ncRNA). The science of epigenetics looks at processes that mark DNA and can change gene expression without modifying the underlying genetic sequence of the DNA.[2] Epigenetics has a long history in development research. Its contributions to gene regulation are known to play a role in the differentiation of cells into distinctive cell types during embryonic development.[3]

Problem

One of the goals of research in the field is to understand how changes in the epigenome can contribute to the developmental path (trajectory) that a child is on. These developmental trajectories can range from being adaptive to maladaptive. Epigenetic modifications can have consequences for child well-being including cognition and social emotional development as well as mental and physical health.

Context

The term ‘epigenetics’ was used in 1869 by the French biologist-anthropologist Armand de Quatrefages who wrote: “Nowadays I admit, with everybody, the doctrine of epigenesis. Every normal egg which gives birth to an abnormal individual is influenced by external agents whatever they are; this is what I call action of the milieu.”[4] Epigenetics was then used in a developmental context by Conrad Waddington where he suggested that the development of the embryo unfolded through what he termed an “epigenetic landscape”.[5] His model illustrated the developmental pathways that an undifferentiated cell might take toward its differentiation (becoming for example a brain or liver cell). In his metaphor there are number of balls (cells) rolling down a hill. Individual balls slow down in the grooves on the slope, and come to rest at the lowest points. These lowest points are the tissue types-each cell eventual becomes, its cell fate. The shape of the landscape (the contours of the hill) is a consequence of the interactions between the embryo’s genes and the environment. The metaphor revealed how gene regulation modulates development. Although knowledge of molecular biology and gene-environment interplay was lacking in Waddington’s time, his insights are still relevant today. Recent epigenetic research has identified the molecular processes involved in development and cellular differentiation.

After cell differentiation, many more changes occur in pre and postnatal development that involve the interplay between genes and the environment. A new field of epigenetic of Behavioural or Social Epigenetics focuses on how our experiences get embedded into our biology.[6]

Recent Research Results

Epigenetic processes

Three epigenetic processes are described here that alter gene expression. The first, DNA methylation, is most highly studied in mammals. DNA methylation operates as a structural overlay

on the DNA. It adds a mark to the DNA and depending on where it is situated on the DNA sequence it can change gene expression, the amount of messenger RNA (mRNA) that the gene makes. Gene regulation is also important for determining which genes are expressed at which times and locations in the developing organism. Scientists have recently discovered that DNA methylation is reversible.[7]

The second process is histone modification. Histones are proteins that serve to wind DNA strands into bundled units like beads on a necklace. Reversible chemical tags can modify specific sections of histone proteins, causing the DNA packaging to relax, allowing genes to be more readily transcribed and expressed, or to constrict, making gene transcription and expression more difficult. Scientists have recently proposed a working theory about a 'histone language,' where different combinations of histone modifications may be responsible for driving certain processes associated with the storage and retrieval of memories, and behaviours associated with cognitive impairment, schizophrenia and depression.[8,9] Of interest, some recent research has demonstrated that it is possible to reverse brain changes due to histone modification of a specific gene known to be related to chronic stress with an antidepressant medication.[10]

mRNA molecules are responsible for conveying DNA instructions for the manufacture of proteins. A third, newly discovered epigenetic process involves small, non-coding RNAs (ncRNAs) that interfere with the expression of specific genes by encouraging the compaction of DNA or by causing transcribed messenger RNA to degrade.[11] These ncRNA molecules have been discovered in plentiful numbers in the brain. Epigenetic marking processes by ncRNAs have been linked to several disorders of cognition and behaviour, for example, Fragile X syndrome.

These three epigenetic processes — DNA methylation, histone modification and ncRNAs — do not operate entirely independently. Recent research has found that DNA methylation encourages other substances to come to the site that decrease histone modification, and the two processes then work together to impede gene transcription. Histone modification can also suppress nearby DNA methylation. Further, small ncRNAs and DNA methylation can also influence each other's presence and effects.[12]

Epigenetic differentiation of cells in embryogenesis

Early embryonic development depends on critical epigenetic programming that occurs within the earliest stages of cell differentiation and development.[13] Before fertilization occurs, an egg and a

sperm cell both undergo extensive and complex epigenetic remodeling processes.[14] Epigenetic modifications that mark the genes of a sperm or egg cell can result in only one parental gene copy being expressed and this impact has been observed across nearly 400 human genes. After conception, a further, highly regulated epigenetic calibration process takes place, affecting the expression of about 20,000-25,000 genes responsible for coding proteins.[2]

Research Gaps

Neurodevelopment, dynamic variation and an epigenetics

Brain development in mammals requires a precisely coordinated sequence of gene regulation events, some of which are epigenetic, in order to produce and spatially locate neurons and glial cells.[2] Epigenetic regulation in the brain can also influence a variety of complex neural functions, such as memory formation, learning and the calibration of stress response circuitry.[15] The causal mechanisms involved in the relationships between epigenetic marks, how the brain develops and functions remain to be elucidated.

Widespread and regionalized shifts in DNA methylation and histone modifications have been shown to take place with key phases of normal brain development[16,17] and with specific disorders of development and mental health.[18,19,20] DNA methylation, histone modifications and ncRNAs may explain differences in susceptibility to various forms of psychopathology between males and females.[21,22] Scientists have also found a correlation between distinctive epigenetic marks within hundreds of gene loci among patients with autism spectrum disorder and other neurodevelopmental syndromes.[23,24] Epigenetic processes may also explain why Down syndrome children do not show an expected 50 per cent greater expression of the triplication of chromosome,[21] indicating that co-occurring cognitive deficits might be due to epigenetic processes and therefore, be potentially modifiable with targeted drug interventions.

Research challenges

There are significant challenges for scientists studying the human epigenome. Epigenetic marks are most often not associated with changes in gene expression. Changes in gene expression can arise from many mechanisms only some of which involve epigenetic modifications. The epigenome can activate or deactivate genes in response to environmental signals and conditions. Different tissue types have different epigenetic profiles, so conclusions cannot be drawn reliably from one type to another. For example, epigenetic states in brain cells are not the same as those

found in epithelial cheek cells. Some tissue types like brain tissue are only available on a post-mortem basis, so large-scale studies must rely on surrogate tissue. Most animal and human studies of the relationship between the epigenome and experience show correlation rather than causation; new research must aim to take these correlations to the level of causations. Since it has been easier to focus on studying DNA methylation to date, there is still much to discover about the functions of other epigenetic marking processes.

Conclusions

The epigenome can alter the expression of genes without changing the underlying DNA sequence and is responsible for cell differentiation in early embryonic development. Experiences and environmental exposures, especially those early in life, can result in the placement or removal of epigenetic marks, which is thought to regulate the neurodevelopment that underlies learning, behaviour and risks for compromised mental health.

Implications

Given recent discoveries that some epigenetic processes are reversible and demonstrate potential mechanisms of developmental plasticity,[7] scientists are working on targeted drugs for the treatment of chronic stress,[9] cancer, neurological and psychiatric disorders.[24]

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