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Exploring post-translational modifications of histones in RNA polymerase II-dependent transcription

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Chair of Cell Biology, Institute of Molecular and Cell Biology, University of Tartu, Estonia

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals.

I. **Sein, H.**, Värv, S., Kristjuhan, A. (2015) Distribution and maintenance of Histone H3 lysine 36 trimethylation in transcribed locus. PLoS ONE 10(3): e0120200

II. **Sein, H.**, Reinmets, K., Peil, K., Kristjuhan, K., Värv, S., Kristjuhan, A. (2018) Rpb9-deficient cells are defective in DNA damage response and require histone H3 acetylation for survival. Sci Rep 8(1):2949

III. Peil, K., **Jürgens, H.**, Luige, J., Kristjuhan, K., Kristjuhan, A. (2020) Taf14 is required for the stabilization of the pre-initiation complex in *Saccharomyces cerevisiae*. Epigenetics & Chromatin 13(1):24

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My contribution to these articles is as follows:

Ref. I – participated in experimental design, performing the experiments, data analysis and manuscript preparation.

Ref. II – participated in experimental design, performing the experiments, data analysis and manuscript preparation.

Ref. III – participated in performing the experiments, data analysis and manuscript preparation.

LIST OF ABBREVIATIONS

AA	anchor away
aa	amino acid
ac	acetylation
6-AU	6-azauracil
BD	bromodomain
bp	base pair
CoA	coenzyme A
CPD	cyclobutane pyrimidine dimer
CPF	cleavage and polyadenylation factor
CUT	cryptic unstable transcript
C-terminal	carboxy-terminal
DDR	DNA damage response
DPF	double PHD finger
DSB	double-stranded breaks
DSIF	DRB sensitivity-inducing factor
GGR	global genomic repair
GTF	general transcription factor
HAT	histone acetyltransferase
KAT	lysine acetyltransferase
KDAC	lysine deacetylase
HFD	histone fold domain
HMG	high mobility group
HR	homologous recombination
HU	hydroxyurea
Ig	immunoglobulin
JmjC	jumonji C catalytic domain
LSD1	lysine-specific demethylase 1
MMS	methyl methanesulfonate
MPA	mycophenolic acid
NDR	nucleosome-depleted regions
NELF	negative elongation factor
NER	nucleotide excision repair
NHEJ	nonhomologous end joining
N-terminal	amino-terminal
NTP	nucleoside triphosphate
PTM	post-translational modification
RF	replication fork
RNAPII	RNA polymerase II
RSC	remodelling the structure of chromatin

S. cerevisiae	*Saccharomyces cerevisiae*
Set2	SET domain-containing 2
SRI	Set2-Rpb1 interaction
SUT	stable unannotated transcript
TBP	TATA-binding protein
TCR	transcription-coupled repair
TL	trigger loop
TSS	transcription start site

INTRODUCTION

In the nuclei of eukaryotic cells, DNA wraps around a set of evolutionary conserved histone proteins to form a nucleosome, which makes up the basic unit of chromatin. By packaging the DNA into chromatin, the cell can achieve various levels of compaction to balance its structural needs with functional requirements. The dynamic nature of chromatin architecture plays a major role in the regulation of most of the cellular processes, including RNA polymerase II (RNAPII)-dependent transcription. For efficient transcription, chromatin near the gene to be transcribed needs to be reorganized to allow the formation of pre-initiation complex and the processes of initiation, elongation and termination. Among various factors that control DNA accessibility, post-translational modifications (PTMs) of histones are key players since they regulate chromatin structure. Modifications of histones function either by modulating the stability of nucleosomal particles, directly altering chromatin accessibility or by regulating interactions with PTM-specific binding proteins. These effector proteins recognize specific histone modification marks by functionally specialized structural folds, also called "reader" domains to regulate chromatin structure and function.

Given the importance of chromatin structure in the epigenetic regulation of transcription, the mechanisms governing this process have been the focus of intense research within the field of chromatin biology. Although studies in the last few decades have achieved great progress, a lot of research is still needed to elucidate the role of chromatin modifications in transcription regulation. Current thesis explores the mechanisms and impact of histone PTMs and their reader domains in RNAPII-mediated transcription in budding yeast *Saccharomyces cerevisiae*. To clarify how epigenetic landscapes are established and maintained, the distribution and turnover mechanisms of the PTM pattern created during active RNAPII transcription was examined. Secondly, this study explores the importance of histone acetylation in stress conditions where transcription is hampered by depleting one of the RNAPII subunits. Additionally, the essentiality of effector proteins recognizing modified histone marks on cell viability were evaluated and their specificity and impact on transcription regulation investigated.

1. OVERVIEW OF LITERATURE

1.1. Structure of chromatin

In order to fit and regulate the enormously long and fragile genomes of eukaryotic species, our DNA is packaged in cells in the form of chromatin. Olins and Olins reported the first electron micrograph of the "beads-on-a-string" structure of chromatin in 1974, the "beads" representing the basic repeating unit of chromatin – the nucleosome and the "string" being the linker DNA (Kornberg, 1974; Olins and Olins, 1974). The structure of the nucleosome core is relatively invariant from yeast to metazoans, formed by wrapping 145–147 base pairs (bp) of DNA in a left-handed supercoil around an octamer of two copies each of the four core histones: H2A, H2B, H3, and H4 (Figure 1A) (Luger et al., 1997). The core particle of the nucleosome resembles a disc-like structure about 5,5 nm in height and 11 nm in diameter (Zhu and Li, 2016).

Histones are positively charged nuclear proteins with highly conserved sequences, composed of two common regions, the "histone fold" and the "histone tail". Histones are predominantly globular except for their N- and C-terminal tails which are unstructured and rich in basic residues. The main contacts between histones and DNA are made through structurally conserved hydrophobic histone fold domain (HFD), found in all core histones which mediates heterodimerization of H2A with H2B and H3 with H4 (Iwasaki et al., 2013). The HFD consists of three α-helices (α1, α2 and α3) separated by two loops (L1 and L2). Histones assemble in a stepwise fashion on DNA with two heterodimers of H3/H4 first depositing to form a core tetramer followed by two heterodimers of H2A/H2B (Figure 1B). The two H2A-H2B dimers can be removed more easily, as H2A-H2B dimers *in vivo* have a higher rate of exchange than the H3-H4 tetramer. Furthermore, replacement of the H3-H4 tetramer requires the prior removal of the H2A-H2B dimers (Henikoff, 2008; Jamai et al., 2007; Kulaeva et al., 2010). The basic residues in the histone core and the negatively charged DNA phosphodiester backbone interact through electrostatic forces and hydrogen bonding, as well as through non-polar contacts with the deoxyribose sugars. The histone core binds the DNA backbone at 14 superhelix locations, making over 120 direct atomic interactions (Luger, 2003). In addition, higher eukaryotes also have histone H1 that locks the DNA coming in and out of the nucleosome and further condenses and stabilizes the chromatin (Saunders et al., 2006). It is not clear whether *S. cerevisiae* has histone H1, but the protein with greatest sequence similarity to H1 is Hho1. Although several reports have shown that instead another yeast high mobility group (HMG) protein Hmo1 has the ability to compact chromatin (Lu et al., 1996; Panday and Grove, 2016). Whereas the nucleosomal core is compact, eight flexible lysine-rich histone tails protrude outward from the nucleosome, past the DNA, mediating interactions with other nucleosomes and contributing to the formation of higher-order chromatin structure (Luger et al., 1997).

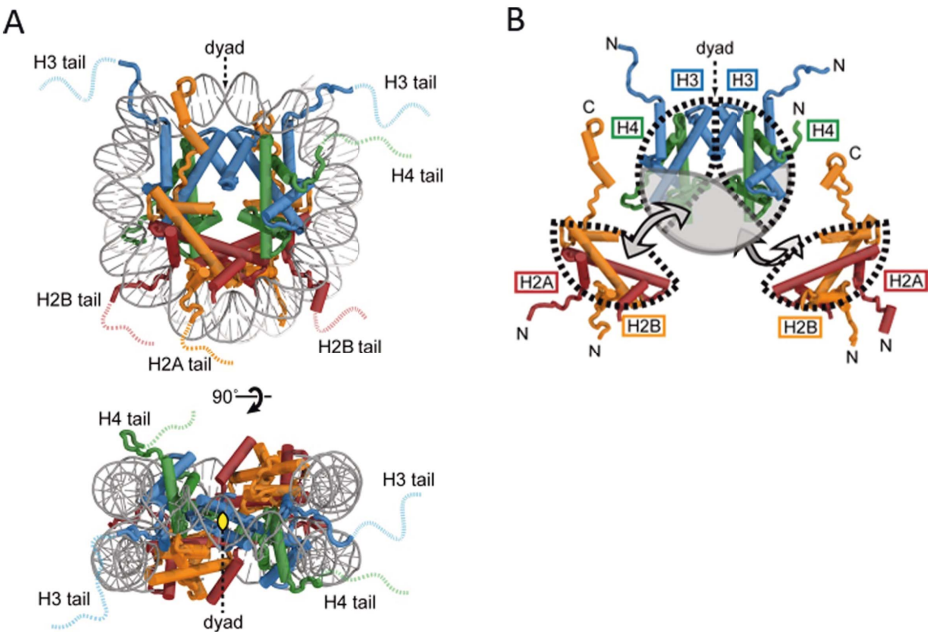

Figure 1. Structure of the nucleosome core particle. A. Top and side view of the 146 bp DNA (double helix shown in grey) in complex with histone proteins (H2A – red, H2B – orange, H3 – blue, H4 – green). Histone tails are shown to protrude outwards from the nucleosome core past the DNA. **B.** Illustration of how H2A/H2B and H3/H4 heterodimers form the histone octamer. Figure adapted from Bowman and Poirier (2015). For the structures PDB coordinates 1KX5 was used (Davey et al., 2002).

1.2. Histone post-translational modifications

Packaging the DNA into chromatin presents a constant physical barrier to any process that needs access to the DNA, including gene transcription, replication and DNA repair. So how are the cells able to gain access to the underlying wrapped DNA? One most prominent answer is to chemically modify the histones to alter their structure and thus their interaction properties to regulate access to the DNA. The N- and C-terminal histone tails extend from the nucleosome core and are targeted by post-translational modifications (PTMs) (Figure 2). All histones can be post-translationally modified, and the sites of modifications are often on the histone tails. However, many reports have identified modifications within the histone core domains, thought to be accessible during nucleosome exchange (Williams et al., 2008).

PTMs affect chromatin structure through three general mechanistic pathways: intrinsic effects on histone-histone interactions, external effects on inter-nucleosome contacts, or by recruitment of effector proteins. Intrinsic effects directly alter physical nucleosome properties such as DNA contacts and mobility, size and conformation, or stability, while extrinsic effects influence interactions between

nucleosomes. Lastly, chromatin-modifying proteins that recognize histone modifications can directly or indirectly alter the physical properties of chromatin (Campos and Reinberg, 2009; Zentner and Henikoff, 2013). Using these modes of action PTMs help open up or compress the chromatin still further, creating transcriptionally active and inactive chromatin in response to environmental and internal signals.

The most abundant modifications are acetylation, methylation, phosphorylation, ubiquitylation and sumoylation, although more than a dozen types of histone modifications and hundreds of modification sites altogether have been found (Arnaudo and Garcia, 2013; Kouzarides, 2007; Tan et al., 2011). Histones can be simultaneously modified in more ways than one, at various amino acid residues. Because of that, there is a wide range of unique modifications and combinations of modifications, each of which yield important functional outcomes. Taken all together, viewing chromatin as a simple structural barrier blocking access to DNA is no longer sufficient, but rather as a dynamic platform linking and connecting various DNA-templated processes.

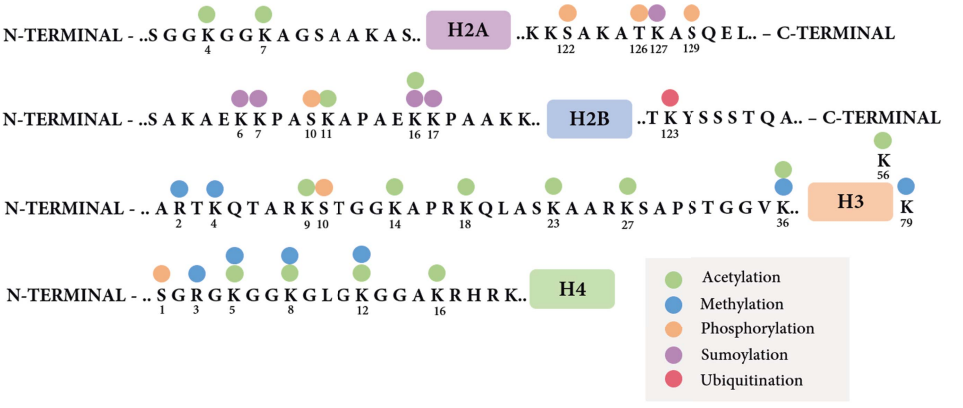

Figure 2. Common histone post-translational modifications in budding yeast. The core histones are indicated schematically as coloured rectangles (H2A – purple, H2B – blue, H3 – orange, H4 – green). Different histone modifications are indicated by the colour code, and the N- and C-terminal tail sequences are shown (acetylation – green, methylation – blue, phosphorylation – orange, sumoylation – purple, ubiquitination – red). The numbers under modified residues indicate amino acid positions.

1.2.1. Histone acetylation

Histone acetylation, discovered in 1961, was the first described histone modification and over the last 50 years it has been extensively studied, making it one of the best characterized PTMs (Phillips, 1963). Acetylation occurs at specific lysine residues on the four core histones through the addition of an acyl group from an acyl-CoA donor to the ε-amino group of the lysine side chain. Acetylation

neutralizes the positive charge of lysine residues, weakening charge-dependent interactions between histones and DNA or adjacent histones, and thus increasing the accessibility to DNA and related processes. This mechanism is amplified by the number of lysine residues present in each N-terminal tail. For example, *in vitro*, tetra-acetylation of the histone H4 tail substantially reduces its affinity for DNA (Hassan et al., 2007). It is also suggested that the cumulative charge neutralization by multiple lysine acetylations influences transcriptional outcomes, rather than the acetylation of specific lysine residues (Dion et al., 2005; Martin et al., 2004). Although, many studies have observed the importance of individual acetylation modifications in different cellular processes, such as histone H3 lysine 14 acetylation shown to be important in rDNA silencing and aging (Xu et al., 2016).

Histone acetylation is a highly dynamic modification, with half-lives ranging from 4 to 15 minutes for the four core histones, enabling DNA accessibility when required (Waterborg, 2001). Lysine residues are acetylated by lysine acetyltransferases (KATs), generally consisting of a catalytic subunit complexed with associated proteins required for enzymatic activity and targeting (Lee and Workman, 2007). In yeast, there are 9 reported KATs, of which some recognizing only a few sites, while others act on many lysine residues on multiple tails. Histone acetylation can be reversed by the enzymatic action of lysine deacetylases (KDACs) (Allis et al., 2007). The interplay between KAT and KDAC activities thus regulates cellular acetylation levels. Nucleosomes are acetylated at promoters and within gene bodies facilitating efficient polymerase passage by loosening histone-DNA contacts and subsequent deacetylation helps to promote the restoration of the chromatin landscape after a round of transcription (Wang et al., 2009b). Furthermore, it has been shown that the majority of histone acetylation is dependent on transcription and nucleosome disruption by RNAPII. It is suggested that acetylation is a consequence of RNAPII promoting the recruitment and activity of histone acetyltransferases (HATs) (Martin et al., 2021). Histone acetylation also plays a role in nucleosome assembly and DNA damage response (Bannister and Kouzarides, 2011; Shahbazian and Grunstein, 2007).

Besides histone lysine acetylation, a repertoire of novel acyllysine modifications have been identified, including propionylation, butyrylation, crotonylation, 2-hydroxyisobutyrylation, β-hydroxybutyrylation, succinylation, malonylation, glutarylation and benzoylation (Chen et al., 2007b; Dai et al., 2014; Huang et al., 2018; Tan et al., 2014; Xie et al., 2012, 2016). These novel modifications tend to act similar to acetylation, accumulating at transcriptional start sites and correlating with gene activity (Tan et al., 2011). Different *in vivo* and *in vitro* studies have demonstrated that the known KAT and KDAC families have expanded acylation and deacylation capabilities. For example, two main histone KATs in yeast Gcn5 and Esa1 have been reported to use crotonyl-CoA as a substrate to catalyze lysine crotonylation (Kollenstart et al., 2019). This would suggest that the differential acylation state of histones could be established by the competition of the different acyl-CoAs for KATs. Therefore, different acylations could reflect the cells different metabolic states, depending on the availability and relative concentration of a specific acyl-CoA form.

1.2.2. Histone methylation

Histone methylation is a key epigenetic modification that regulates many nuclear processes, including transcription, DNA replication and repair. It refers to the covalent attachment of methyl (CH3) group(s) to the amino acid side chains of lysine or arginine residues on histone proteins (Murray, 1964). Histone lysines can be mono-, di-, or trimethylated on their ε-amino group, while arginine residues can be mono-, asymmetrically di-, or symmetrically dimethylated on their terminal guanidinium group (Bedford and Richard, 2005; Low and Wilkins, 2012). Various histone lysine methylations impart either the activating or repressive effect on gene transcription, primarily depending on the site, degree of methylation, genomic location, and the status of other coexisting PTMs. In general, methylations of histone H3 at lysine 4, 36 and 79 (H3K4, H3K36 and H3K79) are linked to the transcriptionally active state, whereas methylations of histone H3 at lysine 9 and 27 (H3K9, H3K27) and histone H4 at lysine 20 (H4K20) are associated with gene silencing (Kouzarides, 2007). While the machinery and the sites of histone methylation are, for the most part, highly conserved from yeast to human, in *S. cerevisiae* only lysines 4, 36, 79 on histone H3 and lysines 5, 8, 12 on histone H4 are subjected to methylation (Green et al., 2012; Kouzarides, 2007; Shilatifard, 2006). Fission yeast and higher eukaryotes have additional sites of methylation, including lysine 9 and 27 on histone H3 and lysine 20 on histone H4 (Jorgensen et al., 2013; Nakayama et al., 2001; Wiles and Selker, 2017). Arginine methylations appear on arginine 2 on histone H3 and arginine 3 on histone H4 (Bedford and Richard, 2005).

Unlike histone KATs, which generally have low substrate specificity, histone methyltransferases are typically more specific about their histone targets. In budding yeast, lysine methylation sites at H3K4, H3K36, and H3K79 are methylated by Set1, Set2 and Dot1 methyltransferases, respectively (Nislow et al., 1997; Strahl et al., 2002; van Leeuwen et al., 2002). Lysines 5, 8 and 12 on histone H4 are methylated by Set5 (Green et al., 2012).

Histone methylation was long thought to be a stable and static modification. However, emerging evidence has shown that methylation can be reversed by histone demethylases. In 2004, the first lysine demethylase was identified, termed as mammalian lysine-specific demethylase 1 (LSD1) (Shi et al., 2004). Because LSD1 requires a protonatable methyl ammonium group, only mono- and dimethyl forms can be used as substrates. This discovery was followed by the identification and characterization of another class of histone demethylases that contain a Jumonji C (JmjC) catalytic domain and are capable of removing all three lysine methylation states (Klose et al., 2006). JmjC enzymes are highly conserved from yeast to human. They demethylate substrate lysines through an oxidative reaction that utilizes Fe (II) and α-ketoglutarate as cofactors (Tsukada et al., 2006). Based on sequence homology predictions, five JmjC domain-containing proteins were identified in the budding yeast proteome: Jhd1, Jhd2, Rph1, Gis1 and Ecm5 (Kwon and Ahn, 2011). Of these, Jhd1, Jhd2, Rph1 and Gis1 were subsequently shown to have bona fide histone demethylase activity (Tu et al., 2007).

1.2.2.1. Histone H3 lysine 36 methylation (H3K36)

Histone H3 lysine 36 (H3K36) can be co-transcriptionally modified by the addition of one (H3K36me1), two (H3K36me2), or three (H3K36me3) methyl groups in budding yeast and other eukaryotes. All three methylation states of H3K36 accumulate in transcribed regions, and H3K36me3 in particular is highly correlated with actively transcribed genome regions (Pokholok et al., 2005).

SET domain-containing 2 (Set2) is the only H3K36-specific methyltransferase in the budding yeast proteome and is central to the regulation of transcriptional initiation and elongation. In 2002, Strahl et al. first purified and biochemically characterized Set2 protein from *S. cerevisiae* and demonstrated that it catalyses mono-, di-, and trimethylation of H3K36 through its catalytic SET domain *in vivo* (Strahl et al., 2002). Set2 associates with the C-terminal domain (CTD) of the largest subunit (Rpb1) of RNAPII through its C-terminal Set2–Rpb1 interaction (SRI) domain (Kizer et al., 2005). In accordance with co-transcriptional deposition of H3K36 methylation, loss of the SRI domain causes loss of both higher methylation states H3K36me2 and H3K36me3 (Youdell et al., 2008). The RNAPII CTD consists of 7-amino-acid consensus sequence (Tyr1-Ser2-Pro3-Th4r-Ser5-Pro6-Ser7) repeated 26 times in budding yeast that are dynamically phosphorylated or dephosphorylated on Ser5 (S5P) and Ser2 (S2P) over the course of transcription. CTD-S5 is phosphorylated at the 5'-end of genes and gradually decreases toward the 3'-ends, whereas CTD-S2 is phosphorylated during transcription elongation, and maintained until the termination stage (Mosley et al., 2009). Importantly, the SRI domain of Set2 preferentially associates with CTD phosphorylated at Ser2 and Ser5 (CTD-S2,5-P)(Kizer et al., 2005) (Figure 3). Consequently, different H3K36 methylation states are distributed over the transcribed locus in distinct patterns, with H3K36me1 predominantly found near the 5′ regions, and H3K36me2 and H3K36me3 ranging from the 5'-ends to 3'-ends of genes (Pokholok et al., 2005). Also, it has been shown that residues from histones H4, H2A and H3 contribute to and form a Set2 recognition site which is needed to maintain proper H3K36 methylation (Du and Briggs, 2010). Set2 co-transcriptionally modifies H3K36, which is in turn recognized by the chromodomain of Eaf3, a subunit of the Rpd3S histone deacetylase complex (Joshi and Struhl, 2005). Rpd3S functions to keep gene bodies deacetylated and thus restores chromatin structure between multiple rounds of transcription. This epigenetic resetting protects genes from inappropriate initiation within the protein-coding regions of actively transcribed genes (Carrozza et al., 2005; Keogh et al., 2005; Lickwar et al., 2009).

Among the five JmJC domain-containing demethylases identified in *S. cerevisiae*, Rph1, Jhd1 and Gis1 have been linked to demethylation of H3K36 (Tu et al., 2007). Rph1 has been classified as a JMJD2 family enzyme that specifically demethylates H3K36me3 and H3K36me2 both *in vitro* and *in vivo* (Kim and Buratowski, 2007; Klose et al., 2007). Jhd1 is shown to demethylate the lower methylation states H3K36me1/2. It has been demonstrated that Jhd1 interacts with H3K4 trimethylation found at the 5'-ends of gene bodies which is proposed

to be required to remove repressive H3K36 methylation surrounding the promoter region and thus promote transcriptional elongation (Tsukada et al., 2006; Shi et al., 2007; Fang et al., 2007; Kim and Buratowski, 2007). Gis1 is a functional paralog of Rph1. Although Gis1 contains a JmjC domain, it is still not clear whether this enzyme possesses bona fide H3K36 demethylase activity. Mass spectrometric analysis of *in vivo* histone modifications demonstrated that H3K36me2 and H3K36me1 accumulate upon gis1 deletion, suggesting that Gis1 specifically demethylates the lower H3K36 methylation states (Tu et al., 2007).

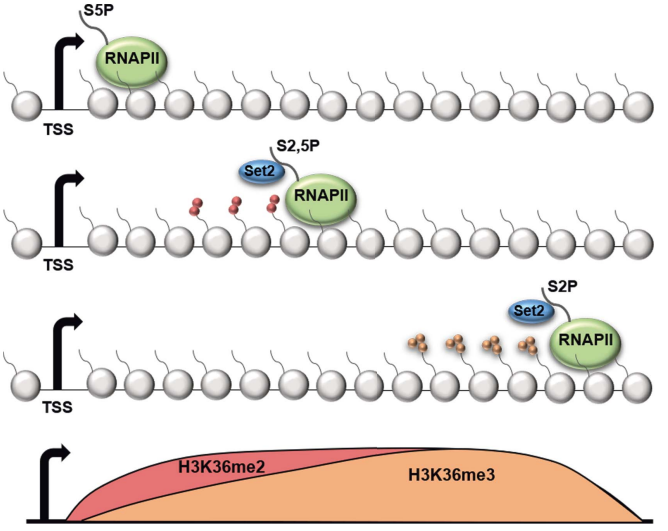

Figure 3. Distribution and regulation of H3K36 methylation pattern. H3K36 methylation pattern increases with distance from the 5'-end of the transcribed gene. Set2 protein associates with the Ser2 and Ser5 phosphorylated (S2,5P) elongating form of the RNAPII CTD. Set2 methylates lysine 36. H3K36me2 ranges from the 5'-ends to the early coding region and H3K36me3 is present primarily near the 3'-ends.

1.3. Readers of histone modifications

Histone writers, erasers, and readers – the protein machinery that adds, removes or recognizes histone modifications have become central figures in understanding the functional outcomes of modifications they associate with. Readers are proteins that recognize either specific post-translational marks on histones or a combination of marks to direct a particular transcriptional outcome on surrounding chromatin. The major protein domain associated with lysine acetylation binding is the bromodomain (BD). BDs are found in a wide range of chromatin associated proteins, including KATs and chromatin remodelling proteins (Zeng and Zhou, 2002). Two other domains, the double PHD finger (DPF) domain and the YEATS domain, also recognize acetylated lysine residues on histone tails (Lange et al., 2008; Li et al., 2014). Methylation does not alter the charge of lysine or arginine

side chains. Instead, methylated residues constitute recognition sites for a range of transcription factors and associated regulatory proteins, which in turn elicit downstream changes in gene expression. Domains that uniquely bind to methylated residues are chromodomains, Tudor domains, WD40-repeats, and PHD fingers (Eissenberg, 2001; Lu and Wang, 2013; Nielsen et al., 2002; Shi et al., 2007; Smith et al., 1999).

1.3.1. YEATS domain-containing proteins in budding yeast

One of the less explored reader protein domains is the YEATS domain, named after the first proteins recognized to contain this module – Yaf9, ENL, AF9, Taf14 and Sas5. YEATS domain is evolutionarily highly conserved, occurring in more than 100 proteins from over 50 organisms (Finn, 2006; Schulze et al., 2009). In *Saccharomyces cerevisiae*, the three proteins that contain YEATS domain (Yaf9, Taf14 and Sas5) are subunits of protein complexes with molecular functions ranging from chromatin remodelling and histone modification to transcription regulation and DNA damage response (Schulze et al., 2009). The YEATS domain has an average length of 83 amino acids and is often located in the N-terminal part of the protein. The three YEATS-containing proteins in yeast are nonessential individually, while deletion of all three proteins is lethal (le Masson et al., 2003; Schulze et al., 2009; Welch and Drubin, 1994; Xu et al., 1999; Zhang et al., 2004). All YEATS domains appear to target acylated lysines on N-terminal tails of histones, but display differences in selectivity for the position and nature of the acyl marks (Li et al., 2014; Shanle et al., 2015).

Yaf9 is a member of histone variant H2A.Z deposition complex SWR1 and the histone KAT complex NuA4. Yaf9 YEATS domain was shown to have the capacity to bind to acetylated histone H3 with a high preference for lysine 27 *in vitro* (H3K27ac) (Klein et al., 2018a). Disruption of Yaf9 binding to H3K27ac impairs the deposition and acetylation of histone variant H2A.Z (Wang et al., 2009a).

Taf14 is the subunit of general transcription factors TFIIF and TFIID, chromatin remodelling complexes INO80, SWI/SNF and RSC and the histone modification enzyme NuA3. The C-terminus but not the YEATS domain of the Taf14 protein is necessary and sufficient for its association with these complexes (Schulze et al., 2010). Taf14 YEATS domain was shown to preferably interact with acetylated histone H3 at lysine 9 (H3K9ac) (Shanle et al., 2015). Crystal structure of Taf14 YEATS domain in complex with H3K9ac peptide reveals an elongated binding site with H3K9ac sandwiched in a threonine-lined aromatic cage formed by Phe62 and Trp81 of the protein. Importantly, disruption of the Taf14-H3Kac interaction by mutating Trp81 to alanine *in vivo* impairs transcription and the DNA damage response (Shanle et al., 2015). Further studies have identified that the Taf14 YEATS domain also binds to histone H3 crotonylated at lysine 9 (H3K9cr) (Andrews et al., 2016).

Sas5 was first discovered in a screen identifying genes that regulate silencing of heterochromatin in mating-type locus in yeast (Xu et al., 1999). Sas5 forms a complex with Sas2 and Sas4, called the SAS complex, which is a KAT complex that acetylates histone H4 at lysine 16 (H4K16ac) (Meijsing and Ehrenhofer-Murray, 2001). The YEATS-domain-containing N-terminus of Sas5 is required for its nuclear localization and import, however its precise role and targets are yet to be determined (Schaper et al., 2005).

1.4. Chromatin dynamics in DNA damage response (DDR)

Preserving genome function and stability is of primary importance for ensuring normal development and cellular homeostasis. Sources of DNA damage include replication errors, base damage, reactive metabolic products, as well as chemicals and radiation. Probably the most severe type of damage to DNA is double-stranded breaks (DSBs), as the loose ends it generates can inappropriately re-combine with other parts of the genome, causing chromosomal aberrations and loss of genetic information. Furthermore, failure to repair DSBs, or mis-repair, can lead to severe genome instability and even cell death (Papamichos-Chronakis and Peterson, 2013).

In the presence of DNA lesions, cells activate pathways referred to as the DNA damage response (DDR). The repair of double-strand breaks depends on the DNA damage checkpoint that detects and signals the presence of DNA damage and arrests the cell cycle progression until resolution of the lesion (Longhese, 2003; Zhou and Elledge, 2000). In budding yeast, the DNA damage checkpoint is initiated by the independent localization of two checkpoint complexes to sites of DNA damage (Figure 4A). Rad24 in complex with Rfc2-5 loads the PCNA-like complex of Rad17, Mec3, and Ddc1 at the site of the DNA lesion. Independently, Mec1 and its binding partner, the Lcd1, are recruited to the DNA lesion in a replication factor A (RPA)-dependent manner (Kondo et al., 2001). Mec1 recruitment leads to the phosphorylation of histone H2A on serine 129 in the chromatin flanking the lesion (Downs et al., 2000). Once recruited to the DNA, Mec1/Lcd1 phosphorylates Mrc1 in response to DNA replication stress and Rad9 in response to double-strand DNA lesions. The key downstream target of Mrc1 and Rad9 is the effector kinase Rad53. Phosphorylated Rad53 in turn activates other downstream damage response proteins important in supressing late origin firing, stabilizing slowed or stalled replication forks (RF) and preventing cell cycle progression until appropriate conditions for the restart of DNA replication arise (Gilbert et al., 2001; Jaehnig et al., 2013; Pasero et al., 2003; Santocanale and Diffley, 1998). Replication defects are the major source of spontaneous genomic instability, as majority of stalled replication sites tend to occur in transcribed genes, increasing the tendency for the collision of transcription and replication bubbles, eventually resulting in DSBs (Azvolinsky et al., 2009; Bermejo et al., 2012). Therefore, S-phase checkpoints are crucial for maintaining genome

integrity, as they respond to RF stalling and intra-S-phase damage by preventing RF collapse and breakdown (Sogo, 2002).

Classically, two pathways of DSB repair have been defined: nonhomologous end joining (NHEJ) and homologous recombination (HR) (Figure 4B). As their names imply, HR is a process in which double-stranded DNA damage is repaired using a replication-based mechanism through the use of an undamaged homologous template, whereas NHEJ essentially involves the direct re-ligation of the broken DNA ends with very little DNA synthesis (Aylon and Kupiec, 2004). HR restores the damaged DNA molecule as it existed before the DSB, because the template sequence used for repair is undamaged. In case of NHEJ if the overhangs on the ends of DSBs are not compatible, imprecise repair and loss of nucleotides occur, leading to mutagenic insertions and deletions at the break site. DSB repair by the process of HR primarily occurs in the S and G2 phases of the cell cycle, while NHEJ is the most commonly used pathway in G1 cells (Daley et al., 2005). It is thought that in unicellular organisms with small genomes like budding yeast, HR is the dominant repair mode, whereas the NHEJ pathway plays a larger role in higher eukaryotes.

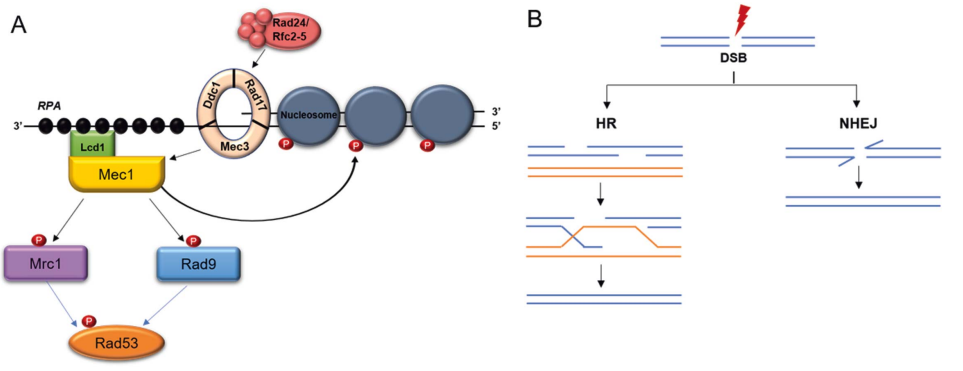

Figure 4. Model of the DNA damage response (DDR) and DSB repair in S. cerevisiae. **A.** Lcd1 (green) binds ssDNA that is covered with RPA (black), while the Ddc1-Mec3-Rad17 (light orange) checkpoint clamp is loaded by Rad24/Rfc2-5 (pink) onto ds/ssDNA junctions. Mec1 phosphorylates histone H2A on serine 129. Checkpoint mediators like Mrc1 (purple) and Rad9 (blue) help activate Rad53 (orange). **B.** Pathways of DNA double-strand break (DSB) repair by homologous recombination (HR) and non-homologous end joining (NHEJ). HR uses an undamaged DNA template to repair the DSB, leading to the reconstitution of the original sequence, while NHEJ ligates the broken DNA ends with no sequence homology. Proteins involved are not shown.

In both NHEJ and HR, chromatin is implicated in regulating DSB accessibility and in an additional role as a regulatory platform that helps to coordinate the overall complex DDR pathway. Among the factors that contribute to the DDR are histones and their PTMs, ATP-dependent chromatin remodellers and histone variants (Papamichos-Chronakis and Peterson, 2013). Although the function of PTMs has remained elusive, a growing number of studies suggest that histone

modifications play vital roles in DDR. While elevated histone acetylation levels lead to more accessible chromatin for repair machinery, specific acetylation sites on histone H3 (K14, 23, 56) and histone H4 (K5, 12, 91) have also been implicated in regulation of DNA repair processes (Ge et al., 2013; Tamburini and Tyler, 2005; Wurtele et al., 2012). For example, in budding yeast, cells with mutated lysines 14 and 23 of histone H3 are sensitive to DNA damage caused by DSBs and are defective in repair of these lesions (Qin and Parthun, 2002). Also, mutation of all acetylatable lysines of histone H4 causes sensitivity to double-strand DNA-damaging agents (Fisher-Adams and Grunstein, 1995). In fission yeast, acetylation of H3K14 is critical for DNA damage checkpoint activation by directly regulating the compaction of chromatin and by recruiting chromatin remodelling complex RSC (Wang et al., 2012).

1.5. RNA polymerase II-dependent transcription

The regulation of gene expression is fundamental to the normal growth, development and survival of an organism. Transcription of the DNA template to produce RNA is the first step in the expression of the genome. Numerous factors regulate transcription by influencing the ability of the RNA polymerase to access, bind and transcribe specific genes in response to appropriate signals.

1.5.1. Structure of RNA polymerase II

Gene transcription in eukaryotic cells is carried out by the three different DNA dependent RNA polymerases: Pol I, Pol II, and Pol III. RNAPI and III transcribe protein noncoding genes, with rRNA being transcribed by Pol I and 5S rRNA, tRNA and other small RNAs being transcribed by Pol III. RNAPII is universally responsible for transcribing all protein-coding genes to mRNAs and some small non-coding RNAs. RNA polymerases are multi-subunit enzymes, Pol I, II and III comprise 14, 12, 17 subunits, respectively and have a total molecular weight of 589, 514, and 693 kDa, respectively (Cramer et al., 2008).

RNAPII consists of a 10-subunit core enzyme and a subcomplex consisting of a heterodimer of Rpb4 and Rpb7 subunits (Figure 5A). From the twelve subunits, some are shared with other nuclear polymerases and some are unique to RNAPII. Five core subunits Rpb5, Rpb6, Rpb8, Rpb10, and Rpb12 are shared between all three nuclear polymerases. Other core domain subunits Rpb1, Rpb2, Rpb3, Rpb9 and Rpb11 and the Rpb4/7 subcomplex are unique to RNAPII but they also contain regions of sequence and structural similarity in other eukaryotic polymerases and have homologues in bacterial and archaeal polymerase (Kusser et al., 2008; Vassylyev et al., 2002; Zhang et al., 1999).

Already in 2000, Cramer et al. solved the first detailed structure of RNAPII, a crystallographic backbone model of the 10-subunit core enzyme from *Saccharomyces cerevisiae* (Cramer et al., 2000). The RNAPII structures revealed that it is

composed of four mobile elements named “core”, “clamp”, “jaw-lobe”, and “shelf” (Figure 5B). About half the mass of RNAPII constitutes the core enzyme which is formed by the two large subunits Rpb1 and Rpb2 that flank the opposite sides of a positively charged cleft that holds the active site, and the smaller common subunits which are arrayed around the periphery. The deep positively charged cleft is located at the centre of the enzyme along which incoming DNA enters into the active site that lies at the base. The “clamp” element, composed of regions from Rpb1 and Rpb2 subunits, is connected to the body of the polymerase by five switch regions. It moves with a large swinging motion over the cleft to control its opening and closing (Cramer et al., 2001; Gnatt et al., 2001).

Three years after the first RNAPII structure, a new crystal form was obtained that included the core enzyme and the Rpb4/7 subcomplex (so-called stalk), providing the complete, 12-subunit RNAPII structure (Bushnell and Kornberg, 2003). The stalk extends from the foot domain at the base of the RNAPII. It is connected by various initiation and elongation factors and its movement helps coordinate opening and closing of the “clamp”. The “shelf” and “clamp” elements locate on the opposite side of the cleft. The “jaw-lobe” element contains the upper “jaw”, which is made of Rpb1 and Rpb9 and also contained in this module is the “lobe”, formed by part of Rpb2. The “shelf” element comprises Rpb5, Rpb6 and regions from Rpb1 subunits, which makes up the lower part of the “jaw”. In the cleft, near the active site resides the “wall”, where the RNA:DNA hybrid separates. (Cramer et al., 2001). The RNAPII loop named “Lid” separates the DNA and RNA strands at the upstream end of the transcription bubble and guides the RNA strands toward the RNA exit groove and the DNA out toward the protrusion, where reannealing of the transcribed DNA occurs (Gnatt et al., 2001).

Structural studies of RNAPII and bacterial RNA polymerase led to an understanding of a mechanism of nucleoside triphosphate (NTP) selection and DNA-directed RNA synthesis. A mobile part of the active centre, called the trigger loop (TL), plays an important role in ensuring transcription fidelity. Binding of the nucleotide to the insertion site involves folding of the TL which closes the active site and secures the selection for correct complementary nucleotide to the templating DNA base (Wang et al., 2006). After catalysis, RNAPII translocates along the DNA by one base pair to liberate the substrate site for bending of the next NTP. TL, together with bridge helix form a Brownian ratchet (Kireeva et al., 2010; Wang et al., 2006). According to the ratchet model, the elongation complex cycles between pre- and post-translocation states. The next incoming NTP can only bind the post-translocated state and thus allowing only forward movement of RNAPII (Guajardo and Sousa, 1997).

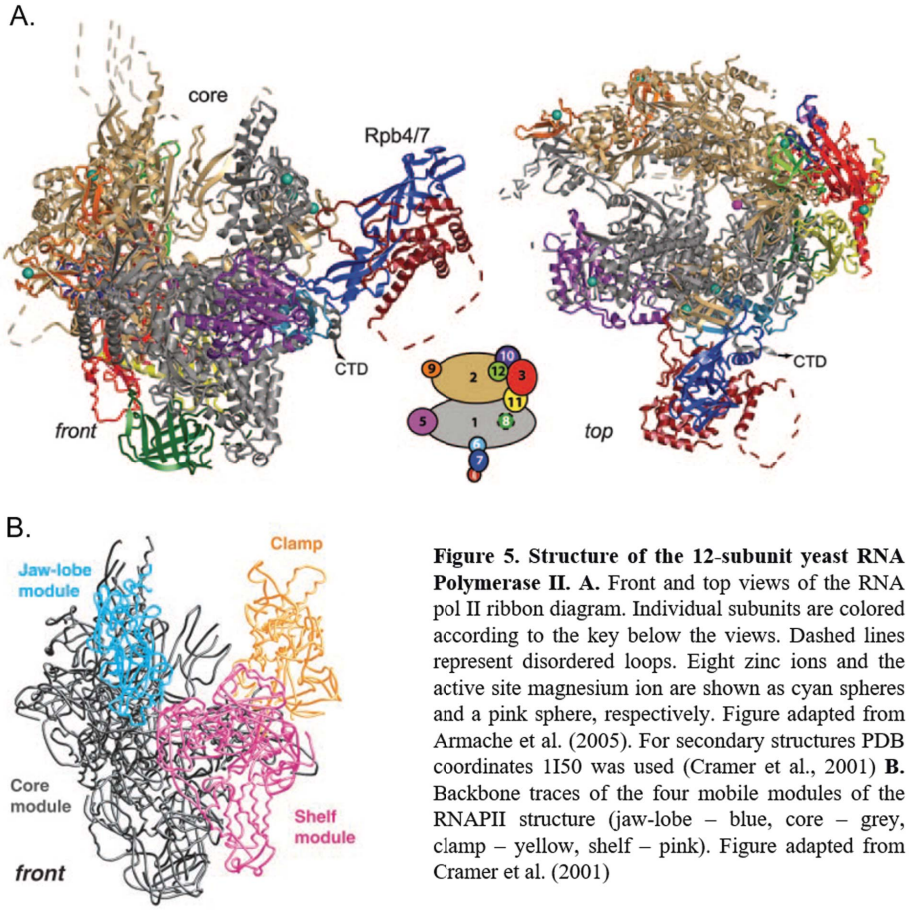

Figure 5. Structure of the 12-subunit yeast RNA Polymerase II. A. Front and top views of the RNA pol II ribbon diagram. Individual subunits are colored according to the key below the views. Dashed lines represent disordered loops. Eight zinc ions and the active site magnesium ion are shown as cyan spheres and a pink sphere, respectively. Figure adapted from Armache et al. (2005). For secondary structures PDB coordinates 1I50 was used (Cramer et al., 2001) **B.** Backbone traces of the four mobile modules of the RNAPII structure (jaw-lobe – blue, core – grey, clamp – yellow, shelf – pink). Figure adapted from Cramer et al. (2001)

1.5.2. Transcription initiation

The RNAPII transcription cycle can be divided into three phases: initiation, elongation and termination. Transcription initiation occurs in the promoter regions at the beginning of a gene. Although there are no universal DNA elements present in all promoters, they can comprise a subset of known core promoter elements (Kadonaga, 2012). These elements include a TATA box or a related sequence, where transcription initiation assembly is thought to take place. The TATA box is found 40–120 base pairs upstream of the transcription start site (TSS) in *Saccharomyces cerevisiae*, with a consensus sequence of TATA(A/T)A(A/T)(A/G) (Basehoar et al., 2004). To access promoter sequences, nucleosomes need to be removed or shifted for transcription to occur (Lorch and Kornberg, 2017). Active promoters are found in nucleosome-depleted regions (NDR), which are flanked by specialized +1 and −1 nucleosome on the downstream and upstream side of these regions, respectively (Talbert et al., 2019). Nucleosomes are

depleted at the promoters of genes and are regularly positioned downstream of the TSS which then gradually decreases from the 5'−3' ends of genes (Jiang and Pugh, 2009; Radman-Livaja and Rando, 2010; Struhl and Segal, 2013). Genome-wide nucleosome organization studies have shown that the distribution of nucleosomes around genes correlates with transcription levels. Compared with lower-expressing genes, highly expressed genes tend to have a greater degree of nucleosome depletion at their promoter regions (Brogaard et al., 2012; Lee et al., 2007).

Transcription begins with the assembly of a preinitiation complex (PIC) at the promoter, composed of the core promoter DNA, general transcription factors (GTFs), including Mediator complex and RNAPII (Buratowski, 1994; Hahn, 2004). Assembly occurs by a step-wise association of the six highly conserved GTFs TFIID, TFIIA, TFIIB, TFIIE, TFIIF and TFIIH (Thomas and Chiang, 2006). Although only 20% of genes in yeast contain canonical TATA boxes, GTFs are located genome-wide on most promoters. This suggests a very similar initiation complex architecture also for TATA-less promoters (Rhee and Pugh, 2012).

The first step in canonical PIC assembly is depositing the TATA box–binding protein (TBP) to the promoter region. TBP is brought to the promoter in complex with TFIID or the conserved cofactor SAGA (Hahn and Young, 2011). In budding yeast, inducible stress-related genes generally contain TATA boxes at their promoters and are predominantly regulated by the SAGA complex, whereas TFIID dominates on so-called "housekeeping" genes without recognizable TATA sequences (Huisinga and Pugh, 2004). TFIID is joined by TFIIB and the auxiliary factor TFIIA, which bind TBP through opposite ends of its crescent structure and stabilize the TFIID–DNA complex (Imbalzano et al., 1994). A RNAPII–TFIIF complex binds to a pre-formed TFIIB–TFIID promoter complex, resulting in the formation of a core initiation complex. This complex binds to TFIIE and TFIIH to form a complete PIC that contains closed, double-stranded promoter DNA. Another general cofactor, Mediator, forms a bridge between activators and the RNAPII initiation machinery and stimulates PIC assembly (Allen and Taatjes, 2015; Jeronimo and Robert, 2017; Malik and Roeder, 2010; Takagi and Kornberg, 2006). During open promoter complex formation, in the presence of nucleoside triphosphates, about 10 bases of the DNA double helix separate by the helicase activity of TFIIH to form a so-called "transcription bubble", where the single-stranded DNA template passes near the RNAPII active site and the complementary RNA chain synthesis is initiated (Kostrewa et al., 2009).

1.5.3. Transcription elongation

For elongating RNAPII to transcribe the full length of a gene in a highly processive manner initiating RNAPII must undergo structural and functional maturation. Promoter escape is the earliest step in this process, during which the polymerase breaks its contacts with promoter-sequence elements and some GTFs and tightens its grip on the nascent RNA (Dvir, 2002). Transcription factors TFIIH and TFIIF regulate this early stage of promoter escape (Dvir et al., 1997; Yan et al., 1999).

TFIIH (subunit Kin28) phosphorylates the CTD of RNAPII subunit Rpb1 specifically on Ser5, RNAPII then loses contact with some GTFs and escapes into early elongation (Phatnani and Greenleaf, 2006).

In higher eukaryotes, before the transition to stable elongating complex RNAPII typically undergoes promoter-proximal pausing 20-120 bp downstream of the TSS. Elongation factors DSIF and NELF help establish RNAPII pausing, which is important in preventing re-initiation of transcription by another RNAPII enzyme, maintaining the promoter in a nucleosome free state and giving time for proper 5'-end processing (Gilchrist et al., 2010; Gressel et al., 2017; Shao and Zeitlinger, 2017; Tome et al., 2018). In budding yeast, efficient elongation requires a further phosphorylation step by Bur1-Bur2 kinase complex (human P-TEFb) on the Ser2 position of the Rpb1 CTD that helps to recruit factors important for transcription elongation and co-transcriptional events such as histone modification and chromatin remodelling (Murray et al., 2001; Yao et al., 2000).

Once RNAPII has escaped from the promoter and the transcription bubble proceeds, RNAPII has to move through the nucleosomal template. This process requires extensive modulation of chromatin structure through the remodelling and/or removal of existing nucleosomes. The histones which were evicted during elongation are rapidly deposited onto the DNA behind the elongating RNAPII with the help of histone chaperones such as Spt6, FACT and Asf1 (Kaplan et al., 2003). Genome-wide studies in nucleosome positioning and also studies on specific genes have shown that the extent of nucleosome loss and positioning varies in different loci (Lee et al., 2007; Värv et al., 2007; Zhao et al., 2005). For example, galactose inducible *GAL* genes in yeast lose nucleosomes from the entire gene locus, which is dependent on the elongating RNAPII (Kristjuhan and Svejstrup, 2004; Schwabish and Struhl, 2004; Värv et al., 2007).

Synthesized mRNAs get co-transcriptionally processed, which includes 5'-end capping and co-transcriptional splicing. During 5'-end capping a reversed orientation 7-methyl-guanosine cap is added to the 5'-end of the RNA acting as a marker for Pol II-transcribed mRNA. 5′-end capping occurs shortly after transcription initiation. The process is stimulated by TFIIH-mediated phosphorylation of the Pol II CTD (Cho et al., 1997). Another co-transcriptional mRNA processing step is splicing, where introns are removed from nascent RNA by the ribonucleoprotein complex spliceosome. Recent evidence show that spliceosome is physically close to RNAPII *in vivo*, implicating that transcription and splicing occur simultaneously (Zhang et al., 2021).

1.5.4. Transcription termination

Transcription cycle ends by its termination when RNAPII and nascent RNA dissociate from the chromatin template, defining the end of the transcription unit. RNAPII transcription termination differs between protein coding genes and non-coding RNA genes, so two main pathways of transcription termination exist: 1) The cleavage and polyadenylation factor-cleavage factor (CPF-CF) pathway,

which terminates transcription of mRNAs and 2) Nrd1-Nab3-Sen1 (NNS) pathway responsible for the production of functional and stable noncoding RNAs, such as the small nuclear (snRNA) and small nucleolar RNAs (snoRNAs) and for the termination of cryptic unstable transcripts (CUTs) and stable unannotated transcripts (SUTs) (Kuehner et al., 2011; Porrua and Libri, 2015). In case of CPF-CF pathway, a large, multi-subunit complex CPF-CF and several additional factors disassemble the elongation complex at the end of genes. Several components of the CPF-CF complex (Rna15, Cft1, Cft2, Yth1, Mpe1 and Hrp1) recognize termination and 3′-end processing signals of the nascent RNA and also directly interact with the polymerase. Subsequently, the RNA is cleaved by the CPF endonuclease Ysh1 at the poly(A) site, and poly(A) tails are added by the CPF-associated poly(A) polymerase Pap1 (Chanfreau et al., 1996; Patel and Butler, 1992). After the mRNA is cleaved, RNA polymerase is released from the DNA template further downstream. The mechanism of RNAPII release is still unclear, but two models predominate. According to the allosteric model, after encountering termination signals, a conformational change of RNAPII destabilizes the elongation complex and commits RNAPII to termination (Kim et al., 2004a; Logan et al., 1987; Richard and Manley, 2009; Zhang et al., 2015). The torpedo model proposes that 5'–3' exonuclease Rat1 enters at the poly(A) cleavage site and degrades the nascent RNA still attached to the transcribing RNAPII, causing termination (Connelly and Manley, 1988; Kim et al., 2004b).

In the other main pathway of termination, the NNS pathway, two RNA-binding proteins Nrd1 and Nab3 recognize short sequence elements of the nascent RNA (GUAA/G and UCUUG) and Nrd1 also interacts directly with RNAPII Ser5 phosphorylated CTD (Carroll et al., 2007; Porrua et al., 2012; Vasiljeva et al., 2008). Subsequently, RNA helicase, Sen1, is loaded on to the nascent RNA, where it dismantles the transcribing polymerase in an ATP-dependent manner and triggers termination (Porrua and Libri, 2013). In the following step, the RNA-bound Nrd1-Nab3 heterodimer recruits the TRAMP (Trf4-Air2-Mtr4) complex, which promotes the degradation of non-coding RNAs by the nuclear exosome (Allmang, 1999; Arigo et al., 2006; Tudek et al., 2014; Vasiljeva and Buratowski, 2006).

Release of RNAPII at the end of transcription requires a dynamic reversal of the associated modifications on the CTD repeats. The RNAPII reverts to its original hypophosphorylated state. Several studies have shown that some of the GTFs can remain associated with the promoter and form a so-called reinitiation scaffold that allows reinitiation by RNAPII during consecutive rounds of transcription (Hahn, 2004; Sarge and Park-Sarge, 2005). The terminal and promoter regions of active genes can interact via a phenomenon known as gene looping (el Kaderi et al., 2009). Transcription initiation factor TFIIB is known to interact with the 3′-end processing complex CPF, which brings promoter and terminator DNA closer together at active gene loci and enables RNAPII recycling and rapid reinitiation (Calvo and Manley, 2003; Singh and Hampsey, 2007).

1.6. RNAPII subunit Rpb9

RNAPII subunit Rpb9 is a 122-amino acid polypeptide with a molecular weight of 14.2 kDa in *Saccharomyces cerevisiae*. RPB9 is highly conserved among eukaryotes, which is underlined by the ability of replacement of the yeast subunit *in vivo* by its human counterpart (McKune et al., 1995). *RPB9* is not essential for viability or mRNA synthesis in *S. cerevisiae*, but deletion of the gene results in slower growth at optimal temperature and sensitivity to high or low temperatures (Woychik et al., 1991).

Rpb9 comprises three distinct regions. The N- and C-terminal regions each contain a zinc-binding domain characterized by the $CX_2CX_nCX_2C$ motif joined by a conserved six amino acid linker region (Figure 6) (Woychik et al., 1991). Rpb9 positions at the edge of the DNA channel at the tip of the so-called "jaws" of RNAPII, mainly occupied by parts of the first and second largest subunits Rpb1 and Rpb2 (Cramer et al., 2001). The N-terminal zinc fold (Zn1, positions 1–39) contacts the Rpb2 "lobe". The linker region (positions 40–52) forms a strong β-addition motif with the "jaw" of Rpb1. The C-terminal zinc ribbon (Zn2, positions 53–122) interacts with the Rpb2 "funnel" (van Mullem et al., 2002).

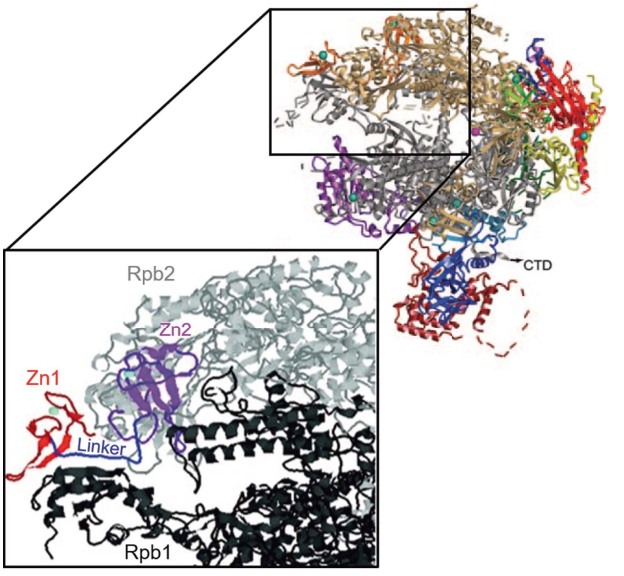

Figure 6. Organization of Rpb9. Localization of Rpb9 on the "jaw" of Pol II complex. Portions of Rpb1 and Rpb2 subunits are shown in black and grey, respectively. The Rpb9 Zn1, Zn2 and the linker domains are shown in red, magenta, and blue, respectively. The zinc ions bound by the Zn1 and Zn2 domains are shown as cyan spheres. Figure adapted from Li et al. (2006). For secondary structures PDB coordinates 1I50 was used (Cramer et al., 2001).

1.6.1. Role of Rpb9 in transcription and genome stability

Rpb9 is shown to be involved in the initiation process of transcription. Deletion or disruption of *RPB9* in yeast cells leads to an upstream shift in the population of start sites at the majority of promoters both *in vivo* and *in vitro* (Hull et al., 1995). Rpb9 mediates the accurate start site selection of transcription by recruiting transcription factor TFIIE and interacting with TFIIF (van Mullem et al., 2002; Ziegler et al., 2003).

rpb9Δ cells are also sensitive to the nucleotide-depleting drugs (e.g. 6-azauracil and mycophenolic acid), which lower the intracellular pool of NTPs and are therefore thought to hamper the process of transcription elongation (Exinger and Lacroute, 1992; Hemming et al., 2000; van Mullem et al., 2002). Consistent with the drug sensitivity, Rpb9 is required, along with transcription elongation factor TFIIS, to assist the transcribing polymerase in bypassing intrinsic blocks to elongation and to stimulate the nascent transcript cleavage activity inherent to RNA polymerase. RNAPII lacking Rpb9 pauses at blocks to elongation at much lower frequency than wild type RNAPII (Awrey et al., 1997; van Mullem et al., 2002). The C-terminal zinc ribbon domain of Rpb9 is very similar to the zinc ribbon found in TFIIS (30% aa sequence identity), which are shown to be critical for elongation activity (Hemming et al., 2000; Hemming and Edwards, 2000; Kaine et al., 1994). Moreover, overexpressing TFIIS suppresses *rpb9Δ* mutant sensitivity to 6-azauracil (6-AU) or mycophenolic acid (MPA) and its transcription elongation defect (Hemming et al., 2000; Tous et al., 2011).

Several studies also suggest a role for Rpb9 in the maintenance of transcriptional fidelity in yeast cells. It has been demonstrated that deletion of *RPB9* causes increased transcriptional errors like base substitutions and insertions and an increase in mismatch extension with the next NTP (Nesser et al., 2006; Walmacq et al., 2009). TL is a mobile element of Rpb1 that moves in and out of the RNAPII active site during elongation, interacting and stabilizing substrate NTPs. Rpb1-E1103G mutation, which contains a substitution within the TL, destabilizes the open conformation of the TL, causing misincorporation of non-complementary NTPs (Kireeva et al., 2008). This low fidelity mutant is synthetic lethal with deletion of *RPB9* gene (Walmacq et al., 2009). It has also been shown that the mushroom toxin α-amanitin, which inhibits TL mobility, eliminates the effect of *RPB9* deletion on the NTP misincorporation. These findings and the proximity of Rpb9 to the TL are consistent with the idea that Rpb9 affects RNAPII activity through the mobility of the TL. Rpb9 indirectly affects TL mobility by stabilization of Rpb1 α-helices 20 and 21 (α20 and α21) and a small connecting loop between them termed the Rpb1 anchor loop (AL). By anchoring the position of α21, with which the TL directly interacts during opening and closing, Rpb9 delays the closure of the TL on the incoming NTP and thereby slows down elongation (Kaster et al., 2016).

Transcription errors produced in *rpb9Δ* cells have also been shown to have effects on cellular health by inducing proteotoxic stress. The error rate of transcription increases with age in yeast, which contributes to the decline in

proteostasis seen in aging cells (Vermulst et al., 2015). It is also evidenced that *rpb9Δ* cells show an increase in genetic instability as detected by hyper-recombination phenotype and DNA damage sensitivity. Also, *rpb9Δ* mutants are impaired in DNA replication at regions actively transcribed. It is proposed that *RPB9* deletion creates transcription intermediates that impair RF progression, which is believed to be the main reason responsible for genome instability in *rpb9Δ* cells (Felipe-Abrio et al., 2015).

Rpb9 is also shown to be involved in transcription-coupled repair (TCR). TCR together with global genomic repair (GGR) are two pathways of nucleotide excision repair (NER). NER is a repair mechanism able to remove a wide range of bulky DNA lesions, including UV-induced cyclobutane pyrimidine dimers (CPDs). In *S. cerevisiae*, Rad26 and Rpb9 have been shown to mediate two sub-pathways of TCR (Li, 2002). The Rpb9 subpathway is strictly transcription-coupled and efficient only when transcription levels are high (Li et al., 2006). The N-terminal Zn1 and linker domains of Rpb9 are essential for TCR function, while deletion of the C-terminal Zn2 domain has almost no effect (Li et al., 2006). A functional connection between TCR and RNAPII degradation has been found. Long-term stalling of RNAPII, either by DNA damage or by other means of elongation pausing, induces polyubiquitylation and subsequent degradation of Rpb1 subunit. The Zn2 domain is essential for Rpb9 to promote Rpb1 degradation, whereas the Zn1 and linker domains are less involved (Chen et al., 2007a). Taken together, it shows that Rpb9 has an important regulatory role in ensuring the correct speed for RNAPII elongation and removal of stalled RNAPII which in turn helps to keep the precision and synchrony of the transcription process.

2. AIMS OF THE PRESENT STUDY

Eukaryotic transcription occurs in the context of chromatin. Post-translational modifications of histones play an important role in altering chromatin landscape by modulating DNA accessibility and providing a variety of interaction surfaces for binding factors. Understanding the function and impact of histone PTMs on chromatin structure and transcriptional regulation as well as their recognition by effector proteins is an essential part of chromatin biology. For transcription machinery to gain access to DNA or restore chromatin after transcription, addition and removal of histone PTMs must be accurately choreographed. Although genome-wide studies have provided us with a detailed view of how histone marks are distributed across the genome and correlate with transcription regulation, they provide little insight into their mechanistic details and regulatory dynamics. The first goal of the current research was to clarify the spreading and turnover mechanisms of the methylation pattern of histone H3 lysine 36 (H3K36) created during RNAPII transcription. Also, to characterize mechanisms involved in the turnover of this modification.

The second objective of this study was to identify and explore histone acetylation sites important in cells where transcription is hampered by depleting the RNAPII Rpb9 subunit. It is well established that histone acetylation is one of the crucial factors involved in chromatin regulation during RNAPII transcription. On the other hand, the importance of histone acetylation in different stress conditions has remained less explored.

The third aim of this study was to analyse the essentiality of acylation reader YEATS domain for cell viability, clarify its interaction targets and impact on transcription regulation. The reader proteins recognizing chromatin modifications are crucial in mediating the transcriptional outcome by recruiting transcriptional machinery and chromatin-associated complexes to specific chromosomal regions. These effector proteins and their reader domains are highly conserved from yeast to human with mutations and deregulation often linked to different human cancers and pathologies. Yet there is still little known about their specificity and function in gene expression.

3. RESULTS AND DISCUSSION

3.1. The distribution and maintenance of histone H3 lysine 36 trimethylation in RNAPII-transcribed locus (Ref. I)

Set2-mediated H3K36 methylation is highly conserved from yeast to humans. Although single gene and genome-wide mapping of H3K36 methylation in *Saccharomyces cerevisiae* show it to be greatly enriched at the open reading frames of protein-encoding genes, trimethylation (me3) correlating with transcription frequency (Pokholok et al., 2005), the impact and maintenance mechanisms of this modification are not entirely clear. To understand whether the H3K36 methylation pattern affects the modification pattern of neighbouring chromatin and what mechanisms impact the regulation of H3K36 demethylation we conducted the following experiments.

3.1.1. Description of the experimental system

For all experiments performed and presented in this thesis *Saccharomyces cerevisiae* strain W303 was used as a model organism. The genome of the budding yeast is relatively compact, containing short genes (average size 1.45 kb) and little space between ORFs, which complicates the studies of transcription-dependent dynamics of histone modifications (Goffeau et al., 1996). To overcome these difficulties, we used a 9.4 kb long non-essential gene *VPS13* at its natural locus as our model (Figure 7). We have inserted a galactose-inducible *GAL10* promoter in front of *VPS13*, so transcription of the *GAL-VPS13* locus could be activated or repressed by changing the carbon source of the growth medium. When adding galactose to the yeast growth medium transcription of the model gene is activated and when glucose is added transcription is repressed (Kristjuhan and Svejstrup, 2004).

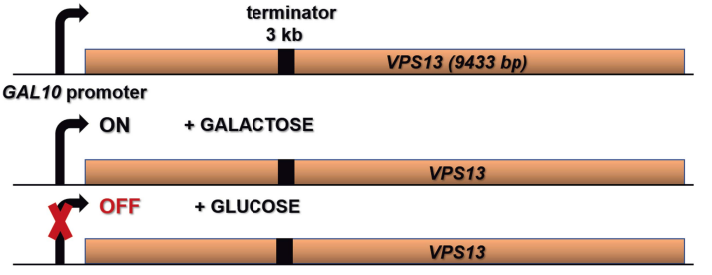

Figure 7. Schematic representation of the *GAL-VPS13* locus and its induction mechanisms. The *VPS13* gene has a galactose-inducible *GAL10* gene promoter in front of the gene and it contains the *FBA1* transcription termination region inserted at 3 kb from the *VPS13* promoter (terminator 3kb, black rectangle). By adding galactose to the yeast growth medium, *VPS13* gene is transcribed (ON) and by adding glucose it is repressed (OFF).

We also inserted a transcriptional terminator sequence at 3 kb downstream of the transcription start site, providing necessary space to investigate the dynamics of chromatin modifications in the *GAL-VPS13* locus without any significant interference from nearby genes.

3.1.2. Distribution of H3K36 trimethylation in *GAL-VPS13* locus

We have previously shown that upon activation of the *GAL-VPS13* locus by adding galactose to the yeast growth medium, we detect an RNAPII-dependent removal of nucleosomes in the promoter and coding region of the gene and a quick restoration of chromatin structure after shut down of transcription (Kristjuhan et al., 2002; Värv et al., 2007). Also, the inserted terminator at 3kb is shown to efficiently terminate RNAPII transcription in this region, leaving downstream *VPS13* gene unaffected (Värv et al., 2007). To determine the distribution of H3K36 trimethylation and nucleosome occupancy in *GAL-VPS13* locus upon RNAPII transcription, cells were grown overnight in the medium containing either glucose or galactose as a carbon source. Nucleosome occupancy was determined by the chromatin immunoprecipitation (ChIP) of E2-tagged histone H3. When transcription of *GAL-VPS13* is repressed in a glucose-containing medium, the allele is highly occupied with nucleosomes and when cells are in galactose-containing medium, *GAL-VPS13* locus is fully transcribed and nucleosomes are efficiently depleted from the regions upstream of the terminator sequence (Ref. 1, Fig. 1B). In conclusion, nucleosome turnover is tightly coupled to transcribing RNAPII.

H3K36 methylation was detected with ChIP using antibodies against H3K36 trimethylation (H3K36me3). We observed H3K36me3 only before the terminator region, which suggests that H3K36 methylation pattern does not spread independently from the ongoing RNAPII transcription, being restricted to actively transcribed sequence (Ref. I, Fig. 1C). This result indicates that methylation associated with active transcription is only limited to the histones located immediately in the transcribed locus, not being able to spread over the nucleosomes and influence chromatin modification patterns of adjacent loci. Likely, keeping the transcription of one gene as if a constrained system is important to prevent unnecessary gene expression. H3K36-specific methyltransferase Set2 is also detected in the transcribed area of *GAL-VPS13* locus, consistent with the H3K36 methylation pattern (Ref. I, Fig. 1D). This result was anticipated, as Set2 is brought to the transcribed loci via its interaction with RNAPII CTD and interactions with nucleosomal residues K44 of H4, L116 and L117 of H2A, forming a docking site for Set2 and proper H3K36 methylation (Du et al., 2008; Du and Briggs, 2010). As all these residues are located in the core of the nucleosome, it is possible that disruption of chromatin and nucleosomes by transcription is needed for efficient binding of Set2 to the locus. Therefore, nucleosomes in non-transcribed regions are less capable of recruiting Set2, which restricts the spreading of H3K36me3 into transcriptionally inactive loci.

3.1.3. H3K36 trimethylation is retained in the transcribed locus at least 60 minutes after transcriptional repression

Having shown that H3K36 methylation is restricted only to transcribed loci, our next question was, for how long the H3K36 methylation pattern is maintained in these loci after transcription shut off. For studying the maintenance of H3K36 methylation, cells were grown overnight in YP-galactose medium and shifted to YP-glucose medium for two hours to repress active transcription of *GAL-VPS13* locus. Nucleosomal structure restored only 5 minutes after shut down of transcription (Ref. 1, Fig. 2A), but H3K36 trimethylation was maintained in the transcribed locus for at least 60 minutes (Ref. 1, Fig. 2B). The persistence of methylation after transcription inhibition, suggests a molecular memory of recent transcriptional activity, where a transcribed region is marked for future activities as methylated histones stay in the composition of chromatin. The levels of H3K36 trimethylation reach background levels after two hours of transcriptional repression. It remains to be determined whether similar kinetics of turnover would be seen for H3K36 mono- and dimethylation.

The distribution and turnover of lysine 4 trimethylation on histone H3 (H3K4me3) present at promoter areas of actively transcribed genes has also been examined (Ng et al., 2003). It was shown that despite the fast dissociation of H3K4 specific methyltransferase Set1, H3K4me3 persists at the promoter area of *GAL10* gene even 5 hours after transcriptional repression. This makes our observed H3K36me3 kinetics relatively fast. Possibly, H3K4 trimethylation persists in the locus for a prolonged period as it marks recently transcribed promoters, making reactivation of transcription quicker if necessary, while H3K36me3 is re-established during transcription in an RNAPII-dependent manner. Furthermore, H3K4me3 turnover was determined at the promoter of an inducible *GAL10* gene and *GAL* genes in *S. cerevisiae* have shown to stay poised after expression for faster reactivation for multiple cell divisions (Kundu and Peterson, 2010). It would be interesting to explore the dynamics of H3K4me3 turnover also in non-inducible conditions.

The enrichment of histone acetylation is associated with the promoter and 5' areas of actively transcribed genes. It has been shown that yeast nucleosomes contain, on average, 13 acetylated lysines per nucleosome, which is the highest level of acetylation known (Waterborg, 2000). In comparison to histone methylation acetylation dynamics are much faster. It has been shown using radioactive acetate labelling that average half-lives of acetylation were 15 minutes for histone H4, 10 minutes for histone H3, 4 minutes for histone H2B, and 5 minutes for histone H2A, emphasizing the dynamic nature of gene regulation by histone acetylation (Waterborg, 2001). Taken together, these observations suggest that the role of acetylation is regulating the short-term dynamic opening and closing of chromatin and methylation has a bigger role in marking transcriptionally active locuses and shaping the epigenetic memory of the cells.

3.1.4. H3K36 trimethylation is removed from transcribed loci in collaboration of histone demethylases and replication-coupled exchange

For some time, methylation was believed to be an irreversible mark. After the discovery of demethylase LSD1, many other such enzymes have been discovered, adding a new level of dynamic regulation within post-translational modification system (Shi et al., 2004). In budding yeast, there are three demethylases associated with H3K36 demethylation – Rph1, Jhd1 and Gis1. While these enzymes have been shown to act on histones, their roles in chromatin remodelling and transcription are largely unexplored *in vivo*. Rph1 has been shown to act on tri- and dimethylated histones, while Jhd1 and Gis1 demethylate mono- and dimethylated H3K36 (Fang et al., 2007; Kim and Buratowski, 2007; Klose et al., 2007; Kwon and Ahn, 2011; Tu et al., 2007). ChIP assay detecting Rph1, Jhd1 and Gis1 on transcriptionally active or inactive loci show low levels of the enzymes being present, correlating with our results of slow H3K36me3 turnover (Kim and Buratowski, 2007). To examine the role of the three demethylases in the persistence of H3K36 trimethylation after transcription termination, we followed the turnover of H3K36me3 in strains lacking *RPH1, JHD1* or *GIS1* genes alone or in combination. As indicated on Ref. I, Fig. 2C-H, nucleosomes were reloaded to chromatin rapidly after transcription shut off in glucose and H3K36 trimethylation persisted in the *GAL-VPS13* locus up to 60 minutes in mutant strains. Compared to wt strain, we detected only minor differences in the dynamics of H3K36 demethylation when individual demethylase genes were deleted, suggesting a redundancy of Rph1, Jhd1 and Gis1 in H3K36 demethylation. Although, the signal decreased to basal level slightly slower in mutant strains, about 30–60 minutes compared to 20–30 minutes in wt. When deleting all H3K36-specific demethylases, we detected a prolonged turnover of the H3K36 trimethylation with methylation mark detectable in the *GAL-VPS13* locus 120 minutes after repression of transcription (Ref. 1, Fig. 2I-J). This result suggests that all three demethylases contribute to a successful demethylation of H3K36me3, possibly a sequential or cooperative action is needed. In accordance with previous studies showing that deletion of H3K36 specific demethylases have minor effects on the overall levels of histone methylation, we did not detect any significant increase of H3K36 methylation in actively transcribed locus in any demethylase deletion strains. This further indicates that demethylases are not directly targeted to transcribed loci, to actively regulate H3K36 demethylation.

Although, deleting H3K36-specific demethylases prolongs the persistence of H3K36me3, it is still lost from the *GAL-VPS13* locus, which raises a need for an alternative pathway how modified histones are removed from recently transcribed locus. Replication-dependent dilution of histones could be another manner to replace modified histones with unmodified versions, as part of routine maintenance of chromatin. To investigate whether replication-coupled assembly of histones participates in the removal of H3K36 methylation, we followed H3K36me3 turnover in G1-arrested cells. In cell cycle arrested cells, the H3K36

trimethylation maintained for a prolonged time, suggesting that in a growing population, replication-coupled exchange would contribute to accelerated removal of H3K36me3 from the chromatin of recently transcribed locus (Ref. I, Fig 3B, E). Since deletion of H3K36-specific demethylases and replication-coupled exchange of histones contribute to the removal of H3K36 methylation pattern with similar kinetics, we hypothesized that both pathways are needed for efficient turnover of H3K36 trimethylation. To test this theory, we detected the dynamics of H3K36me3 turnover in G1-arrested cells where all three demethylases were deleted (*rph1Δjhd1Δgis1Δ*) and found that H3K36 trimethylation signal maintained in the *GAL-VPS13* locus for more than two hours (Ref. I, Fig 3D, E). Taken together, we favour the model where after active transcription, H3K36 trimethylation is removed from the loci in cooperation of histone demethylase activity and replication-coupled exchange of histones.

Recently, genome-wide analysis of H3K36 methylation deposition and removal dynamics has been demonstrated using a light-controlled variant of Set2 as a rapid and reversible tool to measure H3K36me3 addition and turnover mechanisms (Lerner et al., 2020). Consistent with our results, H3K36me3 was shown to decrease over the initial 0–60 minutes and slowing over the subsequent 30 minutes. Also, the turnover was shown to weakly correlate with RNA abundance and followed exponential decay, suggesting H3K36 demethylases act in a global, stochastic manner, which was the conclusion we derived from our results as well. In conclusion, results we gained from our one gene model system have now been extended to genome-wide level.

3.2. Role of histone acetylation in Rpb9-deficient RNAPII-mediated transcription (Ref. II)

RNAPII is a central mediator to all processes requiring access to DNA, including transcription. Unlike histone methylation, acetylation of histone tails weakens histone-DNA and histone-histone interactions, making acetylation one of the most effective chromatin and gene regulation tools. To understand further the role of histone acetylation in RNAPII-mediated processes, we conducted our experiments in yeast cells where RNAPII is defective. Namely, we deleted one of RNAPII nonessential subunits, Rpb9, which gives rise to different phenotypes, such as slow growth, sensitivity to temperature extremes and nucleotide-depleting drugs (Hemming et al., 2000; Woychik et al., 1991). Rpb9 plays roles in transcription elongation, in selection of the correct transcription start site, and in maintaining transcriptional fidelity (Hemming et al., 2000; Hull et al., 1995; Nesser et al., 2006). Rpb9 is also important for the degradation of RNAPII in response to UV radiation (Chen et al., 2007a).

3.2.1. H3 acetylation is required for the viability of *rpb9Δ* cells

First, we wanted to examine the genetic interaction between Rpb9 and acetylation of histone H3. It has been shown that *RPB9* mutants are lethal in cells lacking the histone KAT activity of Gcn5 or other components of the SAGA complex (van Mullem et al., 2002). From these observations we hypothesized that *rpb9Δ* cells might be sensitive to different histone H3 acetylation site mutants important in transcriptional regulation and genome integrity. To test our hypothesis, we systematically mutated H3 N-terminal lysine residues to arginines in cells lacking Rpb9 and examined if any of these combinations of mutations are critical for viability (Ref. II, Fig. 1). In the strain with wt RNAPII we did not detect any considerable effects on growth nor lethality, but in the *rpb9Δ* background, all combinations with three or more H3 acetylation site mutations were lethal. Also, in several H3 lysine double mutants cell viability was affected in *rpb9Δ* strain. This suggests that the overall hypoacetylation of histone H3 is the principal reason for synthetic lethality, rather than specific acetylation site alterations. Although, one common site in all non-viable double mutants was K14 acetylation substitution. This residue is the preferred target of acetyltransferase Gcn5 of the SAGA complex (Grant et al., 1999). In addition to the catalytic HAT domain, Gcn5 also contains a bromodomain that binds acetyl-lysine (Li and Shogren-Knaak, 2009; Syntichaki et al., 2000). It is proposed that after acetylating H3K14 the bromodomain of Gcn5 tethers it to acetylated H3K14 stimulating HAT activity of subsequent acetylation events on other sites on histone H3 (Cieniewicz et al., 2014). Also, H3K14 acetylation is shown to be required for normal levels of H3K4 trimethylation, important for transcription activation (Nakanishi et al., 2008). In fission yeast, acetylation of H3K14 has been shown to be important for DNA repair through recruitment of the chromatin remodelling complex RSC (Duan and Smerdon, 2014). Another study in budding yeast shows K14 mutant to be sensitive to the DNA-damaging agent methyl methane sulfonate (MMS) and defective in homologous recombination (HR) repair (Yang et al., 2013). Taken together, this indicates that H3K14 acetylation plays an important role in regulation of other histone modifications and various processes in the cells. Although the loss of K14 acetylation has the strongest effect on cell viability it was not enough to become lethal. Since we aimed to find out why RPB9 deletion is not viable without H3 acetylation we continued our studies with H3 K9,14,23R triple acetylation mutant.

3.2.2. DNA damage checkpoint activation is impaired in Rpb9-depleted cells

When investigating the mechanisms causing the lethality of H3 hypoacetylated strain in *rpb9Δ* background, we used the anchor-away (AA) method, since mutation of three or more acetylatable lysine residues on H3 were lethal in *rpb9Δ* cells (Haruki et al., 2008). AA technique allows pre-growing cells with intact RNAPII

and subsequent removal of Rpb9 from the nucleus by tethering it to a ribosomal protein eL13 when adding rapamycin to the growth medium, thereby phenocopying *rpb9*Δ cells. It allows us to study Rpb9-dependent survival of H3 hypoacetylated cells in a timely manner after introducing rapamycin to the growth medium. We used H3 K9,14,23R as a representative example of H3 hypoacetylation. Since deletion of *RPB9* causes slower growth, we could detect rapamycin-induced decreased growth rate, similar to that of *rpb9Δ* cells (Ref. II, Fig. 2A) and loss of growth altogether in H3 K9,14,23R strain background. These experiments confirmed the suitability of this model system for our further studies.

As mentioned above, H3K14 acetylation has been shown to be important in DNA repair processes, therefore our next objective was to determine whether depleting Rpb9 would influence the cells' ability to correctly respond to DNA damage induced by different DNA damaging agents. We confirmed that both *rpb9Δ* and H3 K9,14,23R strains were sensitive to DSBs caused by MMS, camptothecin and ionizing radiation (Ref. II, Fig. 2B, S2). This indicates that DNA damage may be tolerated in individual mutants, but becomes lethal in cells where Rpb9 and H3 acetylation is simultaneously depleted. Efficient DNA damage repair response starts with activating DNA damage checkpoints, providing the cells with an opportunity to stall cell division so that proper DNA repair can take place (Campos and Clemente-Blanco, 2020). To assess weather DNA damage checkpoints are activated in Rpb9-deficient cells, we followed the two main checkpoint signals – phosphorylation of H2A and Rad53 after MMS treatment (Ref. II, Fig. 2C). The finding, that both of these modifications were delayed in *rpb9Δ* cells, indicate an inadequate response to DNA damage in cells lacking Rpb9. This may mean that Rpb9-depleted cells go through the cell cycle with undetected damaged DNA which under extensive treatment with genotoxic agents leads to lethality of the whole cell population. H3 K9,14,23R mutant responded quickly to MMS, similar to wt cells, which suggests that in conditions where RNAPII is defective of Rpb9 and under the presence of extensive DNA damage, H3 acetylation may become essential for efficient DNA repair and cell survival.

3.2.3. *rpb9Δ* H3 K9,14,23R cells have high levels of homologous recombination and defective DSB repair

Without external DNA damage induction, aberrant checkpoint response would not affect cell viability, as different checkpoint-deficient strains (*mec1Δ*, *rad53Δ*) are viable (Weinert and Hartwell, 1990, 1988; Zhao et al., 1998). This suggests that Rpb9-depleted cells must additionally induce genomic instability to explain synthetic lethality of *rpb9Δ* and H3 hypoacetylation. To determine, whether loss of Rpb9 induces DNA damage in cells, we monitored Rad52 foci as characteristics of active HR centres for DSB repair (Lisby et al., 2001). During the S phase, Rad52 seeks out and mediates annealing of homologous DNA strands.

When DNA damage occurs, it relocalizes to distinct nuclear foci that are indicative of active DNA repair by HR. Using GFP-tagged Rad52 protein we are able to reveal these recombination sites in cells. As shown in Ref. II, figures 3A and 3D, HR foci accumulate in cells 6 hours after Rpb9 depletion via rapamycin, without any added DNA damage induction. The amount of Rad52 foci in Rpb9-depleted cells was comparable with Rad52 foci detected in wt cells treated with MMS (Ref. II, Fig. 3C, D), emphasizing the severity of the damage induced in Rpb9-depleted cells. Spontaneous occurrence of DNA damage is an indication of genetic instability in cells lacking Rpb9. It has been shown that conflicts between DNA and RNA polymerases may be the source of genetic instability causing an increase in DNA breaks as a consequence of replication fork stalling or collapse leading to elevated recombination activity in these sites (Gaillard et al., 2013). High levels of DNA recombination and impairment of replication fork progression has also been observed in *rpb9Δ* cells, which is an indication that transcription-replication collisions might be the origin of DNA damage in Rpb9-depleted cells (Felipe-Abrio et al., 2015). Furthermore, it has been shown that degradation of stalled RNAPII is inefficient in *rpb9*Δ cells. RNAPII may therefore become a roadblock for resumption of the RF and proper resolution of transcription-replication collisions which in turn could lead to elevated levels of DSBs in the absence of Rpb9 (Chen et al., 2007a).

Rpb9 is also shown to be involved in transcription-coupled repair process, mediating a separate subpathway from another TCR factor Rad26. The question whether impaired TCR could contribute to genetic instability seen in *rpb9Δ* cells arises. As *rad26Δ* TCR-defective mutants do not show hyper-recombination phenotype and are not sensitive to nucleotide depleting drug hydroxyurea (HU) as opposed to *rpb9Δ* cells, it is unlikely that defective TCR would contribute to DNA damage accumulation observed in Rpb9-depleted cells (Gaillard et al., 2009).

The severity of arising DNA damage in Rpb9-deficient cells suggests that the excessive DNA damage may exhaust the checkpoint signalling machinery, with essential components of the pathway becoming limiting for efficient DDR. Moderate increases in the amount of Rad52 foci was also observed in H3 K9,14,23R strain and by additional depletion of Rpb9, the level of Rad52 foci increased even further to nearly 80% of cells (Ref. II, Fig. 3B, D). These results indicate that H3 K9,14,23R and rpb9 depletion mutants have a cumulative effect on HR induction and they act in different pathways of DNA repair.

Several reports have shown the importance of histone acetylation in DNA repair processes (Qin and Parthun, 2002; Yu et al., 2005), which might become essential for viability when spontaneous DNA damage accumulates and signalling for damage is defective as in cells where RNAPII is missing Rpb9. Our next aim was to determine the efficiency of DNA repair in H3 hypoacetylation and rpb9-depleted cells. For this we used the homothallic switching endonuclease HO that is a site-specific endonuclease that cleaves at its recognition site in the *MAT* locus on chromosome III. The DSB is followed by a unidirectional gene conversion event where one of two transcriptionally silent repair cassettes

(*HML* and *HMR*) replaces coding sequences at the *MAT* locus and switches the mating type (Haber, 2012). The HO endonuclease was expressed under the control of a galactose-inducible promoter, allowing synchronous DSB formation at the endogenous *MAT* locus which is primarily repaired by HR (Ref. II., Fig. 4A). Strains that are defective in repair of HO-induced DSB are not able to grow on galactose-containing medium where HO endonuclease is continuously expressed. On glucose-containing media where HO nuclease is repressed wt, Rpb9-depleted and H3 K9,14,23R strains are viable, but on galactose-containing media, only wt and Rpb9-depleted cells were able to grow. This result indicates that repair of the HO-induced DSB was ineffective in the H3 K9,14,23R strain. Next, we wanted to determine more precisely the efficiency of DNA repair, so we followed the intactness of the *MAT* locus after shut down of HO expression by PCR that spanned the HO cut site (Ref. II., Fig. 4B). When cells are grown in galactose-containing medium, the majority of cells contain a DSB in HO recognition site and amplification of the MAT locus by PCR is strongly reduced. When HO expression is shut down in glucose-containing medium, the locus is repaired and can be detected by PCR generating a 1.1 kb product in *MATα* cells or 1.0 kb product in *MATa* cells. Our results confirmed that while in case of Rpb9 depletion *MAT* locus was fully restored after DNA damage, DSB repair is inefficient in H3 K9,14,23R strain (Ref. II, Fig. 4C). This indicates that in conditions where DNA damage checkpoint activation is inefficient as observed for cells in the absence of Rpb9, survival of the cells depends on efficient DNA repair, supported by H3 acetylation. To test whether checkpoint-deficient cells require H3 acetylation for viability in general we introduced H3 K9,14,23R mutation into the checkpoint-deficient *rad53Δ* strain. The cells grew slower than *rad53Δ* with wt H3 and were very sensitive to DNA damaging agents, confirming the importance of H3 acetylation in cells where DNA damage checkpoint is not functional (Ref. II, Fig. 4D).

3.2.4. Abnormal cell morphology and division in Rpb9-depleted and H3 hypoacetylated cells

The anchor away method gives us a very good opportunity to study further the synthetic lethality of Rpb9-deficient H3 K9,14,23R mutant cells by analysing the cell cycle and morphology over time after Rpb9 is depleted from cells. After the loss of Rpb9 from H3 K9,14,23R strain cells do not accumulate at any specific cell cycle phase, on the contrary, the peaks of G1 and G2 subpopulations start to decline and DNA content becomes diverse with some cells containing less DNA than in the normal G1 phase and others with abnormally high DNA content (Ref. II, Fig. 5A). Aberrant distribution of DNA content is indicative of irregular DNA ploidy, which suggests that in the absence of Rpb9, H3 K9,14,23 R cells go through mitosis with unrepaired DNA, leading to unequal chromosome segregation between the daughter cells and aneuploidy.

Furthermore, when we analysed the cell morphology microscopically, large number of Rpb9-depleted H3 K9,14,23R cells presented swollen phenotype and abnormally elongated bud morphologies, as well as unequal distribution of DNA between daughter cells (Ref. II, Fig 5B). In conclusion, our findings demonstrate that when H3 hypoacetylation is combined with the depletion of Rpb9, deficient DDR and unrepaired DNA lesions lead to genomic instability and aberrant segregation of DNA in mitosis, followed by cell death.

3.3 Role of Taf14 in the stabilization of transcription pre-initiation complex (Ref. III)

In addition to the role of reducing interactions between histones with DNA, histone acetylation is a binding site for diverse set of DNA-binding factors involved in transcription, DNA repair, and numerous other processes. Proteins involved in transcriptional regulation are recruited to acetylated lysine residues through specific reader domains. One of these domains is a highly conserved YEATS domain, which in budding yeast can be found in three proteins: Taf14, Yaf9 and Sas5 (Schulze et al., 2009). The YEATS domain was identified for more than a decade ago, but its targets and mechanistic functions are only now becoming clearer.

3.3.1. YEATS domain is non-essential for viability in yeast

It has previously been shown that all three YEATS domain-containing proteins in yeast are nonessential individually, but deletion of all three genes is lethal (Schulze et al., 2009). These data would indicate that the YEATS domain is essential for cell viability. Whereas cells depleted of Taf14 display reduced growth rate, sensitivity to DNA damage, and elevated temperatures, YEATS mutant of Taf14 has only slightly elevated sensitivity to DNA damaging agents (Shanle et al., 2015). Furthermore, *taf14Δ* phenotype can be rescued by expression of the Taf14 C-terminal part that lacks the entire YEATS domain. These notions made us question the essentiality of the YEATS domain. Thus, to elucidate further the function of YEATS proteins in cells, we deleted *TAF14*, *YAF9*, and *SAS5* in all combinations (Ref. III, Fig. 1B). The *yaf9Δtaf14Δ* double-knock-out strain was the only lethal combination detected by the growth assay (Ref. III, Fig. S1A). Based on the observations of previous studies that *taf14Δ* phenotype can be reversed by expressing the truncated Taf14 protein that exhibits only the C-terminal part of the protein, we next replaced full-length *TAF14* with genes encoding YEATS-deleted ($taf14_{\Delta YEATS}$), or YEATS-mutated ($taf14_{W81A}$) versions of Taf14 and introduced them to *yaf9Δ* and *sas5Δ* strains. Surprisingly, Taf14 lacking the YEATS domain or $taf14_{W81A}$ mutant, fully rescues the lethality of triple knock-out strain in which all YEATS proteins were deleted (Ref. III, Fig.

S2 and Fig. 1C). According to this, the YEATS domain is dispensable for the viability of budding yeast and the functions of C-terminal part of Taf14 may hold greater significance for YEATS proteins than previously presumed. Previous studies have demonstrated that Taf14 C-terminus is required for its incorporation into TFIIF, TFIID, INO80, RSC, SWI/SNF, and NuA3 complexes. On the other hand, Taf14 is the only non-essential subunit of TFIID and TFIIF complexes and the integrity and enzymatic activity of these and other complexes were not significantly affected in the absence of Taf14 (Chen et al., 2020; Dutta et al., 2017; Feigerle and Weil, 2016; Henry et al., 1992; Martin et al., 2017; Sen et al., 2017; Tosi et al., 2013). This suggests that Taf14 may have YEATS and C-terminus-independent roles in protein complexes. By dissecting the functional domains of Taf14 we have recently shown that the linker region between YEATS and C-terminal domain interacts with DNA. We propose that this additional DNA binding capacity might be a general role of Taf14 in recruitment of chromatin-associated complexes to DNA (Peil et al., 2022).

3.3.2. Taf14 YEATS domain becomes important when RNAPII is defective

To examine more precisely the functions of YEATS domains, we tested weather Taf14 YEATS mutants can tolerate various stress conditions (Ref. III, Fig. 2). Although another study has reported *taf14*$_{W81A}$ mutant cells to be temperature and MMS sensitive (Schulze et al., 2009), we did not detect any growth defects in our assays, which would differ from the wt strain, except mild cold-sensitivity. The contrasting results with the other study may come from using different yeast strain backgrounds or assay conditions, as we used genomic replacement of *TAF14* with the mutant version in its native locus not plasmid-based expression system.

Since in *S. cerevisiae* Taf14 is physically associated with many critical components of gene transcription, we explored whether Taf14 YEATS domain might have more prominent effects on transcriptional regulation, by analysing the YEATS mutants in cells where RNAPII was defective of Rpb9 or Rpb4 subunits. Similar to deletion of *RPB9*, *rpb4Δ* strain is viable, but displays a slow growth phenotype and has also defects in transcription initiation (Pillai et al., 2001; Schulz et al., 2014). Our results show that deletion of *TAF14* was lethal in both RNAPII mutants, while Taf14 YEATS mutants had synthetic phenotype with *rpb4Δ* and *rpb9Δ*, revealing the relevancy of Taf14 YEATS domain in these strains (Ref. III, Fig. 3 and Figs. S1B−E).

3.3.3. Modified H3K9 is not the critical target of the Taf14 YEATS domain

Many recent studies have been determined to find targets for YEATS domain-containing proteins (Andrews et al., 2016; Klein et al., 2018b; Shanle et al., 2015; Wang et al., 2009a). In addition to acetylated histones Taf14 YEATS domain has been shown to interact with crotonylated lysine residues of histone H3 (Andrews et al., 2016). Acetylated or crotonylated H3K9 was identified as the main target for Taf14 YEATS domain *in vitro* (Andrews et al., 2016; Klein et al., 2018b; Shanle et al., 2015). To test whether H3K9 is the primary target of Taf14 also *in vivo*, we used strains where lysine 9 of histone H3 was substituted for arginine, mimicking unmodified state of the residue. The synthetic phenotype of Taf14 YEATS mutants with *rpb9Δ* strain suggests that recognition of modified H3K9 by Taf14 may become more critical in the absence of Rpb9. To test this, we introduced K9R mutation or Taf14 YEATS mutant to *rpb9Δ* cells and followed the growth kinetics. We proposed that if acetylated or crotonylated H3K9 is the primary target of Taf14 *in vivo*, the *H3K9R* strain should express the same level of genetic interaction with *rpb9Δ* as does the *taf14W81A* strain. Surprisingly, we did not detect synthetic phenotype of H3K9R mutation in *rpb9Δ* background (Ref. III, Fig. 4A). Identical results were obtained using anchor-away technique for Rpb9 removal from the cells (Ref. III, Fig. 4B), indicating that acetylated/ crotonylated H3K9 cannot be the only binding target of Taf14 YEATS domain *in vivo*. These results suggest that Taf14 YEATS domain might have alternative interaction sites in histone tails or in non-histone proteins when H3K9 modification is unavailable. The knowledge from our previous study that mutating multiple modification sites in H3 N-terminal tail is lethal in *rpb9Δ* background prevents us from testing combined modification mutations any further.

3.3.4. Taf14 YEATS domain is required for transcription PIC stabilization

Considering that Taf14 YEATS mutants had synthetic phenotype with RNAPII lacking Rpb9 and Rpb4 subunits, and Taf14 is in the composition of two basal transcription factors TFIID and TFIIF required for PIC assembly, we next wanted to elucidate the role of YEATS domain in PIC formation. For this we used Rpb9 anchor-away strain carrying wt TAF14 or $taf14_{W81A}$ and measured the occupancy of RNAPII, TFIIF and TFIID complexes on promoters of two highly expressed genes *FBA1* and *RPS8A* (Ref. III, Fig. 5). The levels of TFIIF were only slightly reduced in the $taf14_{W81A}$ strain background. It has been previously reported that interactions between RNAPII and TFIIF complexes are strongly reduced in the absence of Rpb9 *in vitro* (Ziegler et al., 2003). Furthermore, the inaccurate start site selection in *rpb9Δ* cells is associated with an impaired interaction between RNAPII and TFIIF (Ziegler et al., 2003). So TFIIF is the most obvious common target of Taf14 and Rpb9. As expected, depletion of Rpb9 had a more significant

effect on the recruitment of TFIIF, regardless of the status of Taf14 (Ref. III, Fig. 5A), confirming the interaction between Rpb9 and TFIIF. Also, the occupation of RNAPII was reduced by depletion of Rpb9 and Taf14 YEATS domain mutant alone and in combination, suggesting a cumulative effect in the reduction of RNAPII (Ref. III, Fig. 5C).

The strongest reduction of all tested PIC components was seen in the recruitment of TFIID in *taf14*$_{W81A}$ cells (Ref. III, Fig. 5B). Since TFIID contains multiple copies of Taf14 protein and at least two Taf14 binding domains have been identified in the C-terminus of Taf2 (Feigerle and Weil, 2016), the stability of TFIID in the PIC may be most dependent on Taf14. Notably, there was only a slight reduction of TFIID levels in Rpb9-depleted cells and no further loss of TFIID in *taf14*$_{W81A}$ cells if Rpb9 was depleted. The rather minor reduction of TFIID occupancy is in accordance with the mild phenotype we observed for Taf14 YEATS mutant strains in stress conditions, suggesting a supportive, rather than critical role of Taf14 in TFIID stabilization. In conclusion, our results indicate that the YEATS domain of Taf14 is one of the factors that stabilize the formation of PIC, although its effect alone is minor, but becomes more relevant when either TFIID or TFIIF recruitment to the PIC is hampered. Taf14 may stabilize the PIC by providing TFIID and TFIIF additional modules for interaction via the YEATS domain binding to modified residues of histones or via the linker region that binds DNA (Peil et al., 2022).

Since Taf14 is a subunit of both TFIID and TFIIF, it has to be considered that *taf14*$_{W81A}$ mutation affects both complexes. To distinguish between the effects resulting from TFIID or TFIIF, we examined the impact of Rpb9 depletion in the *taf2ΔC* strain background. In this strain, the last 147 amino acids from Taf2 C-terminal tail are deleted, which disrupts Taf14 interaction only with TFIID, while Taf14 is incorporated into all other Taf14-containing complexes (Feigerle and Weil, 2016). Depletion of Rpb9 in this strain had a similar synthetic phenotype as Rpb9-deficient *taf14*$_{W81A}$ cells, suggesting that in Rpb9-depleted cells Taf14 is primarily required in complex with TFIID (Ref. III, Fig. 5D). However, we detected an even stronger synthetic phenotype of *taf14*$_{W81A}$ *taf2ΔC* strain in Rpb9 depletion background, indicating that the deletion of Taf2 C-terminus may affect other functions or interactions of TFIID and PIC stability independently from Taf14. In *Komagataella phaffii* Taf14 was found to bind Taf2 side-by-side with Taf8 subunit of TFIID. This suggests that Taf2 C-terminus may be involved in the correct placement of these subunits in TFIID complex (Kolesnikova et al., 2018). It is an interesting notion that in higher eukaryotes TFIID and TFIIF complexes do not contain the Taf14 subunit that is found in yeast. So why does yeast need Taf14 in these complexes? It is possible that by providing additional binding modules for TFIID and TFIIF interaction with chromatin, Taf14 is needed in yeast as a unicellular organism for a faster transcriptional regulation in response to environmental changes.

CONCLUSIONS

Transcription is a highly complex process, where hundreds of factors operate in cooperation for efficient gene expression. This study focuses mainly on the mechanisms of RNAPII-dependent transcription regulation in *Saccharomyces cerevisiae*, examining the role of histone PTMs and effector proteins in this process. To better understand how epigenetic landscapes are established and maintained, the distribution and maintenance of transcription-coupled H3K36 methylation was evaluated in active transcription and after its shut down. This study demonstrates that H3K36 methylation is restricted to transcribed loci and that chromatin has a relatively short molecular memory of recently occurred transcriptional activity. Also, replication-dependent exchange of histones and passive demethylation of H3K36 by demethylases contribute to the turnover of H3K36 methylation mark after transcription inhibition. As RNAPII is a central factor of transcription, the goal was to examine the effect of histone modifications in the context of transcription where RNAPII is defective, by deleting RNAPII subunit Rpb9. It was found that simultaneous mutation of multiple lysine residues in the N-terminal tail of histone H3 is lethal in *rpb9Δ* cells. When studying this synthetic lethality, is was demonstrated that Rpb9-depleted cells are defective in DDR and require H3 acetylation for viability. The studies continued by elucidating the role of histone-binding effector proteins, which through their reader domains recruit or stabilize epigenetic regulators to chromatin and fine-tune gene expression. The YEATS domain is one of these reader domains, whose role in chromatin modifications and transcription is still elusive. The disruption of all YEATS domain proteins in yeast (Yaf9, Taf14 and Sas5) is lethal, but can be rescued by the expression of truncated Taf14 protein lacking the entire YEATS domain, indicating that the YEATS domain is not required for cell survival. It was demonstrated that acetylated or crotonylated histone H3 lysine 9 in not the only interaction target of the Taf14 YEATS domain *in vivo*. Also, the role of Taf14 YEATS domain was explored in transcriptional regulation and found that it participates in PIC stabilization.

Results presented in this thesis will add new knowledge about the molecular mechanisms of transcriptional regulation and the involvement of PTMs of histones and their reader proteins in this process. The obtained knowledge is essential in developing the scientific common knowledge on gene regulation in cells. As this process and proteins involved are also conserved in human cells and their mutation or misregulation is linked to a wide range of human diseases, the knowledge obtained is essential in developing new medical treatment strategies and therapeutic targets in the future.

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SUMMARY IN ESTONIAN

Histoonide post-translatsiooniliste modifikatsioonide uurimine RNA polümeraas II-sõltuvas transkriptsioonis

Eukarüootsetes rakkudes on genoomne DNA pakitud kromatiinina, mille struktuurseteks kordusühikuteks on nukleosoomid. DNA pakkimine tagab geneetilise materjali kompaktsuse, kuid on takistuseks mitmetele DNA-l toimuvatele protsessidele, kaasa arvatud RNA polümeraas II poolt läbiviidavale geenide transkriptsioonile. Kromatiini struktuuri dünaamiline muutumine mängib olulist rolli transkriptsiooni regulatsioonis. Üheks peamiseks mehhanismiks kromatiini struktuuri muutmiseks rakus on histoonide modifitseerimine. Histoonide PTM-d võivad mõjutada kromatiini struktuuri otseselt, muutes DNA ja nukleosoomide vahelist pakituse astet, või kaudselt, luues sobiva pinnase kromatiiniga seonduvatele valkudele. Kuigi on teada, et histoonidel esinevatel modifikatsioonidel on oluline roll epigeneetilises geeniekspressiooni regulatsioonis, on veel palju selguseta.

Käesolevas töös uuriti RNAPII transkriptsiooni mehhanisme ning histoonide post-translatsiooniliste modifikatsioonide ja nendele seonduvate faktorite rolli selles protsessis, kasutades mudelorganismina pagaripärmi *Saccharomyces cerevisiae*. Esmaseks eesmärgiks oli paremini mõista, kuidas histoonide modifikatsioonimustrid kujunevad ja säiluvad, milleks hinnati aktiivses transkriptsioonis esineva histoon H3-e lüsiinijääk 36 metülatsiooni levikut ja püsimist pärast transkriptsiooni toimumist. Selleks kasutati mudelgeenina *GAL-VPS13* lookust, mille puhul on 9,3 kiloaluspaari pikkuse *VPS13* geeni ette viidud kõrgelt ekspresseruva *GAL10* geeni promootor. Tänu sellele on võimalik loodud *GAL-VPS13* lookuse ekspressiooni süsinikuallikaga söötmes reguleerida. Lisades söötmesse galatoosi on lookuse transkriptsioon aktiveeritud ning lisades glükoosi, inhibeeritud. Lisaks, on *GAL-VPS13* kodeerivasse alasse viidud terminaatorjärjestus, millest allavoolu transkriptsiooni ei toimu. Tulemustest selgus, et H3K36 metülatsiooni levik piirneb aktiivselt transkribeeritava alaga ega levi RNAPII-st sõltumatult edasi terminaatoralaga külgnevatele piirkondadele. Pärast transkriptsiooni represeerimist, oli lüsiin 36 *GAL-VPS13* lookuses metüleeritud ligikaudu 60 minutit, mis viitab võrdlemisi lühikesele molekulaarsele "mälule" äsja toimunud aktiivsest transkriptsioonist. Selgitati välja, et H3K36 metülatsioonimärgise eemaldamiseks pärast transkriptsiooni inhibeerimist on vajalik nii demetülaaside ensümaatiline aktiivsus kui replikatsiooni käigus toimuv histoonide väljavahetamine.

Järgmiseks uuriti histoonide modifikatsioonide mõju geeni ekspressioonile olukorras, kus transkribeeriv RNAPII on defektne ühe subühiku, Rpb9, puudumise tõttu. Leiti, et kui samaaegselt muteerida Rpb9 ja histoonil H3 mitu atsetüleeritavat lüsiinijääki on see rakkudele letaalne. Rakud ei suuda korrektselt aktiveerida DNA kahjustustele vastavaid signaaliradu ega kahjustuste tekkimisel

reparatsioonimehhanism neid parandada, mis viib omakorda mitoosi läbimisel ebanormaalse kromosoomide jaotamiseni, olles rakkudele surmav.

Uurimust jätkati selgitamaks histooni modifikatsioonidele seonduvate valkude rolli geeniekspressioonis. Efektorvalgud omavad struktuurseid domeene, läbi mille nad modifikatsioonimärgistega seonduvad. Üheks selliseks domeeniks on kõrgelt konserveerunud YEATS domeen, mille struktuur on teada juba aastakümneid, kuid roll transkriptsioonis ja kromatiini modifitseerimisel veel ebaselge. Tulemustest selgus, et YEATS domeen ei ole pärmi elulemuseks hädavajalik ning varasematest töödest näidatud Taf14 YEATS domeeni eelistatud seondumine atsetüleeritud või krotonüleeritud histoon H3 lüsiinijäägiga 9. positsioonis, ei ole tema ainus sihtmärk. Leiti, et Taf14 YEATS domeen osaleb transkriptsiooni pre-initsatsiooni kompleksi moodustamisel, stabiliseerides transkriptsioonifaktorite TFIID ja TFIIF seondumist.

Kokkuvõtvalt avardavad antud töös saadud tulemused oluliselt teadmisi histoonide modifikatsioonide ja nendega seonduvate valkude olulisusest transkriptsiooni regulatsioonis. Antud protsess ja selles osalevad valgud on inimese rakkudes konserveerunud ning mutatsioone või ebakorrektset regulatsiooni seostatakse paljude erinevate inimestel esinevate haigustega seal hulgas vähktõvega. Tööst saadud teadmised on seega olulised uute ravistrateegiate arendamisel ja terapeutiliste sihtmärkide väljatöötamisel.

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PUBLICATIONS

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2006–2009	University of Tartu, Faculty of Science and Technology, BSc in Gene technology
1995–2006	Haapsalu Gymnasium

Special courses and conferences

2022	EMBL conference on "Transcription and Chromatin", Heidelberg, Germany
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2016	EMBO conference on "Gene Transcription in Yeast: From Chromatin to RNA and Back", San Feliu de Guixols, Spain
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2012	EMBO conference on "Gene Transcription in Yeast: From Mechanisms to Gene Regulatory Networks", San Feliu de Guixols, Spain

Scientific work

My main scientific interest has been to study the mechanisms of eukaryotic transcription and histone post-translational modifications in *Saccharomyces cerevisiae*.

Teaching and supervision at the University of Tartu, institute of Molecular and Cell Biology institute

2022	Molecular Biology of Eukaryotes, seminar on "Maintaining DNA methylation without the *de novo* DNA methyltransferase"
2022	Member of the defence committee of BSc theses in Cell Biology, Developmental Biology, Genetics and Molecular Biology committee
2016–2017	Practical course in Cell Biology, co-instructor
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2018	Supervisor of Katrin Orro (BSc)
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Other professional activities

2013–2015	Practical course in biology for Miina Härma gymnasium students, instructor

List of Publications

Sein, H., Värv, S., Kristjuhan, A. (2015) Distribution and maintenance of Histone H3 lysine 36 trimethylation in transcribed locus. PLoS ONE 10(3): e0120200

Sein, H., Reinmets, K., Peil, K., Kristjuhan, K., Värv, S., Kristjuhan, A. (2018) Rpb9-deficient cells are defective in DNA damage response and require histone H3 acetylation for survival. Sci Rep. 8(1):2949.

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Hariduskäik ja erialane teenistuskäik

2011–…	Tartu Ülikool, Loodus- ja tehnoloogiateaduskond, doktoriõpe, molekulaar- ja rakubioloogia erialal
2011–…	Laborant molekulaar- ja rakubioloogia instituudis, rakubioloogia õppetoolis
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Erialane enesetäiendus

2022	EMBL konverents “Transcription and Chromatin”, Heidelberg, Saksamaa
2017	EMBL konverents “Transcription and Chromatin”, Heidelberg, Saksamaa
2016	EMBO konverents “Gene Transcription in Yeast: From Chromatin to RNA and Back”, San Feliu de Guixols, Hispaania
2014	Wellcome Trust konverents “Chromatin from Nucleosomes to Chromosomes”, Hinxton, Inglismaa
2012	EMBO konverents “Gene Transcription in Yeast: From Mechanisms to Gene Regulatory Networks”, San Feliu de Guixols, Hispaania

Teadustöö

Minu uurimustöö põhisuunaks on eukarüootse transkriptsiooni ja histoonide post-translatsiooniliste modifikatsioonide mehhanismide uurimine pagaripärmis *Saccharomyces cerevisiae*.

Õppetöö ja juhendamine TÜ molekulaar- ja rakubioloogia instituudis

2022 Eukarüootide molekulaarbioloogia, seminar teemal "DNA metüleerituse säilitamine ilma *de novo* DNA metüültransferaasita"
2022 Bakalaureusetööde hindamiskomisjoni liige, rakubioloogia, arengubioloogia, geneetika ja molekulaarbioloogia komisjonis
2015–2017 Rakubioloogia praktikum, kaasjuhendaja
2015–2017 Bakalaureusetööde oponent, molekulaar- ja rakubioloogia instituut
2018 Katrin Orro bakalaureusetöö juhendaja
2016 Merilin Väärtnõu bakalaureusetöö juhendaja
2014 Roman Šõtšovi bakalaureusetöö juhendaja

Muu erialane tegevus

2013–2015 Praktilise bioloogia praktikum Miina Härma gümnaasiumi 12. klassi õpilastele, juhendaja

Publikatsioonid

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