Original Article

SUMO1 modification of histone H4 is involved in the pathogenesis of nodular lymphocyte predominant Hodgkin lymphoma

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Background: Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a distinct and rare subtype of Hodgkin lymphoma (HL) that can be differentially diagnosed from classical Hodgkin lymphoma (cHL). Because of its low prevalence rate and undefined pathogenic mechanisms, a specific treatment for NLPHL has yet to be determined. In NLPHL, which is a malignant B-cell lymphoma, antigen stimulation results in the formation of germinal centers by secondary lymphoid follicles, which promotes the differentiation of germinal center B cells (GCBs) into long-lived plasma cells and memory B cells. Any abnormality during the differentiation can lead to the occurrence and development of NLPHL.

Methods: The GDS4977 data set was selected from the Gene Expression Omnibus (GEO) repository. Differentially-expressed genes (DEGs) were detected with GEO2R. Gene Ontology (GO) enrichment analysis of biological processes (BP) and Reactome pathways was performed withg:Profile. Cytoscape software was employed to screen hub genes, while the core genes were determined using the STRING and Reactome databases.

Results: In total, 623 DEGs, 68 GO-BP pathways, 70 Reactome pathways, 19 hub genes, and 12 core genes were identified.

Conclusions: Histone expressions differ between NLPHL and GCBs, and *HIST1H4B*, *HIST1H4C*, *HIST1H4E*, *HIST1H4L*, *HIST1H2AE*, *H2AFZ*, *HIST1H2BM*, and *H3F3A* jointly form the core histones. During the development of NLPHL, histones are transported by NPM1. The pathogenesis of NLPHL involves SUMO-1 modification of histone H4.

Keywords: Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL); histone; NPM1; small ubiquitin like modifier1 (SUMO1)
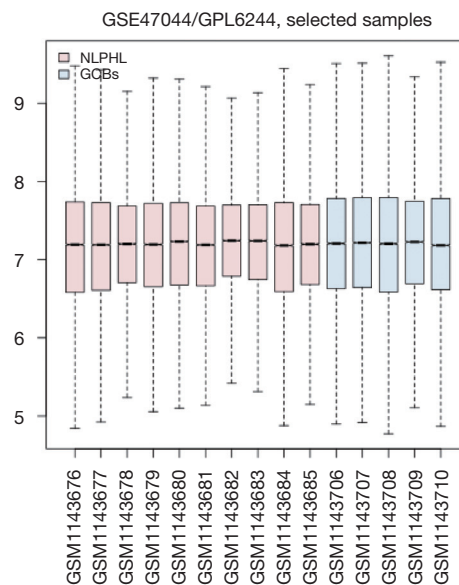
Introduction

Hodgkin lymphoma (HL), a malignant tumor of the lymph nodes or extranodal lymphoid tissue, comprises two main subtypes: classical HL (cHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). Advanced NLPHL is prone to turn into aggressive lymphoma, which is difficult to treat and has a poor prognosis (1) Owing to

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GSE47044/GPL6244, selected samples

Figure 1 Box plot of value distribution.

the low prevalence of NLPHL (about 0.1–0.2/100,000) (2), its etiology and pathogenesis are unclear and need to be investigated through different approaches (2,3). In NLPHL, which is a malignant B-cell lymphoma, antigen stimulation results in the formation of germinal centers by secondary lymphoid follicles, which promotes the differentiation of germinal center B cells (GCBs) into long-lived plasma cells and memory B cells. Any abnormality during the differentiation can lead to the development of NLPHL. Histone post-translational modification (HPTM) can change the chromatin structure in different ways, thus affecting the transcription process. SUMO modification is characterized by covalent combination and dynamic reversibility, it is the only inhibitive HPTM mode found so far, which can prevent the occurrence of active HPTM.

Methods

Data collection

A keyword search of the GEO database was conducted. First, the term "Lymph Nodes" was entered, and then "Homo Sapiens" was selected, yielding a total of 43 datasets. Finally, GDS4977 was identified from the GSE47044 series. This dataset contained 35 samples, including 30 microdissected tumor samples and 5 sorted CD77 samples. The GPL6244 platform, which uses the Affymetrix Human Gene 1.0 ST Array, was used.

Screening and enrichment analysis of differentially-expressed genes (DEGs)

DEGs from 10 NLPHL samples and 5 germinal center B cell (GCBs) samples in GPL6244 were screened using the GEO2R web tool, with the screening conditions adjusted to P value <0.05 and LogFc 5 ≥1.5 or LogFc ≤–1.5. Gene Ontology (GO) enrichment analysis of biological processes (BP) and Reactome pathways was performed using g:Profile.

Screening of hub genes

The EnrichmentMap and CytoHubba plug-ins in the Cytoscape software were used to sort the enrichment pathways and screen hub genes.

Screening of core genes

The screened hub genes were further screened for core genes by comprehensive analysis using the STRING and Reactome databases.

Results

DEGs

In total, 623 statistically significant DEGs were identified using the GEO2R web tool, and the box plot of the value distribution is shown in *Figure 1*. Among them there

were 591 genes were upregulated and 32 genes were downregulated (*Figure 2*; red represents upregulated genes; green represents downregulated genes).

Results of GO-BP and Reactome pathway enrichment analyses for DEGs

Enrichment analysis for DEGs (68 GO-BP pathways and 70 Reactome pathways) was performed using the g:Profile software. The top 10 GO-BP and Reactome pathways with the lowest *p*-values are listed in *Table 1*.

Hub genes

The enrichment results of GO-BP and Reactome pathway
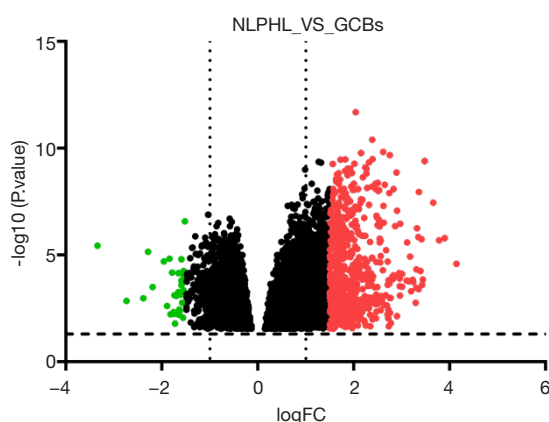
Figure 2 Volcano plot of enrichment analysis for DEGs. DEG, differentially-expressed gene.

analysis in g:Profiler were visualized in Cytoscape using its EnrichmentMap plugin, and a total of 113 nodes and 2,108 edges were yielded. The top 10 pathways were screened by the node degree by using the MCC algorithm in the CytoHubba plugin (*Table 2*). In total, 19 hub genes were identified (*Table 3*).

Protein-protein associations (PPA)

PPA analysis was performed for the 19 identified hub genes in Cytoscape using its STRING plugin. The top 10 PPAs with the highest edge scores in the PPA network were RBBP4(pp)RBBP7, H3F3A(pp)HIST1H4E, H3F3A(pp) HIST1H4B, H3F3A(pp)HIST1H4C, H3F3A(pp) HIST1H4L, YWHAE(pp)YWHAB, HIST1H4B(pp) HIST1H4E, HIST1H4C(pp)HIST1H4E, HIST1H4B(pp) HIST1H4L, and HIST1H4B(pp)HIST1H4C (*Figure 3*).

Core genes

Figure 4 shows the smallest cell cycle pathway with the smallest entities P value (1.11E–16) in the Reactome database. Chromosome maintenance, identified by the POSITION function on the Reactome database, was the cellular process participated in by the largest number of hub genes (*Figure 5*). In the two pathways and sub-pathways above, the core genes *NPM1*, *RBBP4*, and *RBBP7*, together with core histones, participated in nucleosome assembly in the form of a complex (*Figure 6*). The core gene SUMO1 and histone H4 formed a complex (SUMO1-HIST1H4), which participated in the entire cell cycle; in essence,

Table 1 The top 10 GO-BP and Reactome pathways with the lowest P value

GO.ID	Description	P value	FDR	Phenotype
REAC:72689	Formation of a pool of free 40S subunits	5.97E–31	5.97E–31	1
REAC:156827	L13a-mediated translational silencing of Ceruloplasmin expression	1.02E–30	1.02E–30	1
REAC:72706	GTP hydrolysis and joining of the 60S ribosomal subunit	1.48E–30	1.48E–30	1
REAC:72737	Cap-dependent translation initiation	1.71E–29	1.71E–29	1
REAC:72613	Eukaryotic translation initiation	1.71E–29	1.71E–29	1
GO:0045047	Protein targeting to ER	2.15E–27	2.15E–27	1
GO:0006413	Translational initiation	4.22E–27	4.22E–27	1
GO:0072599	Establishment of protein localization to endoplasmic reticulum	8.97E–27	8.97E–27	1
GO:0006614	SRP-dependent co-translational protein targeting to membrane	5.53E–26	5.53E–26	1
GO:0000956	Nuclear-transcribed mRNA catabolic process	1.75E–25	1.75E–25	1

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Table 2 The top 10 GO and Reactome pathways with the highest node degree

Score	GO.ID	Description	P value	Genes
47	GO:0016233	Telomere capping	4.98E–03	*HNRNPD, ATM, USP7, HIST1H4C, HIST1H4L, HIST1H4E, HIST1H4B*
47	GO:0061641	CENP-A containing chromatin organization	2.44E–03	*RBBP7, RBBP4, NPM1, HIST1H4C, HIST1H4L, HIST1H4E, HIST1H4B*
47	GO:0034080	CENP-A containing nucleosome assembly	2.44E–03	*RBBP7, RBBP4, NPM1, HIST1H4C, HIST1H4L, HIST1H4E, HIST1H4B*
47	REAC:2559586	DNA damage/telomere stress-induced senescence	8.74E–03	*ATM, H2AFZ, HIST1H4C, HIST1H2BM, HIST1H4L, HIST1H4E, HIST1H2AE, HIST1H4B*
47	REAC:171306	Packaging of telomere ends	3.94E–03	*H2AFZ, HIST1H4C, HIST1H2BM, HIST1H4L, HIST1H4E, HIST1H2AE, HIST1H4B*
46	REAC:69473	G2/M DNA damage checkpoint	5.06E–03	*YWHAE, SUMO1, ATM, WEE1, YWHAB, HIST1H4C, HIST1H2BM, HIST1H4L, HIST1H4E, HIST1H4B*
46	REAC:73728	RNA polymerase I promoter opening	1.45E–03	*H3F3A, H2AFZ, HIST1H4C, HIST1H2BM, HIST1H4L, HIST1H4E, HIST1H2AE, HIST1H4B*
46	GO:0031055	Chromatin remodeling at centromere	3.38E–03	*RBBP7, RBBP4, NPM1, HIST1H4C, HIST1H4L, HIST1H4E, HIST1H4B*
46	GO:0034724	DNA replication-independent nucleosome organization	1.08E–03	*RBBP7, RBBP4, H3F3A, NPM1, HIST1H4C, HIST1H4L, HIST1H4E, HIST1H4B*
46	REAC:912446	Meiotic recombination	2.60E–04	*MND1, ATM, H3F3A, H2AFZ, HIST1H4C, HIST1H2BM, HIST1H4L, HIST1H4E, HIST1H2AE, HIST1H4B*

histone H4 underwent SUMO1 modification (*Figure* 7).

Discussion

The prognosis of NLPHL, a rare type of HL, is good in the early stages. However, treating advanced-stage NLPHL, because of it typically invasive nature, is challenging and the prognosis is poor (1). Although NLPHL and cHL have different pathological and immunophenotypical features, due to the lack of well-recognized therapies, NLPHL is often treated as cHL. It is difficult to explore the pathogenesis of NLPHL and suitable treatments using whole genomic sequencing technology in large-scale studies; however, core genes can be identified through microanalysis utilizing the currently available databases. In our current study, gene chip analysis in the GPL6244 platform identified 19 hub genes, among which 8 were histone genes, and PPAs existed among histones encoded by these 8 genes. It was proposed that there were differences in histone expressions between NLPHL and GCBs. Histone is an octamer comprising one (H3-H4)2 tetramer and two H2A-H2B dimers. Recent studies on the Telomere

Maintenance pathway also confirmed the hypothesis that the core histone was jointly formed by HIST1H4B, HIST1H4C, HIST1H4E, HIST1H4L, HIST1H2AE, H2AFZ, HIST1H2BM, and H3F3A (4,5).

The nucleosome is the basic structural unit of the chromosomes (6). The core nucleosome, a disc-like structure with 146 bp of DNA wrapped around the core histone octamer (4,7), plays a distinctive role in centromere assembly, correct separation of chromosomes, and normal cell division (8,9). As shown in *Figure 6*, the core genes NPM1, RBBP4, and RBBP7, along with HJURP and RUVBL1, carry CENPA, H4, and CCAN:DNA:CASC5 to bind to histones H2A and H2B, finally presenting CENPA, H4, H2A, H2B, and CCAN:DNA:CASC5 to RSF Complex to complete the assembly of core nucleosomes. During the assembly of core nucleosomes, histones are transported and transferred by the core genes *NPM1*, *RBBP4*, and *RBBP*7. Centromere protein A (CENPA) is a specific variant of centromeric histone H3 and also a characteristic mark of centromere (10,11). Each chromosome has only one centromere. If the centromere is missing, the duplicated chromosomes are separated randomly, leading

Table 3 The 19 identified hub genes

| Gene symbol	Description	Location	Functional consequence
HIST1H4B	Histone cluster 1, H4b	6p22.2	Upstream
HIST1H4C	Histone cluster 1, H4c	6p22.2	Downstream
HIST1H4E	Histone cluster 1, H4e	6p22.2	Downstream
HIST1H4L	Histone cluster 1, H4l	6p22.1	Upstream
HIST1H2BM	Histone cluster 1, H2bm	6p22.1	Downstream
HIST1H2AE	Histone cluster 1, H2ae	6p22.2	Downstream
H2AFZ	H2A histone family member Z	4q23	3_prime_UTR, upstream
RBBP4	RB binding protein 4, chromatin remodeling factor	1p35.1	Intron
RBBP7	RB binding protein 7, chromatin remodeling factor	Xp22.2	coding_sequence, missense
ATM	ATM serine/threonine kinase	11q22.3	genic_downstream, intron, 3_prime_UTR
NPM1	Nucleophosmin 1	5q35.1	Intron, sequence, missense
H3F3A	H3 histone, family 3A	1q42.12	Missense, coding
YWHAB	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta	20q13.12	Coding, synonymous
YWHAE	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon	17p13.3	Intron
HNRNPD	Heterogeneous nuclear ribonucleoprotein D	4q21.22	3_prime_UTR
USP7	Ubiquitin specific peptidase 7	16p13.2	stop_gained, coding_sequence, non_coding, synonymous
SUMO1	Small ubiquitin-like modifier	2q33.1	Intron
WEE1	WEE1 G2 checkpoint kinase	11p15.4	3_prime_UTR
MND1	Meiotic nuclear divisions	4q31.3	intron

to the deletion or doubling of the chromosomes of the daughter cells. This is one of the important mechanisms of oncogenesis (10,12-14).

Histone chaperones are defined as a group of proteins that bind and transport histones and regulate the assembly/deassembly of nucleosomes (4,15). The nucleophosmin (NPM) was the first histone chaperone to be discovered, and nucleophosmin 1 (NPM1) is a key member of the NPM family (16). Studies have shown that NPM1 can maintain genomic stability and regulate cell apoptosis; thus, it possesses both oncogenic and tumor suppressor functions, which are mainly determined by the level of NPM1 expression (17,18). A meta-analysis of 11 published studies involving 997 patients showed that, in solid tumors, the upregulation of NPM might be a potential therapeutic target and NPM overexpression might be a biomarker of poor prognosis (19). Patel *et al.* found (20) that patients with acute myeloid leukemia (AML) with NPM1 mutation

had increased complete response and overall survival rates; in contrast, AML patients with NPM1, FLT3-ITD, and DNMT3A mutations tended to have poor prognosis. RBBP4 and RBBP7 are chromatin remodeling factors, which are involved in histone deacetylation (21,22). As shown in *Figure 6*, NPM1, RBBP4, and RBBP7 exist in the Nucleosome Assembly pathway; after the completion of histone transportation, they bind with HJURP and RUVBL1 and are finally removed from the core nucleosomes. No evidence has shown either RBBP4 or RBBP7 to be a histone chaperone or to be directly bound to histones and, thus, behind the development of NLPHL. It is speculated that *RBBP4* and *RBBP*7 play a regulatory role in NPM1 expression during the occurrence and development of NLPHL.

Histone is a substrate for various post-translational modifications. Histone modification, which is an epigenetic mechanism that regulates gene expression, is the main

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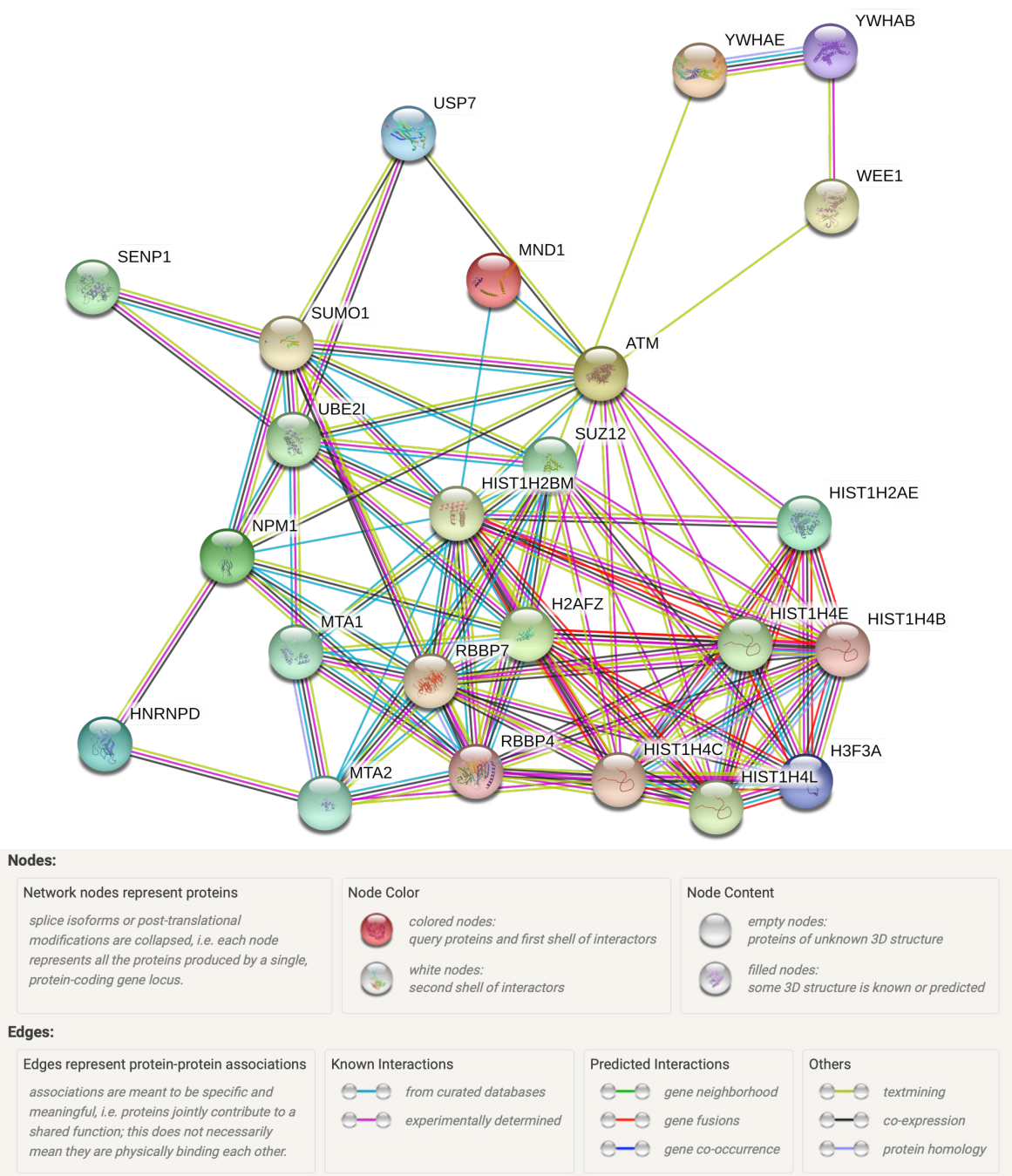
Figure 3 PPA network. PPA, protein-protein association.

source of variation. Common modifications include acetylation/deacetylation, phosphorylation, methylation, citrullination, ubiquitination/deubiquitination, and SUMOylation (14). Based on the POSITION function in the Reactome database, we found 232 SUMO1 positions in the cell cycle pathway, among which 224 positions existed

as proteins, 7 as complexes, and 1 as an interactor; 205 positions were located in the cell cycle (including mitosis, meiosis, and checkpoints) and 27 in the chromosome maintenance. Only SUMO1-HIST1H4 was involved in all four processes of cell cycle; in addition, it is the product of the direct binding of SUMO1 to HIST1H4. We speculate
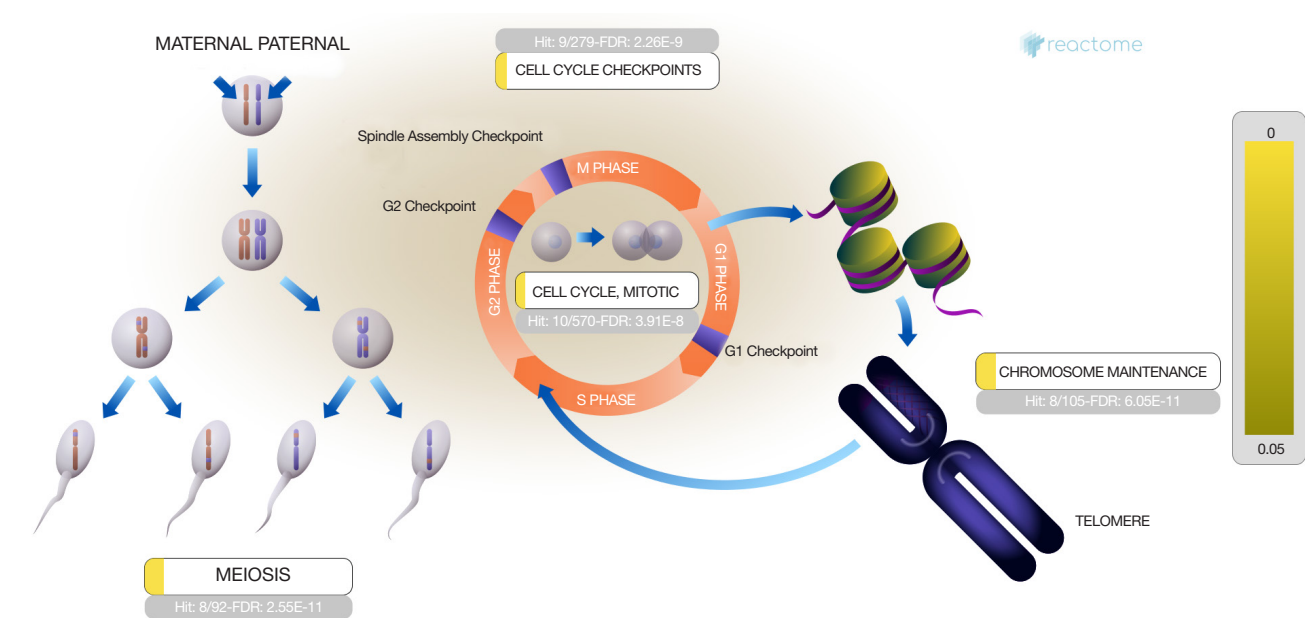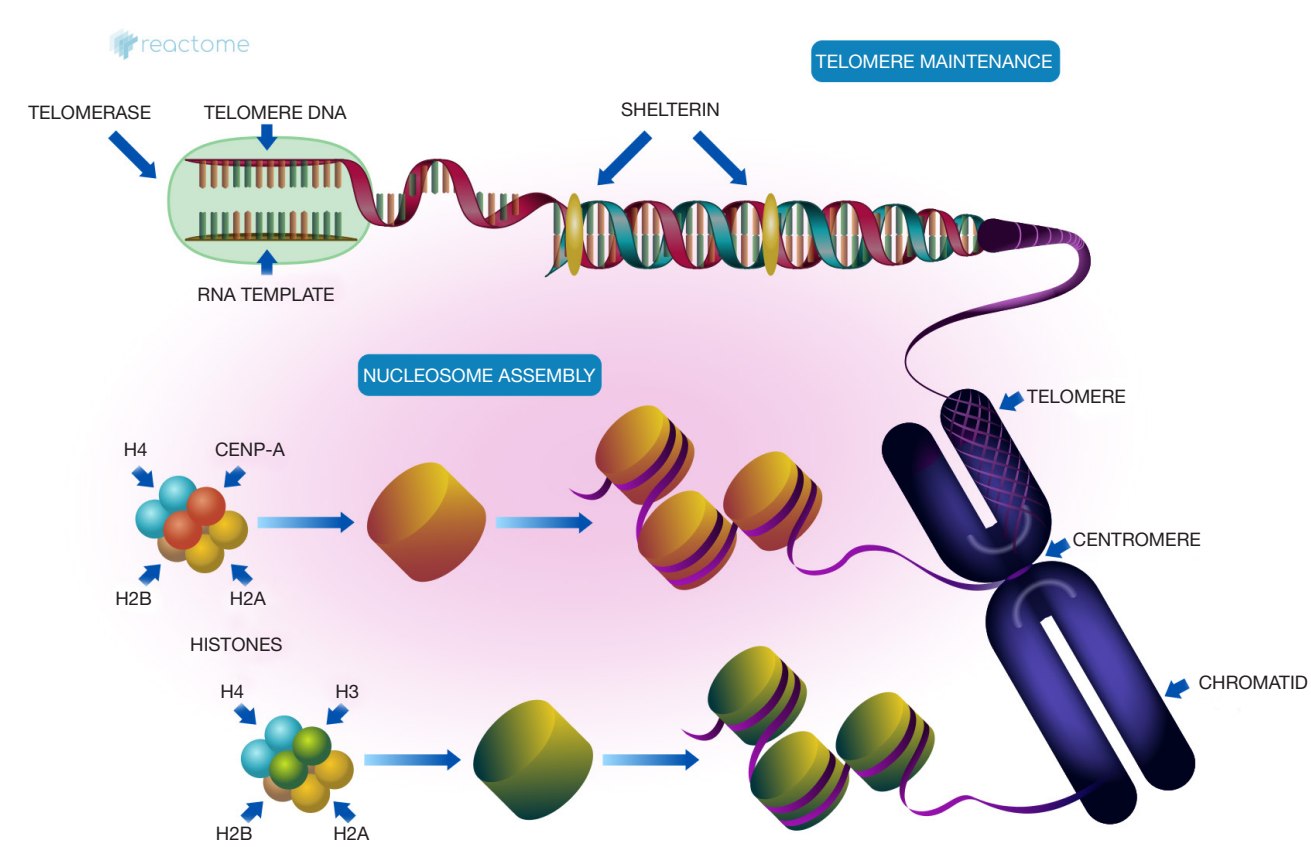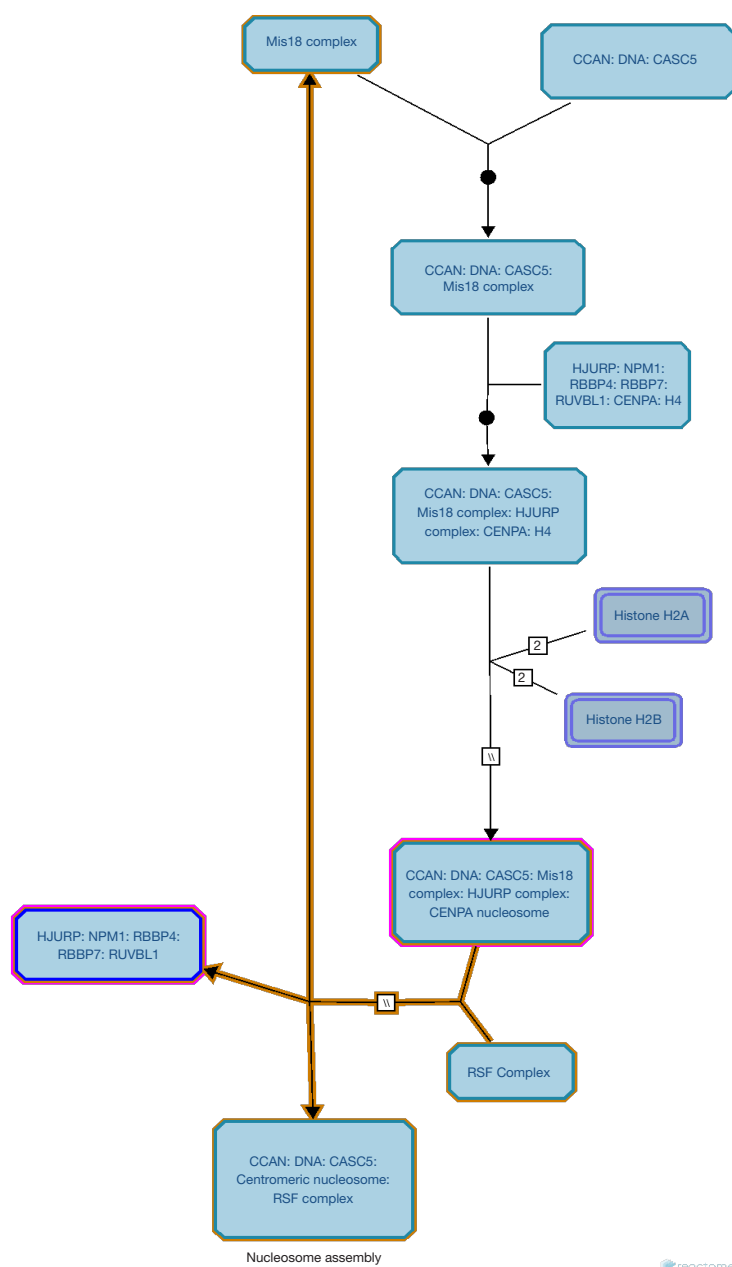
Figure 4 REACTOME pathway.

Figure 5 Telomere maintenance.

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Figure 6 Nucleosome assembly.

that NLPHL involves SUMO1 modification of histones, and the modification site is located on histone H4 (*Figure 7*).

Small ubiquitin like modifier1 (SUMO1) is a member of the SUMO family (23). SUMO is a ubiquitin-like protein, but its function differs somewhat from ubiquitin proteins. It modifies the substrate protein to regulate the activity of the target protein and its interaction with other molecules. It also participates in nucleocytoplasmic transport,

transcriptional regulation, and cell apoptosis (24). Normally, the effects of SUMOylation are negative (25-27). Many studies have shown an association between SUMOylation and a variety of tumors including lung cancer, breast cancer, and ovarian cancer. In primary liver cancer, SUMOylation is also associated with multiple drug resistance (28). The SUMOylated MAFB protein can promote the pathogenesis of rectal cancer, and knockdown of SUMO E1 or SUMO-
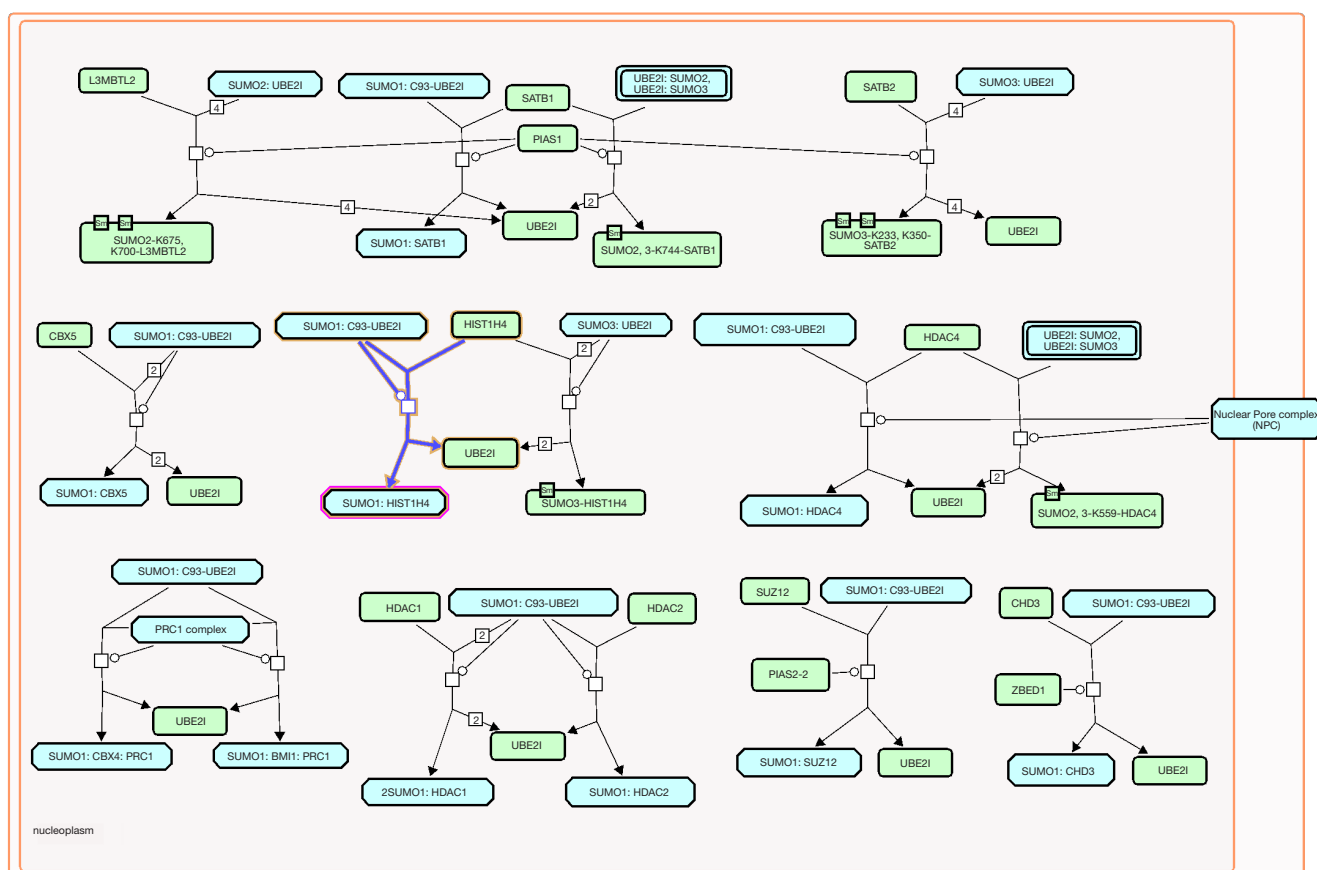
SUMOylation of chromatin organization proteins
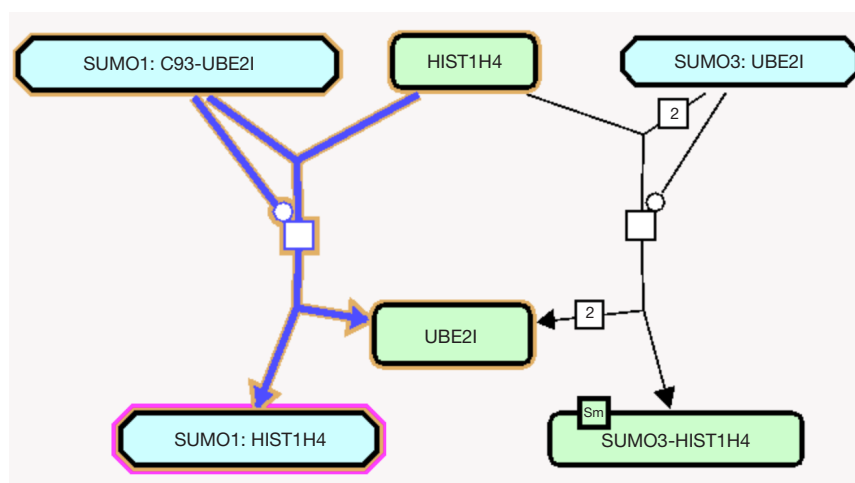
Figure 7 SUMO1 modification of histone H4.

conjugating enzyme (E2) inhibits the maintenance and self-renewal of rectal cancer stem cells (29). SUMOylation is a reversible process. DeSUMOylation is regulated by the SUM0-specific protease (SENP) family (30). However, the SENPs family is large, and different members exhibit

different regulatory effects on tumors. The overexpression of SENP1 and SENP3 has been found to promote tumorigenesis (31,32), whereas high expressions of SENP2 and SENP5 may hinder cancer development (33,34).

In summary, knockdown of NPM1 expression or

mutant NPM1 may interfere with the assembly of core nucleosomes, prevent chromosome separation, and thus suppress tumor occurrence and growth. Moreover, histone modifications can be destroyed by knockout of SUMO1-activating enzyme or overexpression of SENP2/5 to achieve a therapeutic effect in NLPHL; however, new laboratory technology is required to verify our findings. Furthermore the specific site on histone H4 where the SUMO1 modification occurred was not identified in this study, which also warrants further investigation.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1994). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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