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EpiFactors 2022: expansion and enhancement of a curated database of human epigenetic factors and complexes

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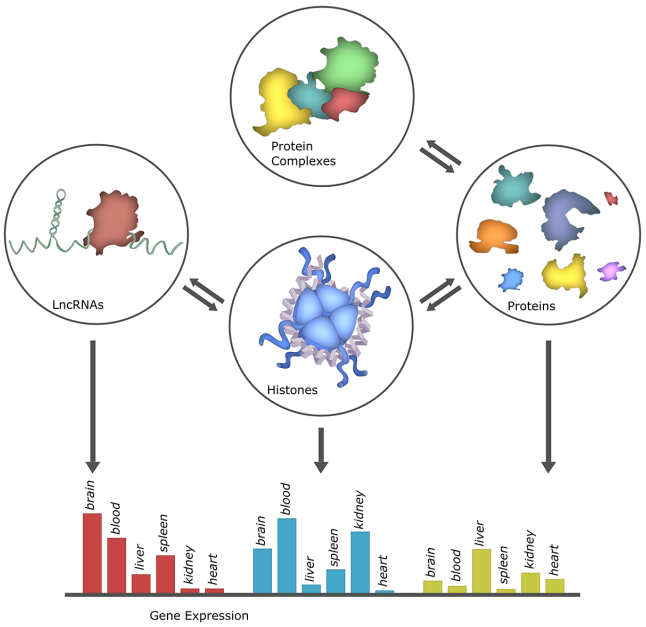
ABSTRACT

We present an update of EpiFactors, a manually curated database providing information about epigenetic regulators, their complexes, targets, and products which is openly accessible at http://epifactors.autosome.org. An updated version of the EpiFactors contains information on 902 proteins, including 101 histones and protamines, and, as a main update, a newly curated collection of 124 lncRNAs involved in epigenetic regulation. The amount of publications concerning the role of lncRNA in epigenetics is rapidly growing. Yet, the resource that compiles, integrates, organizes, and presents curated information on lncRNAs in epigenetics is missing. EpiFactors fills this gap and provides data on epigenetic regulators in an accessible and user-friendly form. For 820 of the genes in EpiFactors, we include expression estimates across multiple cell types assessed by CAGE-Seq in the FANTOM5 project. In addition, the updated EpiFactors contains information on 73 protein complexes involved in epigenetic regulation. Our resource is practical for a wide range of users, including biologists, bioinformaticians and molecular/systems biologists.

GRAPHICAL ABSTRACT



INTRODUCTION

Epigenetics is a rapidly growing area of molecular biology covering changes in chromatin often leading to alteration in gene expression without any change in the DNA sequence. An epigenetic factor could be described as a molecule that initiates, modifies, and acts upon epigenetic modifications. Epigenetic regulatory pathways generally affect DNA accessibility or recruitment of other regulatory molecules by modification of DNA or histones (1).

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The ultimate result of such regulation may be both fine-tuning and major changes in expression gene profiles (2–5). Various fundamental cell processes such as proliferation, differentiation, cell death, and response to conditional changes in metabolic demand are controlled by epigenetic mechanisms (6–8). Moreover, dysregulation of epigenetic factors is often associated with neurological, cardiovascular and metabolic diseases, various cancers, and other human disorders (6,9–12). Thus, the information about epigenetic regulators and their complexes is extremely relevant for understanding fundamental biological processes and human disorders.

EpiFactors database has been originally developed to provide a compilation of functional information about human and mouse epigenetic regulators, their complexes, and expression in multiple cell types to facilitate the work of researchers in the field of epigenetics (13). The information included in EpiFactors served different user needs and had multiple applications. EpiFactors has been used in such rapidly growing areas as organoid formation, pan-cancer driver mutation screening, and Sars-CoV-2 infection research (14–16). Recently, EpiFactors served as a reference epigenetic protein atlas to profile the genetic determinants of chromatin accessibility with single-cell CRISPR screening (17).

Guided by an original definition of epigenetic factors, we avoided an enormous expansion down the regulatory networks with no clear boundaries between epigenetic and non-epigenetic regulation. The majority of borderline cases were not included at that time since their role in epigenetic regulation was not understood. However, recently an increasing evidence supports new molecules and mechanisms of epigenetic regulation. Thus, it is necessary to further curate and update Epifactors in order to maintain its relevance.

Long noncoding RNA (lncRNA) are finally acknowledged as key players in epigenetics, making it critical to systematize information about their role in epigenetic regulation. LncRNAs represent transcripts longer than 200 nucleotides that do not encode functional proteins. This broad definition covers a large and highly heterogeneous group of RNAs with different biogenesis and functions (18,19). According to different estimates, there are 16 000–100 000 lncRNAs in human cells. The ability to bind various proteins, DNA and RNA molecules enables lncRNAs to affect replication, transcription, translation, DNA repair, and chromatin regulation (20). During the development of the first version of Epifactors database, they were considered borderline cases since at that time the role of RNAs was not clear for the majority of the cases. Despite the fact that this field is still largely unexplored and information about the functions of numerous lncRNAs remains unknown, recent studies have shown that a growing number of lncRNAs affect gene expression through epigenetic regulatory pathways (20–22).

There are several mechanisms for lncRNAs to affect gene expression in epigenetic manner. Synthesis of lncRNAs can affect transcription on the same or the opposite strand causing the displacement of Pol II from it or changing the choice of exons to be included in the transcript or acting as promoter switch (23). They can directly bind DNA generating hybrid DNA-RNA structures (both double and triple helices) or nascent RNA which could be recognized by transcription factors and histone modifiers and therefore influence chromatin accessibility and mediate gene silencing or activation (24–26). LncRNA can also act as a scaffold for protein complexes. It can serve as a factor driving chromatin looping between enhancer and promoter regions (27). By binding proteins, lncRNAs can either sequester them or modulate their activity, for example, regulating the ability of proteins to bind chromatin (28,29). Being bound to an epigenetic protein or a protein complex, lncRNA can also function as a guide and attract its partner to specific genomic locations (30). Taking into consideration a vast number of reported lncRNAs in the genome and a huge variability of their function, carefully curated and summarized data on lncRNAs may help researches to uncover their role in transcription regulation and in reconstruction of regulatory networks.

Since information about lncRNAs is extremely relevant for researchers in the field of regulatory genomics, various databases compile lncRNA data. NONCODE and LNCipedia databases (31,32) provide information about the majority of annotated lncRNAs regardless of their functions. They annotate lncRNA transcripts with general information about their sequence, structure, expression, conservation, and disease relevance with expression profile. In addition, LNCipedia accompanies entries with information about their secondary structure information, protein-coding potential and microRNA binding sites (32). LncRNAdb (33) was a database containing comprehensive annotations of eukaryotic lncRNAs including functional evidence. However, it is currently unavailable. Databases DIANA-LncBase (34) and LnCeCell (35) compile information on lncRNAs acting as miRNA sponges. DIANA-LncBase represents a source of experimentally supported miRNA targets on non-coding transcripts, while LnCeCell illustrates cell-specific lncRNA-associated ceRNA networks. dbEssLnc (36) is a database focused only on lncRNAs which are important in establishing minimal genomes of living cells or involved in cancerogenesis. It considers lncRNAs with non-epigenetic mechanisms of action as well as lncRNAs acting as epigenetic regulators. HiMoRNA (37) database is focused on lncRNAs presumably involved in regulation of histone modifications. It provides a comprehensive collection of lncRNA–genomic loci for which lncRNA expression is significantly correlated with the histone modification signal across multiple cell types and tissues but it does not incorporate information on lncRNA known functions in epigenetic regulations.

Thus, despite the availability of resources on both epigenetic regulation and lncRNAs, neither of them provides a compilation of functional information about the epigenetic functions of lncRNAs. Here we present an update of the EpiFactors database with a new section for long noncoding RNAs as a new epigenetic regulator class. The section contains 124 entries annotated with information on their function, mechanism of action, targets, and general data with relevant references and PubMed IDs supporting this information. We also updated the database sections for protein and protein complexes with 91 entries in addition to the previously added entries.

EPIFACTORS CONTENT UPDATE

The main feature in the EpiFactors update is the addition of lncRNAs as a new type of regulators. The respective novel section is populated with 124 new entries. Previously existing sections of the database were updated with current information about the existing entries and 91 new regulators: 81 proteins, six histones and four protein complexes.

Updating the definition of the epigenetic factors

The original version of EpiFactors introduced the definition of epigenetic factors allowing to decide which proteins should be included. This definition covered the core proteins involved in epigenetic regulation such as histones, histone variants, protamines, histone chaperones, histone modifiers, readers of histone modifications, chromatin remodelers, DNA and RNA modifiers, readers of DNA and RNA modifications, and protein cofactors forming complexes with epigenetic factors if they are important for the activity of the complexes. To include a new type of regulators in the database, this definition has been extended with lncRNAs that regulate gene expression at the transcriptional level or regulate the expression of other epigenetic factors at any level.

Data sources

To find new protein epigenetic regulators we manually screened the UniProt database with 'human' as species and keywords 'methylation', 'chromatin', 'histone', and 'protamine' as they were used previously for the same purpose. We selected only reviewed instances published in 2015 and later. To include RNA modifiers, we used 'RNA modification' and 'RNA methylation' keywords. To update protein complexes, we used the Complex Portal database with 'Homo sapiens' as species and the 'chromatin' keyword. The database search was performed in May 2022.

As a starting point to select lncRNAs involved in epigenetic regulation, recent reviews have been used (20–22) and complemented by lncRNAs collected from literature over the years in the lab. Further, results were manually checked to extract records that fit the definition of an epigenetic factor. Thus, only molecules with a proven role in epigenetic regulation were actually included in the database.

Change of annotation

To annotate entries of the new lncRNAs section the following fields were used: 'HGNC approved symbol', 'HGNC ID', 'HGNC approved name', 'Entrez gene ID', 'Alternative names', 'HGNC gene family tag', 'HGNC gene family description', 'Function', 'PMID for information on the function', 'Target molecule', 'Target entity', 'PMID for information on target', 'Comment'.

Field 'function' contains possible ways of epigenetic regulation mediated by lncRNAs. As mechanisms of lncRNAs action are very diverse, we decided to characterize them with the following categories to define groups of lncRNAs:

- Chromatin remodeler/Histone modifier/DNA modifier/TF/Splicing factor recruitment
- Protein sequestration
- Modulation of protein functions
- Chromatin looping
- Promoter switching
- Transcription machinery interference
- miRNA sponging
- RNA binding
- Protein binding

A category 'Protein binding' was used to characterize lncRNAs which are shown to bind their target proteins but the exact mechanism by which these lncRNA–protein complexes implement their function is unknown.

EPIFACTORS STRUCTURE AND CONTENT MODIFICATION

The Epifactors database was modified by adding a new section 'lncRNAs' for a new class of epigenetic regulators. The simplified/detailed scheme of updated database tables is shown in Figure 1 and in Supplementary Figure S1 respectively.

Content summary statistics

In total, six histone variants, 118 complexes, 124 lncRNAs, and 81 proteins were found during the search for updated information on epigenetic factors with UniProt, Complex Portal, and literature sources. After manual filtering, only 81 proteins, 124 lncRNAs, six histone variants, and four protein complexes were included in the database. The added 124 lncRNA were annotated based on their function (Supplementary Table S1) and the function of their targets (Supplementary Table S2).

Also, six proteins in the databases were updated with new information about complexes they are involved in, and UniProt references for the links supporting complex formation have been reported.

Proteins added to the database since 2015 are presented in table S3 in several functional groups. Chromatin remodeling proteins MIS18A, MIS18BP1, and OIP5, members of a complex Mis18 (also included in the database), regulate epigenetic states of centromeric chromatin. The complex interacts with DNMT3A and DNMT3B recruiting them to the centromeric region. As Mis18 provides access of CENPA-specific chaperone HJURP to centromeres, it defines centromeric localisation of CENPA and maintains normal chromosome segregation during mitosis (38).

RNA modificators METTL3, METTL14, WTAP, ZC3H13, CBLL1 and VIRMA are members of a methyltransferase complex WMM. It establishes degradation mark m6A in RNA molecules affecting their stability. Thus, WMM is implicated in regulation of cell differentiation of embryonic and hematopoietic stem cells by destabilization of transcripts (39). WMM also mediates random X-inactivation by methylation of Xist-RNA (40).

A large group of proteins involved in alternative splicing was added to the database as well. For example, ACINU, EIF4A3, KHDRBS1, MAGOH, PQBP1, RBM11, RBM8a, RNPS1, RBM5 and ZBTB7A are shown to regulate alternative splicing of apoptotic regulators (41–45).

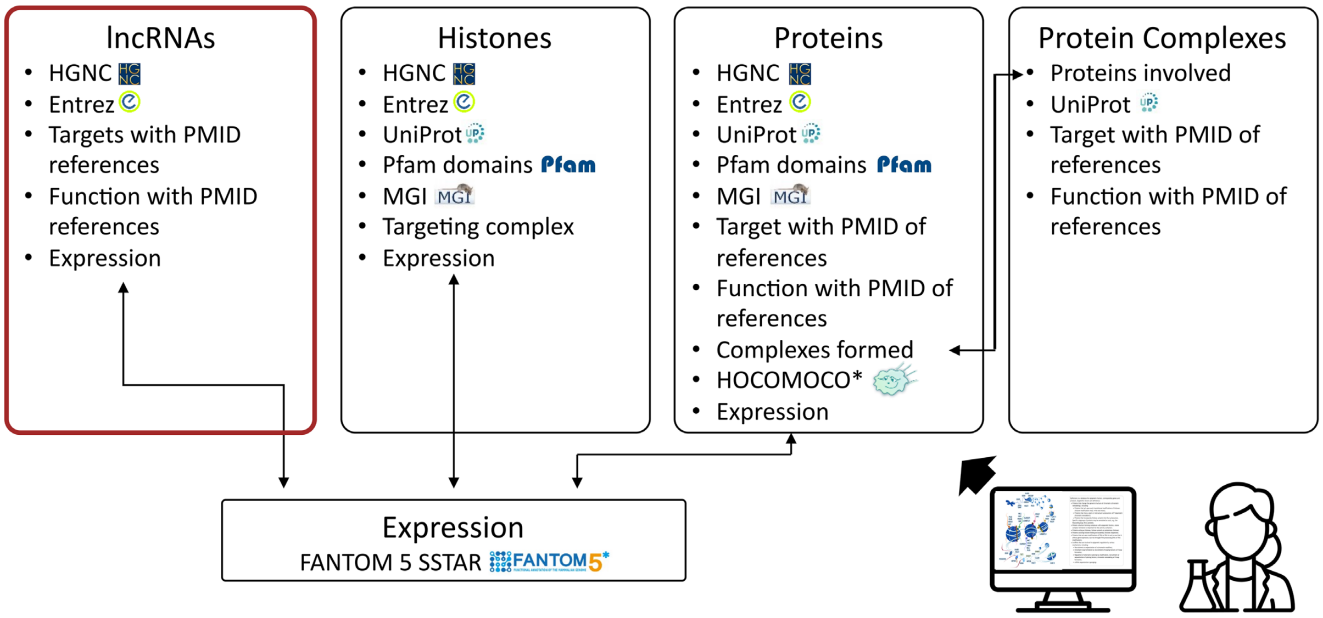

Figure 1. Simplified structure of the Epifactors DB.

CELF family proteins and RBM24 control muscle differentiation (46,47). SRRM regulates alternative splicing events in genes with important neuronal functions such as the RE1-silencing transcription factor (48). DDX5 and DDX17 are coregulators of master transcriptional regulators of differentiation and control several layers of gene expression (47).

Besides WMM and Mis18 complexes mentioned above, complexes containing proteins reported in the first release of EpiFactors were also added. Particularly, there is MSL histone acetyltransferase complex is composed of MSL1, MSL2, MSL3, KAT8 proteins. The complex is responsible for genome-wide H4K16 acetylation and regulates transcription and DNA damage repair processes (49). Proteins DDB2, DDB1, RBX1, CUL4B and CUL4A form CUL4-DDB-ROC1 histone ubiquitination complex. It is involved in DNA repair. CUL4-DDB-ROC1 recognizes UV-induced cyclobutane pyrimidine dimers in chromatin, ubiquitinates histones and other chromatin-associated proteins located around the DNA lesion. Ubiquitination marks promote the removal of ubiquitinated histones from the nucleosome and initiate DNA repair (50). All new complexes are represented in table S4.

USE CASE

EpiFactors can be used in multiple ways. For example, lncRNA JPX has been known for a long time as an activator of XIST in a dosage compensation mechanism (51). Only recently the mechanism of JPX functioning has been discovered: JPX binds CTCF and extricates CTCF from one of the XIST alleles, in this way activating it (52,53). Additionally, JPX interacts with miRNAs miR-145-5p and miR-155-5p acting as a molecular sponge (54,55). All this information with appropriate links is summarized on a JPX page available by direct search by lncRNA name as well as by screening the lncRNAs page (see Figure 2). By filtering only cell types and tissues with the highest expression of JPX (expression, RLE > 10, quantile over all genes > 0.9) a user gets an idea that JPX is highly overexpressed in pineal and pituitary glands, thalamus, globus pallidus, substantial nigra and other parts of the subcortical structures of the brain. Thus, EpiFactors provides an essential summary information on the lncRNA JPX and facilitates further research.

IMPLEMENTATION, WEB INTERFACE AND VISUALIZATION

EpiFactors is available online via a user-friendly web interface implemented as a Ruby-on-Rails front-end with an SQLite back-end. We updated the front page of the database, so now the additional section can be accessed through 'lncRNA' link as well as through 'Genes', 'Complexes', 'Histones and protamines' and 'Expression', either directly or by using keyword search. Each data table contains a customizable set of columns presenting information on respective entities. A user can also browse individual histones, protamines, epigenetic modifiers, their complexes and lncRNAs.

DOWNLOADS

All tables from the current version of the EpiFactors can be downloaded in a csv (comma-separated values) format. The downloaded file contains all rows and columns that are currently visible, as well as corresponding external links to facilitate downstream analysis. The previous version of the EpiFactors can also be downloaded as a .csv file.

EPIFACTORS SUMMARY

EpiFactors is a web-accessible database that provides carefully curated information about human and mouse proteins

HGNC approved symbol	JPX
HGNC ID	HGNC:37191
Alternative names	NCRNA00183, ENOX, LINC00183, DCBALD06
HGNC approved name	JPX transcript, XIST activator
Entrez gene ID	GeneID:554203 (SSTAR profile)
HGNC gene family tag	#
HGNC gene family description	Long non-coding RNAs with non-systematic symbols
Function	Modulation of protein functions, miRNA sponging
PMID for reference on function	PMID:23791181, PMID:31253987, PMID:30091314, PMID:34856126
Target molecule type	RNA, Protein
Specific target	CTCF, miR-145-5p, miR-155-5p
Target UniProt ID	CTCF_HUMAN
PMID for reference on targets and products	PMID:23791181, PMID:31253987, PMID:30091314
Comment	Jpx bind CTCF and regulates its anchor site selection therefore controlling formation of chromosome loops. Jpx activates Xist by evicting CTCF from one Xist allele.
Status of entry	New

Expression statistics

Expression range:	5.98 to 184.96
Mean expression:	33.27 ± 19.54
Median expression:	27.87

Sample class	Sample	Expression (RLE-normalized CAGE tags per million)	Quantile over all genes
		>10	>=0.9
▲ TISSUE (8)			
tissue	pineal gland, adult, donor10252 (FANTOM5 SSTAR)	185.0	0.943
tissue	pituitary gland, adult, donor10252 (FANTOM5 SSTAR)	166.9	0.952
tissue	pituitary gland - adult, donor10196 (FANTOM5 SSTAR)	129.3	0.939
tissue	spinal cord, adult, donor10252 (FANTOM5 SSTAR)	123.0	0.912
tissue	thalamus, adult, donor10252 (FANTOM5 SSTAR)	113.7	0.922
tissue	substantia nigra, adult, donor10252 (FANTOM5 SSTAR)	105.8	0.916
tissue	globus pallidus, adult, donor10252 (FANTOM5 SSTAR)	104.2	0.912
tissue	caudate nucleus, adult, donor10252 (FANTOM5 SSTAR)	95.6	0.904

Figure 2. Summary for an lncRNA Jpx in the EpiFactors. Information mentioned in the text is highlighted.

and complexes involved in epigenetic regulation (see Figure 1). The current version is expanded by the addition of lncRNAs involved in epigenetic regulation. We believe that the database will be a valuable resource for researchers working in the rapidly growing field of epigenetics.

FUTURE DEVELOPMENTS

We keep collecting the information related to the content of the EpiFactors. Repeated literature searches are planned to allow for the identification and integration of new entries into the database on a regular basis. Cross-references to HiMoRNA or other databases related to lncRNAs will be added shortly. We will also consider the inclusion of data for other model organisms, to broaden the scope of the database to a larger audience. Any input from groups and individuals with specific areas of epigenetic expertise is welcome.

DATA AVAILABILITY

Code of the databases is openly available at https://github.com/autosome-ru/epifactors_webapp/tree/master.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

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Conflict of interest statement. None declared.

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