Available online at www.sciencedirect.com
ScienceDirect
Behavioural Brain Research 192 (2008) 70–87
BEHAVIOURAL BRAIN RESEARCH
www.elsevier.com/locate/bbr

Review article

Epigenetic codes in cognition and behaviour

Johannes Gräff, Isabelle M. Mansuy *

Brain Research Institute, Medical Faculty of the University of Zürich and Department of Biology, Swiss Federal Institute of Technology, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Received 30 January 2008; accepted 30 January 2008
Available online 12 February 2008

Abstract

The epigenetic marking of chromatin provides a ubiquitous means for cells to shape and maintain their identity, and to react to environmental stimuli via specific remodeling. Such an epigenetic code of the core components of chromatin, DNA and histone proteins, can thus be stable but is also highly dynamic. In the nervous system, epigenetic codes are critical for basic cellular processes such as synaptic plasticity, and for complex behaviours such as learning and memory. At the same time, epigenetic marks can be stably transmitted through mitosis and meiosis, and thereby underlie non-genomic transgenerational inheritance of behavioural traits. In this review, we describe recent findings on the role and mechanisms of epigenetic codes in the brain, and discuss their implication in synaptic plasticity, cognitive functions and psychiatric disorders. We provide examples of transgenerational inheritance of epigenetic marks that affect simple morphological traits or complex processes such as disease susceptibility, and point to the potential implication of epigenetic codes in medicine and evolution.

Keywords: Epigenetic mechanisms; Synaptic plasticity; Memory; DNA methylation; Histone; Cognition; Environment; Transgenerational inheritance

Contents

* Corresponding author.
E-mail address: mansuy@hifo.uzh.ch (I.M. Mansuy).

0166-4328/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2008.01.021

1. Introduction

The importance of epigenetic modifications has long been recognized in the areas of stem cell research, cancer and developmental biology. But it is only recently that their relevance has also been acknowledged in the field of neuroscience, for both developmental processes and higher-order brain functions such as cognition. Epigenetic modifications of the chromatin are diverse and complex, and their study in neurobiology has been inspired by work in disciplines such as developmental and evolutionary biology. The integration of findings in these diverse fields has stirred new concepts and perspectives for the understanding of the intimate mechanisms of basic and higher brain functions, and for the processes that underlie the heritability of behavioural traits across generations, which is key to evolution.

2. History and terminology

The term epigenetics derives from the Greek prefix "epi" that literally means "above" or "in addition to" genetics. It refers to processes that physically occur with or on genes, and involves the physical support of genetic processes, the chromatin. Originally, long before the notion of chromatin even existed, the developmental biologist Conrad Hal Waddington (1905–1975) defined epigenetics as "... the interactions of genes with their environment which bring the phenotype into being", emphasizing that epigenetic mechanisms vary in response to a given environment [1]. Waddington later referred to an equally important characteristic of epigenetic modifications by stating that "...it is possible that an adaptive response can be fixed without waiting for the occurrence of a mutation..."[2]. This notion of non-genetic transmission of acquired morphological and behavioural traits had already been proposed by Jean-Baptiste Lamarck (1744–1829), but met with fierce criticism, essentially due to Lamarck's inclination to place his observations in the perspective of adaptive evolution. The modern definition of epigenetics now integrates Waddington's early assumptions, but excludes most of Lamarck's views. Epigenetics is nowadays most commonly defined as the ensemble of alterations in gene functions that are heritable through both mitosis and meiosis, but that cannot be explained by changes in the DNA sequence itself [3] (reviewed in [4,5]).

At the molecular level, epigenetic mechanisms are biochemical modifications of the DNA and histone proteins, the major constituents of chromatin (Fig. 1A). Recent findings have revealed that additional mechanisms involving RNA interference and prion proteins also contribute to epigenetic regulation [6], but these mechanisms will not be covered in this review. Chromatin modifications are multiple and complex, and comprise methylation of DNA at cytosine-guanine dinucleotides, and posttranslational modifications of histone proteins. Histones are basic proteins consisting of a core and an N-terminus tail composed of a loosely-structured sequence of amino acids [7]. Posttranslational histone modifications occur primarily on the N-terminus tail, and include acetylation, methylation, phosphorylation, ubiquitination (reviewed in [6]) and sumoylation (Fig. 1B). Because of their chemical properties, these modifications influence the condensation of chromatin, and thereby modulate the accessibility of DNA to the transcriptional machinery (Fig. 2A and B).

DNA methylation occurs throughout the genome but is functionally most relevant when present in sequences rich in CpG dinucleotides, called CpG islands, often found in promoter regions. DNA methylation is commonly associated with transcriptional silencing because it can directly inhibit the binding of transcription factors or regulators, or indirectly recruit methyl-CpG binding proteins (MBPs), which have repressive chromatin-remodeling functions [9,10]. However, DNA methylation can also occur in actively transcribed genes, suggesting a potential positive role in transcription regulation as well [11,12]. Because of the covalent nature of the binding of methyl groups to the C_5 carbon in cytosine, DNA methylation is thought to be the most stable epigenetic mark [9].

Posttranslational modifications of histone tails also play a critical role in the regulation of gene transcription. First, histone acetylation is associated with transcriptional activation. It results in the neutralization of the positive charge of the ε-amino group of lysine (K) residues in the histone tail, which decreases the affinity between the protein tail and the DNA, and relaxes the chromatin structure [13]. In contrast, histone methylation has a dual impact on transcriptional activity and is associated