Seminars in Immunology 28 (2016) 359–367

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Epigenetic memory: A macrophage perspective

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ARTICLE INFO

Article history:
Received 9 February 2016
Received in revised form 16 June 2016
Accepted 23 June 2016

Keywords:
Memory
Monocyte
Macrophage
Nucleosome
Transcription factor
Epigenetics

ABSTRACT

The molecular basis of cellular memory is a fascinating topic that progressed with great strides during the last few decades. In the case of cells of the immune system, cellular memory likely extends beyond cell fate determination mechanisms, since immunity can tailor its responses to a potentially hostile environment that is a priori variable if not unpredictable. One particularly versatile innate immune system cell type is the macrophage. These phagocytes occur in all organs and tissues as resident cells or as differentiation products of recruited circulating blood monocytes. They come in many flavours determined by the tissue of residence and by external factors such as microbes. Recently, macrophage epigenome profiling has revealed thousands of chromosomal loci that are differentially active in macrophages, revealing chromosome elements that drive macrophage gene expression. The most dynamic epigenomic mark is nucleosomal histone acetylation. This mark is found at gene promoters and enhancers and correlates very well with gene expression changes. A second mark is H3K4me3, which sharply decorates the promoters of most protein coding genes that are (potentially) expressed. H3K4me3 at promoters is surrounded by its precursor H3K4me1. However, most often H3K4me1 occurs without H3K4me3 at enhancers where it appears together with histone acetylation, but can persist long after acetylation decreased. Hence, the biochemical signal H3K4me1 embodies appears to be a key to the plasticity of macrophage gene expression potential.

Contents

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http://dx.doi.org/10.1016/j.smim.2016.06.003

1. Introduction

The development of an adult organism from a zygote remains one of the most wondrous biological phenomena. Over a century of scientific research indicates that the molecular basis of this extraordinary feat is coded by the respective organism's DNA genome. The intricate ballet of cellular migrations that occurs during early embryogenesis produces functional cells in all organs within one body with very high fidelity. This implies that very high levels of determinism are ultimately encoded in the DNA sequence. Clearly, the genome harbours a detailed blueprint to make and maintain a body. The question we will address here is how chromosomes store information such as 'memories', with a focus on macrophages.

2. From chromatin to chromosome domains

How does a differentiating monocyte acquire and maintain its macrophage (Mf) identity at the hand of a DNA code common to every other cell? Part of the answer to this question lies in the 46 human chromosomes and their biochemical milieu, namely chromatin. The diploid human genome contains ~6 10^9 bp. This represents about 2 m of DNA, which fit in a cell nucleus that is 10–20 μm in diameter. Except during cell division, when chromosomal DNA is highly compacted to enable sister chromatid segregation to the daughter cells, each chromosome occupies a distinct territory within the nucleoplasm and intermingles little with other chromosomes [1,2].

Chromosomal DNA is packaged in arrays of nucleosomes. These are discs, ~11 nm in diameter and 5.5 nm in height, that consist of an octamer of histone proteins ($H3_2$-$H4_2$)(H2A-H2B)$_2$ and ~147 bp of DNA [3]. The length of the linker DNA between any two nucleosomes varies from less than 10 to over 90 bp, with dominant nucleosome repeat lengths of 190–200 bp in human blood cells [4]. In fact, the nucleotide composition of DNA can help to rotationally position DNA on the nucleosome surface through phased TA, TT, AA and GC dinucleotides positioned every 10/11 bp or multiples thereof, suggesting that the DNA strands' sequences themselves can influence nucleosomal DNA packaging [5–7]. Because nucleosomes can stack in various solenoidal structures, some of which are favoured by short or long linker lengths [8], arrays of nucleosome can form higher order structures that are often modelled as one- or two-start solenoids of polynucleosomal fibres [9] that are ~30 nm wide [10].

Some 20,000 protein coding genes are distributed along the length of the human chromosomes. Every gene has one or more promoters from which transcription of mRNAs by RNA polymerase II (RNAPII) can start [11]. Furthermore, distal elements called 'enhancers' modulate the activity of the promoters [12,13]. Different cell types activate gene expression differentially by utilizing different parts of the genome's regulatory repertoire of *cis*-acting elements. The mechanisms underlying the differential use of the genomes' regulatory elements involve physical changes in chromatin that promote or inhibit gene expression [14–16].

From a regulatory perspective, the genome is partitioned in several thousand independently functioning 'topologically associated domains' (TADs). These have been defined using formaldehyde-fixed cellular chromosome restriction cleavage followed by ligation, allowing interacting chromosome segments to be detected as ligation products that are amenable to next-generation DNA sequencing [17]. TADs are relatively invariant, even across mammalian orders such as primates and rodents [18], although it is possible that TADs vary in conformation during ontogeny [19]. An early study reported ~2000 TADs ranging in size from 80 kb to 10 Mb [18]. Considering that DNA sequences located within one TAD are crosslinked significantly more often than segments located in adjacent TADs, the current model is that genes within one TAD can be influenced by *cis*-acting regulatory elements within that TAD through DNA looping, while genes outside the TAD are much less likely to be contacted [20]. Much research indicates that a protein ring consisting of cohesin works together with a very tight DNA binding protein called CTCF to establish TAD boundaries, presumably by forming the basis of stable chromatin loops [21–24]. It is thought that they act as 'boundaries' because they can interrupt or prevent enhancer-promoter contacts [25]. Intriguingly, inter-chromosomal clustering of a select number of TADs marked by the repressive H3K27me3 histone modification has been documented recently in embryonic stem cells [26–28]. Furthermore, some TADs correspond to nuclear lamin associated domains [29]. The biophysical properties of topologically associated chromatin domains remain to be elucidated.

3. Epigenetic mechanisms

Currently, epigenetic mechanisms encompass post-transcriptional molecular systems, such as production of microRNAs, which can regulate mRNAs *in trans* through base pairing, leading to translation inhibition or mRNA degradation [30]. However, most epigenetic mechanisms described to date implicate protein-DNA interactions that affect gene expression at the level of mRNA synthesis, either by chemically modifying DNA bases, as is the case for 5-methyl cytosine, or by recruiting protein complexes involved in nucleosome modification and remodelling that modulate chromatin structure to promote or inhibit transcription initiation or elongation. The concept of epigenetics as formulated by Conrad Waddington in 1942 for ontogenesis [31], by Mary Lyon for X chromosome inactivation in female eutherians [32] and by Arthur Riggs [33] and Robin Holliday [34] for 5-methyl cytosine suggests that epigenetic mechanisms are involved in establishing heritable chromatin states [35]. Hence, epigenetics could be said to deal with mechanisms to establish durable decisions, while gene control may also describe more punctual fluctuations in transcription levels. Still, the distinction between transcription control and epigenetic control of gene expression is probably a semantic one when considering the question at the molecular level since nucleosomes are involved in both cases [36]. DNA-bound histones in the form of nucleosomes are ideally suited to perform molecular memory-related tasks because their residence time on DNA can be of the order of many hours [37–39].

3.1. Chromatin remodelling

Nucleosomal histones can recruit proteins that harbour histone binding domains [40–42]. When those interactions are promoted or disrupted by post-translational modification of histone residues such as lysines and arginines the function of the underlying DNA can change [43–48]. The protein domains that recognise modified histones are commonly called 'readers' of the histone modifications, and by analogy the enzymes that deposit and remove the modifications are called 'writers' and 'erasers'. Crucially, next to covalent histone modification, several sub-types of SNF2-type ATP-dependent nucleosome remodelling enzymes are involved in inserting and extracting histone H2A variants into existing nucleosomes [49–51], sliding nucleosomes along DNA [52–54], and in the transfer of nucleosomes from one DNA segment to another [55]. Similar to histone code 'writers', some of the SNF2-family members reside in large multi-subunit protein complexes that not only bind nucleosomes to remodel them, but also harbour 'reader' domains that target their activity to specifically modified nucleosomes.

A first complicating aspect of the writer/reader system of histone modifications is that 'reader' and 'writer' domains often co-occur in the same protein complex. A second complicating