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Full Length Article

H3/H4 Histone Genes Variations and its Effect on Post Translational Modifications in Various Strains of *Sordaria fimicola*

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Abstract

Histones are major determinants and key players to regulate gene expression. Core histones (H3 and H4) are highly conserved in all eukaryotes and control various cellular processes i.e. organization of chromatin material, transcription, replication and repair of DNA. Histones and all other proteins undergo different type of alterations after translations, which are necessary for their proper functions, known as post-translational modifications (PTMs). These are done by the addition or deletion of compounds i.e. carbohydrates, lipids, acetyl group, phosphoryl group and methyl group. In this study, H3 and H4 gene of *Sordaria fimicola* were amplified for the first time in order to make effort towards the completion of its whole genome study. According to BLAST, there was more than 80% match of this gene with *Neurospora*. In order to determine the variations in nucleotides and amino acid sequences, histone gene and protein of *S. fimicola* were compared with other organisms (*Neurospora crassa*, *Caenorhabditis elegans*, *Mus musculus* and *Arabidopsis thaliana*). There are many amino acid variations in H3 and H4 histones of fungi and other organisms. H3 protein of *S. fimicola* resembled *N. crassa* and *A. thaliana* and H4 protein of *S. fimicola* resembled *N. crassa*. Predictions of PTMs (H3 and H4) for *S. fimicola* and *N. crassa* are same at some residues but mostly predictions of *S. fimicola* are different as compared to all other organisms. © 2018 Friends Science Publishers

Keywords: Modifications; Phosphorylation; Histone 3 and 4; Glycosylation; *S. fimicola*

Introduction

The histone proteins are elementary units of chromatin, involved in stratified packaging of DNA into chromatin material and provide a substantial resistance to all cell functions that involve DNA (Peterson and Laniel, 2004; Butt *et al.*, 2011). Hence, chromatin material dynamics and compaction is essential for cell regulatory activities (i.e. transcription, replication, recombination and repair). Histone proteins are in the form of octamer to which DNA is wrapped in condensed form. There are 147 nucleotide bases in 1.7 super helical turn around each octamer of histone. About 75% of this octamer is in the form of globular structure, onto which the DNA is wrapped; some form long tails at N-terminal which are rich in lysine and arginine (Fucha *et al*., 2011). In histone octamer, eight N-terminal tails are hanging from nucleosome and they can make inter-molecular connections. The linker histones in most of the eukaryotes provide an additional 20 bp of DNA to complete the nucleosome and to establish higher order chromatin structures (Lin *et al*., 2013; Smolle and Workman, 2013).

Long N-terminal tails play critical role in chromosomal processes, which is obvious in post-translational modifications. The function of N-terminal tails in different modification state is the addition of regulatory proteins that affect chromatin structure indirectly; thus the N-terminal tails directly modulate nucleosome compaction. The compaction chromatin fiber and different regulatory mechanisms provide evidence that the folding of chromatin arrays is due to the presence of linker histone (Robinson *et al*., 2008).

The H3 and H4 are highly conserved histone genes. Their side chains attach to terminal fragments of DNA that enter and exit the nucleosome. Moreover, nucleosomes which assemble *in vitro* form H3 and H4 tetramers keep their capability to delay or disrupt the transcription. As chromatin does not provide accessibility to the hereditary material, the proteins helping in transcription must prevail over this by regulating the histone condensation/de-condensation. Disruption of chromatin structural design is done by (i) chromatin remodeling proteins, which repositions the nucleosome to the prime DNA which is to be transcribed and (ii) the H3 and H4 modifying enzymes, which change the histones in the nucleosomes. Along these lines, histone proteins govern the transitions between euchromatin and heterochromatin (Ramakrishnan, 1997).

In post-translational modifications distinct biochemical functional moieties such as phosphate, acetate,

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various lipid and carbohydrates are added or removed from amino acids residues by proteolytic processing of the protein termini, or the formation of covalent bridges between domains of the protein (Basu *et al*., 2010). Kinases add a phosphate group to the histones proteins. Nearly all proteins are post-transnationally regulated with the help of enzymes such as: transferases (i.e. kinases, methyltransferases, acetyltransferases, and glycosyltrasferases) and proteases, which remove a group i.e., deacetylases, glycosidases, and phosphatases etc. (Moraes *et al*., 2015).

There are many types of histone protein modifications including methylation of lysine (K) and arginine (R), phosphorylation of serine (S) and threonine (T) and acetylation of lysineetc. (Zentner *et al*., 2011). These changes alter the histone structure, mostly at the N-terminal stretches and act epigenetically to regulate gene expression. There are several effector proteins regulating chromatin and post-translational chemical changes of histone tails. Histone modifications act as epigenetic passengers that can pass to daughter cells to maintain ancestral transcriptional profiles (Creyghton *et al*., 2010). In chromatin field, understanding of histone modifications is a main focus. Acetylation of histones is thought to be involved in the control of transcription, whereas de-acetylation of histones is correlated with silencing. The linker histone H1 is not associated with acetylation. It phosphorylates and this kind of phosphorylation of the linker histone H1 is associated with modifications in chromatin structure (Yun *et al*., 2011).

All histone proteins maintain their capability to arrange within the nucleosomes. This suggests a crucial purpose of histone proteins is performed by their globular structure. Deletions of some regions of the foundation of H4 are fatal. Moieties inside the globular core domain of the nucleosome are substrate for modifying enzymes (Hyland *et al*., 2005; Rada-Iglesias *et al*., 2011). Acetylation of Lys18 and Lys 27 results in histone and gene activation that add to histone acetylation transferases to acetylate other lysine amino acids (Jin *et al*., 2011).

It is postulated that PTMs function as a signal platform to recruit effector modules to local chromatin and it is the effectors/readers that ultimately determine the functional outcome of certain PTMs. For example, methylation of H3 and H4 controls both transcriptional repression and activation, and chromatin state is dependent on the particular amino acid being methylated (Moraes *et al*., 2015). The objectives of the current study were to amplify the H3 and H4 genes in different strains of *S. fimicola* and to study the post-translational modifications of the Histone 3 and Histone 4 in model organisms.

Materials and Methods

Research Specimen

Genus *Sordaria of* order Sordariales has extensive distribution with 12 species. *S. fimicola* was our research specimen. Six strains were provided by Molecular Genetic Research Laboratory, University of the Punjab, Lahore, Pakistan. Four generations were raised from the original parental strains. *S. fimicola* is an ascomycetic coprophilous fungus that grows on the herbivore dung. It has characteristics which make it favorable organism for genetic studies. It is easy to grow in laboratory due to its short life cycle and non-pathogenic nature. Fungi were grown on PDA (Potato Dextrose Agar LAB 098, Lab M limited). Petri dishes were incubated at 17ºC in dark for 15 days until perithecia were formed and fungus was fully matured. Under the aseptic conditions in the laminar air flow cabinet, a drop of autoclaved distilled water was poured on a glass plate and a perithecium was taken from mature fungus and ruptured by using sterilized fine needle to expose and release group of asci. The ascospores were allowed to separate from each other and single spores were isolate in order to obtain pure cultures.

Polymerase Chain Reaction (PCR)

In order to amplify histone 3 (H3) and histone 4 (H4) gene using PCR, primer set 5’ ACTAAGCAGACCGCCCGCAGG 3’, 5’ GCGGGCGAGCTGGATGTCCTT 3’ was used and about 50 µL of PCR master mix was prepared by adding 5 µL PCR buffer, 5 µL dNTPs, 1 µL Taq polymerase, 5 µL $MgCl_2$ and 29 µL ddH_2O. Then 50 µL of master mix was transferred in each PCR tube having 3 µL template DNA and 2 µL primer. Tubes were placed PCR (Veriti® Thermal cycler) for amplification. PCR optimized conditions were initial denaturation (95ºC for 5 min) following the 35 cycles of denaturation (94ºC for 1 min), second step of annealing (60ºC for H3 and 57ºC for H4 for 1 min), third step: elongation (72ºC for 1 min) and final step: elongation (72ºC for 5 min) and hold at 4ºC.

Data Analysis

Genomic and protein sequences of the amplified products (H3 and H4) were analyzed for the variations and similarities by NCBI blast (https://blast.ncbi.nlm.nih.gov/Blast.cgi); Clustal Omega (https://www.ebi.ac.uk/Tools/msa/clustalo/); SIAS (Sequence Identity and Similarity) (http://imed.med.ucm.es/Tools/sias.html) and Uniprot Database (Universal Protein Resource) (http://www.uniprot.org/). For post translational modifications, computational analysis was done by using different online servers such as YinOYang 1.2, NetPhos 3.1 (http://www.cbs.dtu.dk/services/); PAIL (Prediction of Acetylation on Internal Lysines) (http://bdmpail.biocuckoo.org/) and PMes.

Results

According to dendrogram based on nucleotide sequences of

histone gene, *S. fimicola* and *N. crassa* gene was found to be closely related to *A. thaliana*.

Protein Sequence Analysis

In order to detect any protein polymorphism, sequence of histone proteins of model organisms (*Neurospora crassa*, *Caenorhabditis elegans*, *Mus musculus* and *Arabidopsis thaliana*) was retreived from Uniprot database and was further analyzed. According to phylogenetic tree based on protein sequences, H3 of *S. fimicola* closely resembled that of *N. crassa*. Higher organisms like *C. elegans* and *M. musculus* are genetically very much similar (evolved). The nucleotid sequence of *A. thaliana* is closer to fungus as compared to animals.

Predictions of Post-translational Modifications (PTMs)

Various online servers were used to predict histones modifications. Comparison were done to detect variations and conservations in PTMs and only best server results are discussed in Tables 1–5.

PTMs of Histone Protein

The stability and function of histone proteins was controlled by various types of histone modifications, like glycosylation, phosphorylation, cleavage, acetylation and methylation. Following are the predictions of residual sites of histone 3 protein. The protein sequences to assess similarities/variations in histone 4 protein were taken directly form uniprot database.

Discussion

In H3 residual, phosphorylation of Ser10 assists chromosome condensations/de-condensations in transcription (Cheung *et al*., 2000). Furthermore, phosphorylation of Ser10 in BKPyV virions regulates the viral assemblage (Dahl *et al*., 2007). On the basis of observations made in this study it may be assumed that phosphorylation of Ser11 may play the same function in *Neurospora*, *Caenorhabditis*, *Mus* and *Arabidopsis* while in *S. fimicola* Ser12 may be involved in the condensation/de-condensation of chromosomes. As a result of this organisms were divided into two groups: Group A included *Sordaria*, while Group B included *Neurospora*, *Caenorhabditis*, *Mus* and *Arabidopsis* (Table 1). H3 phosphorylation is extremely vigorous, it mostly occurs on serines, threonines and tyrosines residues (Goto *et al*., 2007). Phosphorylations on similar residues (Ser/Thr/Tyr) were also observed in the present study. A total of 18 sites for phosphorylation were predicted in *S. fimicola*, 16 in *N. crassa*, 11 in *C. elegans* and 12 in *A. thaliana* and *M. musculus* (Table 2).

Less is known regarding the roles of histone phosphatases. Certainly, given the extremely rapid turnover of specific histone phosphorylations, there must be a high phosphatase activity within the nucleus e.g., the PP1 phosphatase works antagonistically to Aurora B, the kinase that lays down genome-wide H3S10ph and H3S28ph at mitosis (Goto *et al*., 2007). The site 29S was found post-transcriptionally conserved in all five model organisms under study and several common kinases (PKG, PKA and unsp) were involved in phosphorylation in *N. crassa*, *M. musculus*, and *A. thaliana* while in *S. fimicola* RSK catalyzed this reaction instead of unsp. H3S29ph in these 5 model organisms may play important role in the regulation of mitosis as mentioned above. Current investigations were further supported by Oki *et al*. (2007) who also found that several kinases and phosphatases are involved in controlling the phosphorylation of H3 protein in eukaryotes respectively.

Table 1: Sequence identity and similarity (SIAS) of H3 gene in *S. fimicola* and its comaprison with model organisms

Identity Results				
M. musculus	34.75%			
A. thaliana	28.71%	72.26%		
C. elegans	38.64%	47.88%	74.93%	
N. crassa	15.92%	27.61%	0%	100%
	S. fimicola	*M.musculus*	*A.thaliana*	*C. elegans*
Similarity results				
M. musculus	21.33%			
A. thaliana	57.32%	42.74%		
C .elegans	19.81%	42.52%	37.88%	
N. crassa	35.12%	17.05%	25.76%	59.94%
	S. fimicola	*M. musculus*	*A. thaliana*	*C. elegans*

Histone phosphorylation on residue i.e. Thr22 is related with prostatic carcinomas (Metzger *et al*., 2008; Luebben *et al*., 2010). There are 7 sites in, *A. thaliana* and *M. musculus*, 5 in *N. crassa* and 6 in *C. elegance* for Thr residue phosphorylation (Table 2). Threonine phosphorylation on position 7, 12 and 46 were found conserved in organisms belonging to group B but these sites were not common for *S. fimicola*. In *S. fimicola* 12S is phosphorylated instead of H312T. Tyrosine phosphorylation on 100Y was observed only in *N. crassa*, while tyrosine modification at this site was absent in remaining four organisms.

Another type of PTM named as glycosylation was an alterable modification responsible for cell survival, immunity, signaling and transcription (Kuo *et al.*, 2008; Shen and Casaccia-Bonnefil, 2008; Zhang *et al*., 2011). Seven conserved potential sites for glycosylation were depicted in H3 of four organisms but these sites are not conserved in *S. fimicola* (Table 2) in H3. Glycosylation on position H311S residue can be considered to be involved in the regulation of H3 in these model organisms.

Acetylation on 10 sites was predicted in this study. Eight out of these 10 sites were conserved in *N. crassa*, *C. elegans*, *A. thaliana* and *M. musculus* but not in *S. fimicola* (Table 3). According to various investigations, acetylation on three positions i.e. 5K, 10K and 56K are evolutionary important that play significant role in the deposition of

Table 2: Prediction of phosphorylation and glycosylation sites in Histone-3 protein in *S. fimicola* and model organisms

Phosphorylation					Glycosylation				
S. fimicola	*N. crassa*	*C. elegans*	*M. musculus*	*A. thaliana*	*S. fimicola*	*N. crassa*	*C. elegans*	*M. musculus*	*A. thaliana*
2T	7T	7T	7T	7T	2T*	4T	4T	4T	4T
6S	11S	11S	11S	11S	6S*	7T*	7T*	7T*	7T*
12S	12T	12T	12T	12T	12S*	11S*	11S*	11S*	11S*
29S	23S	23T	23T	23T	56T	12T*	12T*	12T*	29S*
39Y	29S	29S	29S	29S	60T	23S	23T	23T	33T*
51T	32S	33S	32S	33T	83S	29S*	29S*	29S*	46T*
56T	33T	46T	33T	46T	89S	33T	33S*	33T	81T
60T	46T	58S	46T	58S	90S	81S	46T*	46T*	119T*
66T	58S	81T	58S	81T	96S*	87S	58S*	81T	
73T	81S	87S	81T	87S	114T	96S*	81T	119T*	
89S	87S	119T	87S	119T	115S*	119T	87S		
90S	96S		119T		116T*		119T*		
94S	100Y				117S				
96S	103S				146S				
115S	119T								
116T	122S								
146S									
153S									

Table 3: Prediction of acetylation and methylation sites in H3 protein of *S. fimicola* and model organisms

Acetylation					*Methylation*				
S. fimicola	*N. crassa*	*C. elegans*	*M. musculus*	*A. thaliana*	*S. fimicola*	*N. crassa*	*C. elegans*	*M. musculus*	*A. thaliana*
-	5K	5K	5K	5K	8R	9R	9R	9R	9R
10K	10K	10K	10K	10K	19R	10K	10K	10K	10K
41K	15K	15K	15K	15K	70R	15K	15K	15K	-
124K	19K	19K	19K	-	154R	18R	18R	18R	18K
	24K	24K	24K	24K		19K	19K	19K	37K
	28K	28K	28K	28K		24K	24K	24K	38K
	37K	37K	37K	37K		27R	28K	27R	41R
	38K	38K	38K	38K		28K	37K	28K	43R
	57K	57K	57K	57K		37K	38K	37K	57K
	116K	116K	116K	116K		38K	41R	38K	65K
						41R	43R	41R	70R
						57K	57K	43K	80K
						65K	65R	57K	116K
						70R	70R	65K	117R
						80K	80K	70R	
						84R	84R	80K	
							116K	84R	
							117R	116K	
							123K	117R	
								123K	

Table 4: Prediction of Glycosylation and Phosphorylation sites in H4 protein of *Sordaria fimicola* and Model organisms

Glycosylation					*Phosphorylation*				
S. fimicola	*N. crassa*	*C. elegans*	*M. musculus*	*A. thaliana*	*S. fimicola*	*N. crassa*	*C. elegans*	*M. musculus*	*A. thaliana*
4T	2T*	2S	72T	72T	2T	2T	2S	2S	2S
7S	72T	72T	145T*	83T	31T	31T	31T	31T	31T
91T	83T		222T		48S	48S	48S	48S	48S
130S	84S				52Y	52Y	52Y	52Y	52Y
148S					72T	72T	72T	72T	72T
					73Y	73Y	73Y	73Y	73Y
					81T	81T	81T	81T	81T
					97T	97T	97T	97T	97T

*= YinOYang sites

histones (Parthun, 2007). We have also predicted the acetylation on the similar positions in these organisms. The H3K56 side chain points towards the major groove of DNA, suggesting that acetylation would affect histone/DNA interaction, a situation significant for the proposed effects of acetylating the histone N-terminal tail Lysines (Tjeertes, *et al.*, 2009).

Histone methylations mostly take place on the side

Table 5: Prediction of Acetylation and Methylation Sites in H4 protein in *Sordaria fimicola* and Model organisms

Acetylation					*Methylation*				
S. fimicola	*N. crassa*	*C. elegans*	*M. musculus*	*A. thaliana*	*S. macrospora*	*N. crassa*	*C. elegans*	*M. musculus*	*A. thaliana*
15	6	6	6	6	8R	21K	21K	9R	9R
23	9	9	9	9	48R	36R	36R	36R	36R
33	13	13	13	13	49R	37R	37R	37R	37R
35	17	17	17	17	64R	40R	40R	40R	40R
41	21	21	21	21	119R	41R	41R	41R	41R
53	45	45	45	45	137R	96R	96R	96R	78R
88	78	78	78	78					96R
	80	80	80	80					
	92	92	92	92					
			156						
			159						
			163						
			167						
			171						
			195						
			228						
			230						
			242						

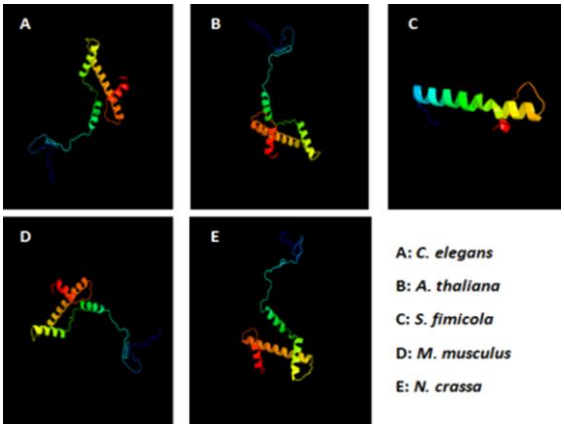

Fig. 1: Three dimensional images of H3 Protein in five model organisms

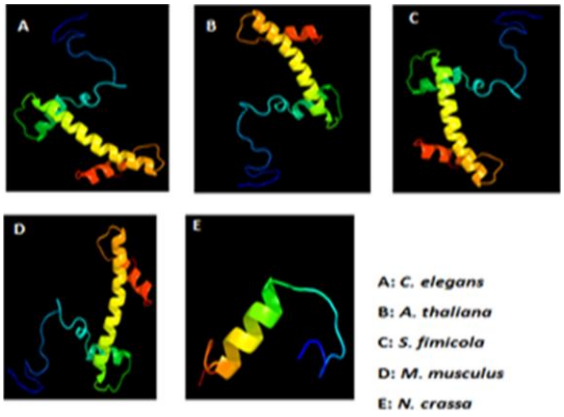

Fig. 2: Three dimensional images of H4 protein in five model organisms

chains of R and K. Unlike acetylation and phosphorylation, the histone methylation does not change the charge on the histone protein (Bedford and Clarke, 2009). In the current study, methylation on similar residues (Arginine and Lysine) was observed such as in group A at position 19, R got methylated while in group B K was also methylated (Table 3). K acetylation on 7 sites was conserved in group B while R acetylation at four positions was conserved in group B but not in group A.

This work presents major evidence that serine and threonine residues in histone proteins are modified by the post-translational addition of an *O*-linked acetyl glucosamine (termed *O*-GlcNAc), phosphate group and methyl group. *O*-GlcNAcylation, analogously to protein phosphorylation, takes place as a revocable post-translational modification of proteins that play important role in cell signaling, stress responses, and during cell growth (Zhang *et al*., 2011). This glycosylation involving the addition of a single sugar molecule, β-*N*-Acetylglucosamine, to the hydroxyl group of serine or threonine residues is termed as *O*-GlcNAc (Forsythe *et al*., 2006). This may lead to a reciprocal regulation of protein function because phosphorylation and *O*-GlcNAcylation may compete with each other for the same amino acid residue. In *Caenorhabditis elegans*, glycosylation contributes in insulin resistance as its deletion suppressed the induction of dauer formation in a genetic background defective for insulin signaling (Hanover *et al*., 2005). H4 protein was also subjected to glycosylation (Table 4). In *S. fimicola* 3 sites were acetylated. Ten acetylation sites in *N. crassa*, *C. elegans*, *M. musculus* and 9 sites in *A. thaliana* were predicted. The K10 site is said to be conserved in all organisms under discussion. All these modifications also effect the protein organizations in all the model organisms that can be seen in the 3D structures of H3 and H4 histones (Fig. 1 and 2).

Acetylation of K91 was considered to be related with the occurrence of two methyl groups on arginine residues 92 and/or 95. This modification was for the first time recognized in bovine histones by peptide mass fingerprinting

and later on confirmed by electron capture dissociation (Zhang *et al.*, 2003). Hence, H4 K91 acetylation also appears to be highly conserved. The histone H4K91 acetylation plays a vital role in assembly of chromatin network and this modification takes place in the nucleosome and might affect the interaction of H2A/H2B dimers with H3/H4 tetramers and, hence, regulates the formation of histone octamers during chromatin assembly (Adams and Kamakaka, 1999).Current study reports that acetylation on 9 position was conserved among members of group B and among these 9 sites, H4K92 is considered to be evolutionary important, because this site is quiet close to H4K91 (Table 5).

Conclusion

The PTMs of histone H3 and H4 which are highly conserved in studied organisms have been identified and these findings will help in understanding the role of different types of PTMs in determining the functions of Histone proteins particularly the regulation of gene expression.

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