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A Histone Cycle: A Systematic Overview on Histone (Octamer Protein) Replication

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ABSTRACT

Genetic information plays an important role in each individual for their differentiation. DNA replication is a highly conserved process that accurately copies the genetic information from one generation to the next. The processes of chromatin disassembly and reassembly during DNA replication also have to be precisely regulated to ensure that the genetic material is compactly packaged to fit into the nucleus while also maintaining the epigenetic information that is carried by the histone proteins bound to the DNA, through cell divisions. So, for the synthesis of genome or gene a group of eight proteins collectively known as octamer proteins or histones plays a crucial role. Colloid of chromosomes is converts into the double stranded DNA structure with intermediate structure of histone proteins. As eukaryotic replication disrupts each nucleosome as the fork passes, followed by incorporation of newly synthesized histones into nucleosomes in the daughter genomes. For the cellular machinery to access the DNA, the chromatin must be unwound and the DNA cleared of histone proteins. In this review, we focus on the process of replication-coupled nucleosome assembly to understand how characteristic steady-state nucleosome landscapes are attained. Recent studies have begun to elucidate mechanisms involved in histone transfer during replication and maturation of the nucleosome landscape after disruption by replication. A fuller understanding of replication-coupled nucleosome assembly will be needed to explain how epigenetic information is replicated at every cell division. We also give details about regulation of histone in human and the DNA Damage Response.

Keywords: Histone, Chromatin assembly, Histone replication, DNA damage response, Translation and transcription, Histone cycle.

INTRODUCTION

As we know every time when cell divided to form a new cell then there is also DNA (Deoxyribose Nucleic Acid) material get equally distributed into that duplicate cells. [27] In this process DNA replication in cell varies proteins are used involved which are interact with each other. [38] Abnormally in any step of cell division leads to cell death and genetic instability leads to cause disease condition in human. [1] Each step of DNA replication is effectively regulated in the eukaryotic cells. One of the important feature is DNA strongly associated with histone which is a basic protein wrapped around the DNA consist octameric (8 units) basic proteins structure called nucleosomes. [27,28]

The nucleosomes and associated DNA are commonly known as chromatin. [27] Presence of nucleosomes is one of the major principle differences between eukaryotic and prokaryotic DNA replication cause change in whole chromatin structure. [2] Since nucleosomes remove transiently chromatin remodeling depends upon assembly and disassembly of nucleosomes. This chromatin remodeling factors and

protein are able to destabilize interaction between histones and DNA. Hence, the destabilized reaction allows them to interact with other DNA complexes. [3] Nucleosomes are help in DNA packing during S-phase about 30 million nucleosomes are synthesized. [2] Histone production is coupled with DNA synthesis and shut off process when replication finishes. Histone regulation is important avoid histone accumulation of free histone chromatin is acts as structural barrier and also play important role in regulation. [39]

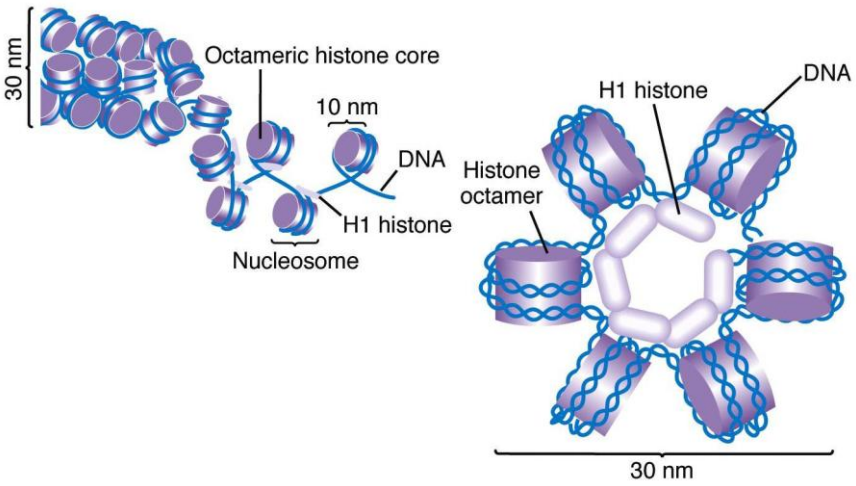

Figure 1 : Histone Octamer[128]

Histone replication in respect to chromatin: -

Early stage influence of chromatin on replication of histone: -

The replication of DNA requires series of proteins in initial stage in any organism. This series of proteins ultimately leads to loading two hexameric DNA helicases. [40] This protein starts unwinding of DNA which is required for replication. In eukaryotic cells pre-complex formed by two MCM-7 (Minichromosome Maintenance-7 complex) binds to ORC (origin recognition complex) rings. [41] The formed complex is inactive in nature which is activated by Dbf_4 (Dumbell former-4 protein) dependent kinase (DDK) and cyclin dependent kinase (CDK). [4] DNA-replication takes place when DNA sequence contains nucleosome free region (NFR). [5,6,7,8] In drosophila follicle cells histones round's origin of DNA replication initiations (ORIS) are hyper acetylated and change level of acetylation which affects on ORC binding. [9] Methylation of histone H_4 also helpful in ORC recruitment and promotes ORC binding by methyl transferase SET_8. [10]

When ORC bind to DNA protein CDC_6 (Cell division cycle 6) and CDT (DNA replication factor), this helps to load two MCM2-7 helicases to DNA. [11] This influence by acetylation of H4 due to recruitment of histone acetyltransferase HBO to ORC by CPT_1 (camptothecin 1) regulation of firing depends on MCM helicase activation by phosphorylation of some subunit by DDK and CDK kinase that allows CDC_{45} and GINS complex recruitments. [12,13,14] Once this all proteins loaded then replication starts. The spatial arrangement of chromatin helps to define replication domain. [15] The domain containing megabases of contiguous DNA that replicate early than others and this correlated with acetylation levels of H_4. [16,17] The recruitment and activity of replication machinery is influenced by chromatin is influenced by chromatin. When machinery fully set up then replication fork is progressed and DNA starts replicate after nucleosome displacement. [18]

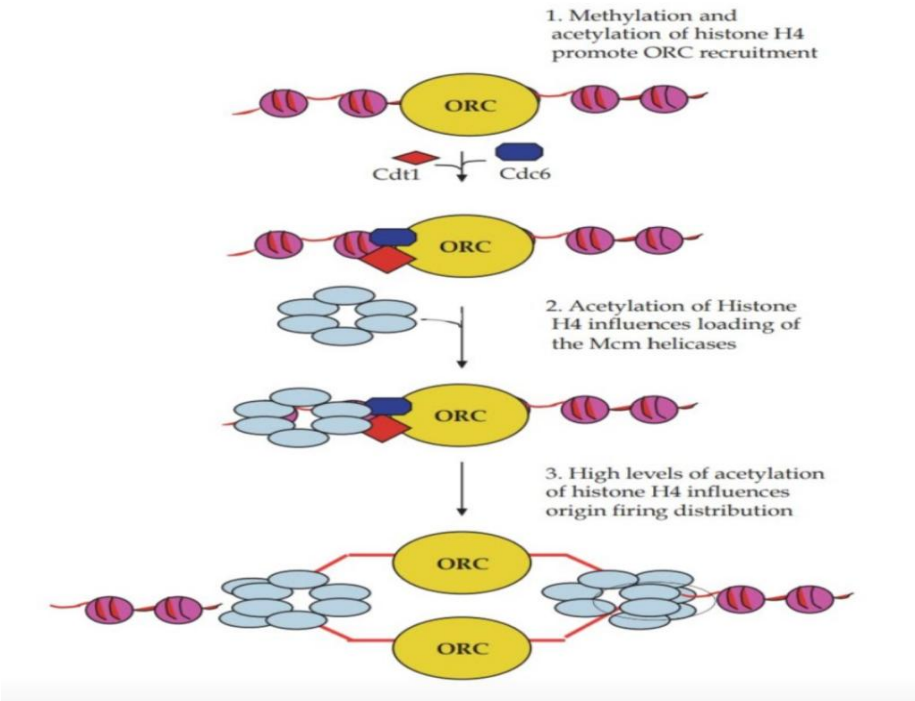

Figure 2 : Early Stage Chromatin Influence on Replication[132]

Nucleosome arrangement around replication fork: -

During progression of replication fork many proteins and DNA strongly interact with each other. [19,20] Chromatin is condensed before replication fork in mammalian cells. [21] This condensation process leads to increase mobility of histone H_4 by cyclin A-CDK complete phosphorylation. [22] It is still not clear that nucleosome decondensed before replication is due to passage of replication machinery or chromatin remodeling. [3] Proteins are able to react with chromatin complete and make them unstable for transcription. After transcription they interact with DNA. [42] The major two complexes involved in H2A and H2B displacement is FACT (facilitates chromatin transcription complex) and NAP_1K (nucleosome assembly protein kinase) and for H_3/H_4 displacement ASF_1 and CAF_1 present [in this N-terminal of both H_2A and H_2B binds with FACT to form complex with nucleosomes. The mid domain of nucleosomes attached with H_3-H_4 tetramer [$(CH_3$-$CH_4)_2$] to displace H_2A-H_2B dimer from nucleosomes. [43] During displacement the subunit of FACT complex i.e. Spt_{16} and SSRP (structure specific recognition protein), are play important role which shows indirect effect on nucleosome reorganization. [23,24] The other NAP (nucleosome assembly protein), complex shows disassembly of nucleosomes when it combined with RSC complex. [25,26] Asf_1 and CAF_1 combined to cause deposition of histone H_3/H_4 in passage of replication fork by binding with PCNA (Proliferating cell nuclear antigen), replication factor C and MCM helicase complex due to deposition of histone octamer DNA wrapped around nucleosome. [29,30] H_3/H_4 tetramer recycled after each DNA strand replication and new tetramer deposited over other strand of DNA. [31] CAF plays role in leading and lagging strand by PCNA. Depletion in CAF_1 cause decrease chromatin replication and increase DNA damage. [32,33] Finally, H_1 proteins cause chromatin compaction S-phase progression. [34] Due to DNA polymerase polarity on 5`to3` lagging strand chromatin landscape occurs which generate short fragment of DNA known as okazaki fragment. [35] This fragment needs to be goes under process of maturation for that flap endonuclease (FEN_1) and DNA ligase-1 plays important roles. This enzyme cause

flap processing and ligation of okazaki fragments. [36,37]

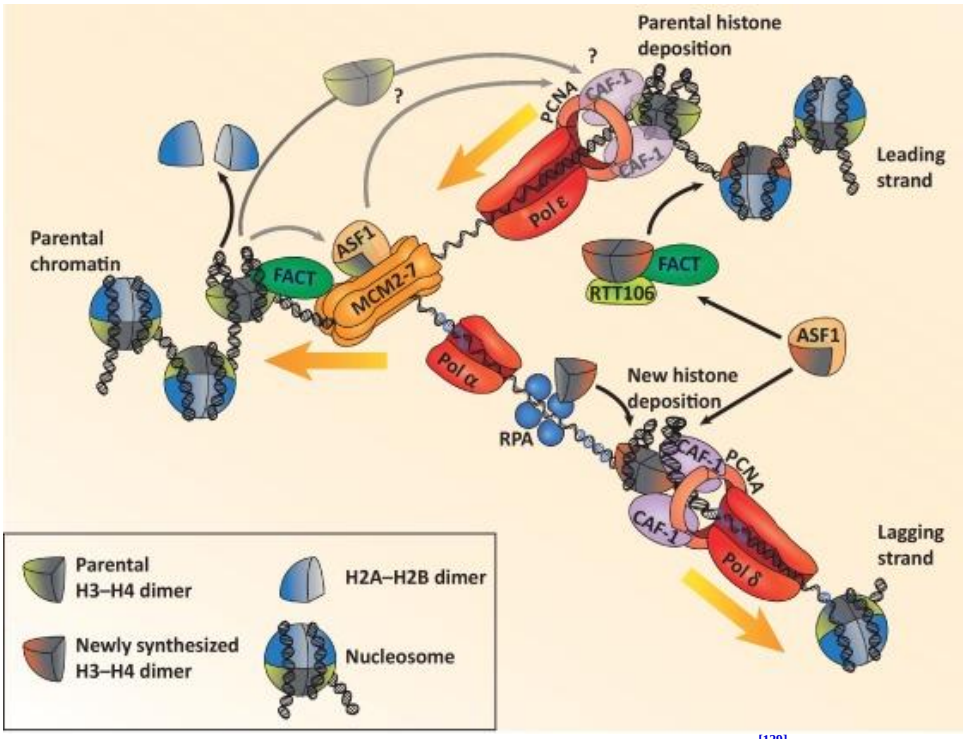

Figure 3 : Nuclosome Rearrangement around Replication Fork [129]

Maturation of chromatin and centromere formation: -

When nucleosome attached to DNA there is two processes are takes place i.e. maturation of chromatin and centromere formation. Histone starts to take some place and causes modification before DNA reposition. [57] Newly formed chromatin is highly acetylated and it need to be deacetylate or methylated to reach compact state. [58] Deacetylation cause due to enzyme deacetylase and methylation cause due to enzyme DNA methyl transferase in compaction state other post-transcriptional modifications are happening and establish some epigenetic code transfer to daughter cells. [54,55] This epigenetic memory is important for differentiation. [56] All processes do not happen in replication some of also takes place in mitosis. Chromatin replication near centromere ensures segregation during mitosis. The heterochromatin named CENP-A (Centromere protein A) helps for binding kinetochore during mitosis. [59] Correct segregation leads to formation of spindle fibers. [53] The highly diversified protein called heterochromatin (CENP-A) replaces histone H_3 at centromeric DNA. [51,52] This heterochromatin interspersed with canonical nucleosomes and promotes folding of chromatin during metaphase. [49] This formed complex allows kinetochore and microtubule attachment. [49] Heterochromatin positioned on centromeric chromatin during telophase after chromosome separation. [50] Defect in this process cause genetic instability, chromosome loss and cell death. [46,47,48] Several studies show that proper homeostasis between H_3 and heterochromatin (CENP-A) is help for distribution of centromeric variant and chromosomal segregation. [44,45]

Histone regulation: -

Nucleosomes are more than structural bricks for DNA and cause modification on histone to maintain epigenetic state. Hence, DNA replication is interdependent on chromatin reorganization. [61] Highly cell-cycle regulated genes are histone genes because cell generation needs high amount of histone replication. [60] The

histone mainly regulated by transcription, translation and post-transcription way but metabolism depends on organisms. [62,63] The bacterial species like s-cerevisiae shows transcriptional regulation. [64] While in the mammalian cells post-transcriptional and translational mechanism seen. [65]

1) Transcriptional regulation of histone: -

It is most important in bacterial species i.e. S. cerevisiae regulated in G1 phase of cell cycle or life cycle. [66] In higher eukaryotic it happens all of histone stages. [67] Histone expression must be stoichiometric if imbalance cause then it leads to deterioration of cell or disruption cell. [44,45,68] In S-phase replication expression increased by three to five folds. [69] In each histone cluster consist at least five canonical histones. Which are well organized and co-ordinated octamer-binding transcription factor (OTF_1) for H_2B activates coding region sequence in H_2A, H_3 and H_4 genes. [70,71]

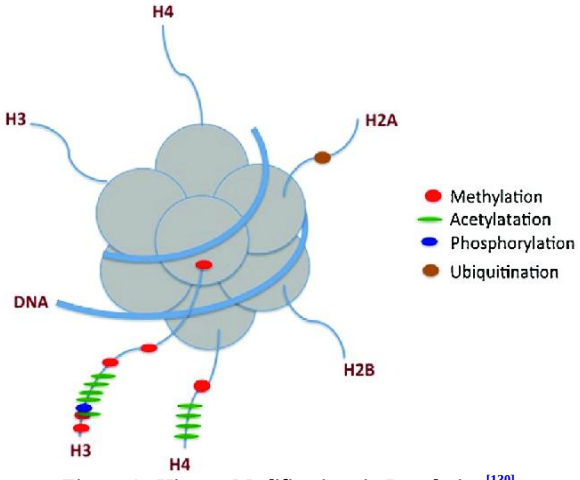

Figure 4 : Histone Modifications in Regulation[130]

Nuclear protein ataxia-telangiectasia's (NPAT) is required for activation of histone gene for S-phase Progression. [72] NPAT locates next to histone locus bodies and undergoes phosphorylation by cyclin E-CDK_2` and increase gene transcription. [73,74] Histone gene express and promotes upstream activating sequences (UAS) for recruitment of Spt_{10} and SBF. [75] Histone gene also consist negative regulatory site for replication under stress condition. [76,77,78] The HIR (histone regulator) complex responsible for transcription is formed by proteins named HIRA, $ubinuclein_1$ and $cabin_1$. The HIRA associated with chromatin assembly during transcription. [79] Overexpression of HIRA cause blockage of transcription in S-phase HIRA phosphorylated by cyclin E-CDK_2 and cyclin A-CDK_2. [80,81]

2) Post-transcriptional and translational regulation of histones: -

Mammalian histone mRNA contains 3` UTR (untranslated region) sequence for loop formation but they lack o f introns and poly (A) tail. [69] The transcripted histone localize to cajal bodies which express NPAT and mature $U_7$snRNA of histone locus bodies. [82] Maturation occurs after 3`end formation by endonucleolytic cleavage. This cleavage occurs between stem loop and histone downstream element (HDE). [83,84] This cleavage involved by specific proteins like SLBP, $LSM_{1\text{-}11}$, U_7snRNA and ZFP_{100}. stem-loop binding protein (SLBP) is major protein for translation and post-transcription process for regulation of histones. SLBP is major protein known as cell cycle regulated protein accumulate in G_1 phase and ends in S-phase. [85] SLBP helps to cleavage during mRNA maturation facilate circulation of histone and translated by polyribosomes and also increase histone mRNA stability and prevent histone degradation when DNA replication inhibits then SLBP also get degraded some of studies shows degradation of H_2B transcript by some component of exosomes. [86,87,88] Length of poly (A) is cell-cycle dependent it decreases in G_1 phase and progress in S-phase and progress in S-phase to G_2 phase. [89]

Regulation of histone by controlled level of protein: -

Studies shows that histone mRNA level controls the histone protein level. [90] The regulation pathway involves action of

CHK_2 and Rad_{53} which play important role in DNA damage response. [1,91] Degradation of histone involves rad_{53} action with E_2 ubiquitin ligases. [92] The mechanism of degradation involves phosphorylation of tyrosine and ubiquitylatin before proteolysis histone degradation does not involves kinases. [93]

DNA damage response (DDR): coupling of DNA and synthesis of histone: -

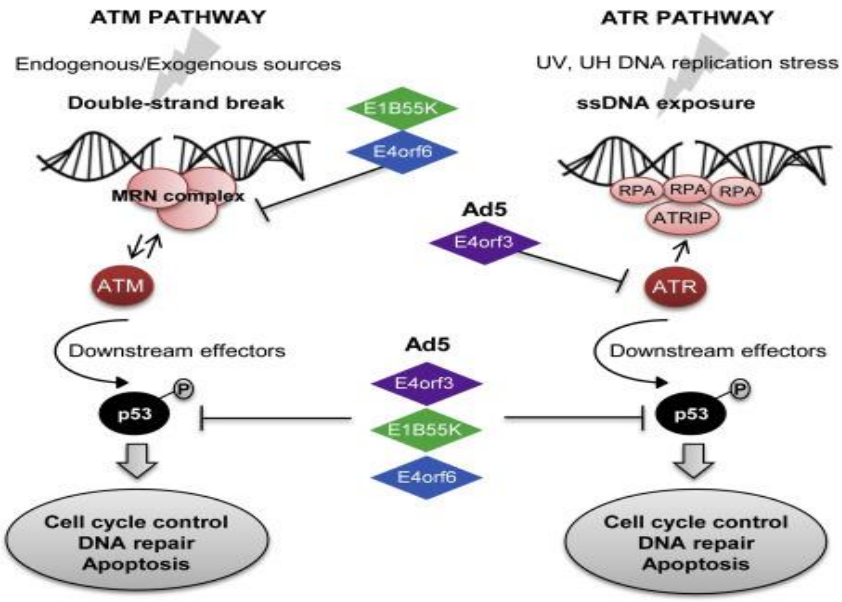

Figure 5 : DNA Damage Response Pathways [131]

DDR is one of the most important checkpoint in cell damage when DNA sense damage. [101] DDR activation leads to action of kinase cascade which leads to correct the cell damage. [102] If DDR is not activated then cell damage will not repair and enters into apoptosis programs and after apoptosis cell will die. [94] Cell cycle involves proper functioning so that it maintains genome integrity and mutations in disease conditions. DDR can resist G_1-phase s-phase and G_2 - Phase. [95] Two enzymes i.e. ATM (ataxia-telangiectasia mutated) and ATR kinase (ATM and Rad3-Related) are important in human cell and Tel_1 and Mec_1 are important enzymes in bacteria S-cerevisiae for activation of DDR. The ATM kinase directly involved in histone expression. [102,103] In human cells NPAT phosphorylation by cyclin E-CDK_2 is required for human gene transcription. In S-phase NPAT activation is important for histone expression. [72] Activation of ATM, P_{53} and P_{21} required for synthesis of histone upon DNA damage. [103] E-CDK_2 complex activity resist by enzyme P_{21}. Due to complex (cyclin E-CDK_2) inhibition the enzyme NPAT is dephosphorylated and activates the transcription. [96] The histone repression cause by change in HIRA activity for or location damage of DNA strands also cause post-transcriptional degradation of histone mRNAs. [104] Histone m RNA undergoes oligouridylation while cell treat with hydroxyl urea (HU). [97] This oligouridylation of m RNA histone depends on UPF_1 which binds to SLBP to recruit 3` terminal uridylyl transferase (TUT-ase). The 3` oligo (U) tails triggers the Lsm_{1-7} complex for progression of m RNA degradation by exosomes and Xrn_1. [97] Rad_{53} pathway not directly plays as part of DDR but it could be important for important for destruction of translated histones. Studies shows that Asf_1 and Rad_{53} plays important role in histone repression process. [105] The stable complex of Asf_1 and Rad_{53} is dissociate by phosphorylation due to Mec_1 phosphorylate in activation of DDR. [106] DNA repair involves DDR checkpoint activation and chromatin remodeling in which Asf_1 plays crucial role. [98] The other

important enzyme named Rad_{53} can available in G_1, G_2 and M-phase in hypophosphorylated form which is depend on Cdc_{28} (A homologue of human CDK_1 and CDK_2). HIR complex will leads to form precipitation with Asf_1. This leads to nucleosomes assembly and DNA template. [99] Asf_1 lacking in mRNA cause abnormalities in S-phase. [100] The dissociation of Asf_1 – Rad_{53} complex is important in histone transcription. [105]

Free histone formation: -

During a normal cell cycle DNA replication is unbalance due to histone supply unbalancing. [114] There are two possible scenarios for histone supply in which first occurs due to difference between rate of DNA synthesis and supply of histone during DNA replication. [107,108] More replication forks are used in S-phase and also replication stress affect on speed of replication fork. [109,110,111,112] In second situation cell can use free histones during G_2-phase of cell cycle. All free histones should be degrading after balanced ratio of histone H_3 and CENPA cause finished replication by chromosomes segregation. [104,116] So, here we can say that abnormality or imbalance of above two histone types (H_3 and CENPA) taken active participation in replication of cells which will lead to high incidence rate of chromosomes loss. [113]

Free histone transcription: -

Assemble and disassembly of nucleosomes is also required in transcription of chromatin template after passing of RNA polymerase II (RNA Pol-II). This transcripted chromatins are the main source of free histone formation. Due to imbalance between histone supply and demand the free histone amount is rises. The FACT complex is mainly involved in the transcription process along with RNA polymerase-II. [116,117] FACT complex stimulates the enzyme RNA Pol-II for elongation process in transcription. [118,119,120,121,122] FACT complex linked with H_3/H_4 tetramer and H_2A and H_2B dimer shows integrity towards one of the subunit. [123,124] Spt_{16} is play important role in reassembly of H_3 and H_4 histones. [125] Chromatin dysfunction cause generation of Spt_{16} proteins leads to free histone accumulation. This combined with $Rad_{53}K^{227}A$ cause degradation of histone and increase the amount of free histones. [126] H_2A-H_2B expression causes suppression of this mutants ($Rad_{53}K^{227}A$) and promotes expression of H_2A-H_2B mutation of Spt_{16} and histone level having correction. [126] The another protein factor called Spt_6 is helping in H_3-H_4 reposition during transcription and having strong negative interaction with mutant i.e. $Rad_{53}K^{227}A$. free histones forms due to chromatin reassembly detects during transcription with involvement of Rad_{53} which negatively interact with proteins involved in chromatin related processes. [127] Some of this factors are involved during chromatin related transcription processes. [127,126]

CONCLUSION

As we know the DNA is helpful for transmission of genetic information from one generation to another generation in the form of genomics or genetic code which having a particular sequence of genome in it. This topic highlights the histone cycle which is main protein in DNA transcription process. As we know the DNA is mainly found in eukaryotic organisms but it also found in some of the aracheabacterial species. (B. Thermophiles) which is the oldest colonies of bacteria living on earth. In this DNA forms a nucleoprotein complex called chromatin helps in compaction of genomic DNA in smaller space of nucleus. Hence, the chromatin works as a building block in nucleosome formation. The cell has its own unique and complex machinery to carried out various processes involving DNA needs to modify chromatin first. Chromatin mainly acts as a regulation machinery which carries epigenetic code which are important as one of contained of DNA in cell. In higher organisms with large and complex genome the particular cell require particular fraction of genome is

active. For this a brief passage of replication fork around replication coupled assembly is required. Histone synthesis is coupled to replication of genomic DNA and the existent of specific factor CAF-1 (chromatin activating factor-1) which targets newly synthesized histones to replicating DNA. The post-translational modifications and protein degradation may be involved in regulating the activity CAF-1 in in a cell-cycle-specific manner. Outside replication fork nucleosome assembly independent on histone H_3 variant and replication-independent pathways. Apart from an inherent of replication –coupled assembly to impose basal silencing, inheritance of post translationally modified histones at silent domains could play additional roles in maintenance of silent states. This topic also focuses on balance level of histones during chromatin formation and avoids deleterious effects due to generation of free histones. As a potential carrier of epigenetic information the recycling of parental histones after the passage of the replication fork is important for the inheritance of chromatin states. Recent structure studies revealed extensive details on the co-operation among replisome (responsible for unwinding of DNA & promotes replication) especially the co-operation among the replicative helicase and DNA polymerase (DNA Pol-II). This evidence strongly supports replisome components that directly contribute into histone cycle.

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