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Mini-review

Histone metabolic pathways and chromatin assembly factors as proliferation markers

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Abstract

The structural organization of DNA into chromatin is of key importance to regulate genome function and stability. Maintenance of such an organization is thus crucial to preserve cellular identity. At each cell cycle, during S phase, this is achieved by duplication of chromatin structure in tight coordination with DNA replication. Such a coordinate process requires histone synthesis and their deposition onto DNA by chromatin assembly factors to be efficiently coupled to DNA synthesis. In this review, we highlight the intimate relationship between these chromatin-related events and DNA replication and we show how it is possible to take advantage of this coupling in order to identify cells with high replicative potential such as tumor cells. On the basis of recent data, we discuss the potential use of chromatin-associated factors as new proliferation markers of interest for cancer diagnosis and prognosis.

Keywords: Histones; Chaperones; Chromatin assembly; DNA replication; Proliferation marker; Cancer

1. Introduction

The functional organization of DNA in the nucleus of eukaryotic cells is chromatin (from the Greek *khroma* meaning coloured), a name given by Flemming based on the property to retain basic dyes [1]. This nucleoproteic structure is organized periodically and its basic unit is the nucleosome [2]. The nucleosome core particle now described in great details at the structural level [3] consists of 146 bp of DNA wrapped around a histone octamer, comprising two copies of each core histone H2A, H2B, H3 and H4. Such an organization can provide, in addition to the DNA sequence, another layer of information, which is termed 'epigenetic' since it is not genetically encoded, yet can be transmitted throughout multiple cell generations as defined by Russo et al. [4]. Indeed, in addition to DNA methylation, histone composition (variants and combination of covalent modifications) up to higher order chromatin organization constitute major epigenetic marks. Histone modifications have been hypothesized to participate in a so-called 'histone code' [5,6] whereby combinations of histone modifications define different chromatin states through the recruitment of specific proteins. Epigenetic information being a key component in

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the regulation of gene expression, it has to be maintained to preserve cellular identity. Notably, disruption of epigenetic integrity has been associated with numerous diseases including cancers and cancer-prone disorders [7–9]. A crucial time for the maintenance of chromatin integrity during cellular life is obviously S phase, the stage at which a faithful duplication of chromatin organization has to be achieved in tight coordination with DNA replication. In this review, we emphasize how histone synthesis and their subsequent deposition onto DNA stimulated by histone chaperones are coupled to DNA replication during cell cycle progression and we discuss the potential use of chromatin-associated factors as new tools to identify proliferating cells.

2. Chromatin integrity and cell cycle progression

A growing body of evidence now clearly integrates chromatin into the control of cell cycle progression (reviewed in [10]). Not only is chromatin a major target of cell cycle checkpoint responses, but aberrant chromatin structures can also be detected by checkpoint mechanisms leading to cell cycle arrest, highlighting that stability of chromatin structure ensures normal cell cycle progression. Chromatin integrity is threatened upon DNA damage or any destabilization event. At each cell cycle, doubling of the DNA material in S phase requires additional histones in order to maintain a proper DNA–histone ratio. Chromatin stability is particularly challenged during this replicative process, which involves large-scale chromatin modifications. Upon replication fork passage, chromatin structure is disrupted and parental histones are randomly distributed onto both DNA strands [11] providing half of the histones that are required to duplicate chromatin structure. The additional supply of histones that is necessary for completion of chromatin restoration is achieved by histone neosynthesis and incorporation of newly synthesized histones into nucleosomes, which is termed de novo nucleosome assembly. Importantly, maintenance of chromatin organization requires a tight coordination between de novo histone incorporation and transfer of parental histones. A major challenge is thus to coordinate efficiently histone synthesis and their deposition onto DNA with DNA replication in addition to maintain epigenetic marks.

3. Coupling between histone synthesis and DNA replication

The majority of histone synthesis is restricted to S phase, in a way that is strictly coupled to DNA replication [12] in order to provide material necessary to assemble chromatin onto newly synthesized DNA. Notably, one major contribution to this cell cycle regulation of histone biosynthesis occurs at the mRNA level in all eukaryotes [13]. Histone expression is dependent upon ongoing DNA synthesis as attested by the use of replication inhibitors, which elicits an evolutionarily conserved response leading to a decrease in histone mRNA levels though using slightly different strategies among eukaryotes. In yeast it is based essentially on transcription regulation [14] whereas an important additional contribution at the level of mRNA stability has been described in higher eukaryotes [15,16]. While affecting DNA replication has a strong effect on histone synthesis, conversely depletion of histone pools by repression of histone gene transcription can itself cause cell cycle arrest in yeast, which arrests after completion of one round of DNA replication when histone synthesis is blocked [17]. Recently, a comparable mechanism was proposed in human cells that showed an S phase arrest under conditions affecting histone mRNA level [18]. Taken together, these data highlight how tightly histone expression can be coupled to cell cycle progression. This coupling ensures a delicate balance between histone synthesis and their incorporation into chromatin during DNA replication, minimizing the amount of free histones, which could potentially trigger cellular defects [19,20]. Interestingly, recent data have evidenced a mechanism in yeast, which leads to the degradation of excess histones that are not packaged into chromatin [21]. Whether a similar surveillance mechanism exists in higher eukaryotes will be important to examine.

Besides S phase related histones, minor forms of histones have been found expressed also outside of S phase [22]. These histone variants, called replacement histones, have been identified for all histones except H4. They are structurally similar to