ELM—the database of eukaryotic linear motifs

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ABSTRACT

Linear motifs are short, evolutionarily plastic components of regulatory proteins and provide low-affinity interaction interfaces. These compact modules play central roles in mediating every aspect of the regulatory functionality of the cell. They are particularly prominent in mediating cell signaling, controlling protein turnover and directing protein localization. Given their importance, our understanding of motifs is surprisingly limited, largely as a result of the difficulty of discovery, both experimentally and computationally. The Eukaryotic Linear Motif (ELM) resource at http://elm.eu.org provides the biological community with a comprehensive database of known experimentally validated motifs, and an exploratory tool to discover putative linear motifs in user-submitted protein sequences. The current update of the ELM database comprises 1800 annotated motif instances representing 170 distinct functional classes, including approximately 500 novel instances and 24 novel classes. Several older motif class entries have been also revisited, improving annotation and adding novel instances. Furthermore, addition of full-text search capabilities, an enhanced interface and simplified batch download has improved the overall accessibility of the ELM data. The motif discovery portion of the ELM resource has added conservation, and structural attributes have been incorporated to aid users to discriminate biologically relevant motifs from stochastically occurring non-functional instances.

INTRODUCTION

Short linear motifs (SLiMs, LMs or MiniMotifs) are regulatory protein modules characterized by their compact interaction interfaces (the affinity and specificity determining residues are usually encoded between 3 and 11 contiguous amino acids (1)) and their enrichment in natively unstructured, or disordered, regions of proteins (2). As a result of limited intermolecular contacts with their interaction partners, SLiMs bind with relatively

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low affinity (in the low-micromolar range), an advantageous attribute for use as transient, conditional and tunable interactions necessary for many regulatory processes. Due to the limited number of mutations necessary for the genesis of a novel motif, SLiMs are amenable to convergent evolution, functioning as a driver of network evolution by adding novel interaction interfaces, and thereby new functionality, to proteins. This evolutionary plasticity facilitates the rapid proliferation within a proteome, and as a result, motif use is ubiquitous in higher eukaryotes.

SLiMs play an important role for many regulatory processes such as signal transduction, protein trafficking and post-translational modification (3,4). Their importance to the correct functionality of the cell is also reflected by the outcome of motif deregulation. For example, point mutations in SLiMs have been shown to lead to severe pathologies such as ‘Noonan-like syndrome’ (5), ‘Liddle’s syndrome’ (6) or ‘Retinitis pigmentosa’ (7). Furthermore, mimicry of linear motifs by viruses to hijack their hosts’ existing cellular machinery plays an important role in many viral life cycles (8). However, despite their obvious importance to eukaryotic cell regulation, our understanding of SLiM biology is relatively limited, and it has been suggested that, to date, we have only discovered a small portion of the human motifs (9).

Several resources are devoted to the annotation and detection of SLiMs [Prosite (10), MiniMotifMiner (11) and Scansite (12)]. Here, we report on the 2012 status of the Eukaryotic Linear Motif database.

THE ELM RESOURCE

The ELM initiative (http://elm.eu.org) has focused on gathering, storing and providing information about short linear motifs since 2003. It was established as the first manually annotated collection of SLiM classes and as a tool for discovering linear motif instances in proteins (13). As it was mainly focused on the eukaryotic sequences, it was termed the Eukaryotic Linear Motif resource, usually shortened to ELM. The ELM resource consists of two applications: the ELM database of curated motif classes and instances, and the motif detection pipeline to detect putative SLiM instances in query sequences. In the ELM database, SLiMs are annotated as ‘ELM classes’, divided into four ‘types’: cleavage sites (CLV), ligand binding sites (LIG), sites of post-translational modification (MOD) and subcellular targeting sites (TRG) (Table 1). Currently, the ELM database contains 170 linear motif classes with more than 1800 motif instances linked to more than 1500 literature references (Table 1). Each class is described by a regular expression capturing the key specificity and affinity determining amino acid residues. A regular expression is a computer-readable term for sequence annotation and is used by the ELM motif detection pipeline to scan proteins for putative instances of annotated ELM classes. The search form for sequence input is shown in Figure 1, while the results page showing the putative and annotated instances is illustrated in Figure 2.

The ELM resource is powered by a PostgreSQL relational database for data storage and a PYTHON web framework for data retrieval/visualisation. The main tables within the database contain information about ELM classes, ELM instances, sequences, references, taxonomy and links to other databases [the database structure is described in greater detail in (14)].

New ELM classes

Since the last release (14), 24 new ELM classes have been added to the ELM database (Table 1) and several more have been updated. One of the newly annotated motif classes is the AGC kinase docking motif (LIG_AGCK_PIF), consisting of three distinct classes. It is present in the non-catalytic C-terminal tail of AGC kinases that constitute a family of serine/threonine kinases consisting of 60 members that regulate critical processes, including cell growth and survival. Deregulation of these enzymes is a causative factor in different diseases such as cancer and diabetes. The motif interacts with the PDK1 Interacting Fragment (PIF) pocket in the kinase domain of AGC kinases. It mediates intramolecular binding to the PIF pocket, serving as a cis-activating module together with other regulatory sequences in the C-tail. Interestingly, in some kinases the motif also acts as a PDK1 docking site that trans-activates PDK1, which itself lacks the regulatory C-tail, by interacting with the PDK1 PIF pocket. PDK1 in turn will phosphorylate and activate the docked kinase. Other novel classes (Table 2) include phosphodegrons, which are important mediators of phosphorylation-dependent protein destruction, and the LYPxL motif, which is involved in endosomal...

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Table 1. Summary of data stored in the ELM database

| Number of functional site entries | ELM motif classes | ELM motif instances | Links to PDB structures | GO terms | Pubmed links |
|----------------------------------|-------------------|---------------------|------------------------|----------|--------------|
| Totals                           | 115               | 170                 | 1840                   | 195      | 340          | 1561         |
| By category                      |                   |                     |                        |          |              |              |
| LIG                              | 111               | Human               | 1004                   | Biological process | 173          | From ELM motif | 787  |
| MOD                              | 30                | Mouse               | 160                    | Cell compartment | 74           | From instance | 1071 |
| TRG                              | 21                | Rat                 | 102                    | Molecular function | 93          |              |      |
| CLV                              | 8                 | Fly                 | 67                     | Other      | 417          |              |      |
|                                 |                   | Yeast               | 90                     |           |              |              |      |

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sorting of membrane proteins but is also implicated in retrovirus budding.

New ELM instances

Annotated ELM instances serve as representative examples of the respective ELM class. They are also invaluable for the computational analysis and classification of motifs (15). Therefore, special emphasis has been put on the curation of more than 500 novel ELM instances (in 40 different classes) by scanning and annotating more than 400 articles. The number of protein databank (PDB) entries annotated have been increased to 195 (Table 1), meaning that for ~10% of all instances there is a 3D
protein structure annotated, giving more detailed information about the biological context of the respective motif.

NEW FEATURES

The ELM website at http://elm.eu.org can be used in two ways: first, as a front-end to explore the ELM database of curated ELM classes and instances, and second, to run the motif detection pipeline to detect putative SLiM instances in query sequences. Both interfaces have been improved with the most notable changes listed below.

User interface

The database user interface, having been stable for many years, has been overhauled and replaced by a novel interface introducing several new features (Figure 1). Up-to-date web technologies have been used to improve the general user experience: the PYTHON framework DJANGO (http://www.djangoproject.com) dynamically creates and serves all HTML pages, while JavaScript was used to make the whole site more interactive and thus improve the user experience. In particular, the ELM detail pages (Figure 3), which hold the most

Figure 2. ELM motif detection pipeline output page. The top legend explains the different colors/symbols used. The graphical output of ELM concentrates the output of multiple sequence classification algorithms; phosphorylation sites from Phospho.ELM, protein domains detected by SMART/Pfam, disorder predictions by GlobPlot and IUPred and secondary structure (18). The lower part contains the annotated and putative ELM instances for the given protein sequence (Epsin1, UniProt accession Q9Y6I3). The background is colored according to the structural information available. Each box represents one ELM instance, the color of which indicates the likelihood that this instance is functional: grey instances are buried within structured regions, while shades of blue represent instances outside of structured regions and hint on sequence conservation, with pale blue representing weak sequence conservation and dark blue indicating strong sequence conservation. Red ellipses or boxes mark instances that are annotated in the query sequence or a homologous sequence, respectively.
important information about each ELM class including references, regular expression, taxonomic distribution and gene ontology terms (Table 3), have been updated by annotating the protein domain interacting with the respective motif. Where available, a 3D model of representative protein databank structures of linear motif interactions was added to the ELM detail page (Figure 3, top right).

To cope with the increasing amount of annotated classes as well as instances, a novel query interface was introduced to assist the user in finding information of interest. The ELM browser (Figure 4) now features a search interface for free text search. In addition, the search results can also be filtered and reordered using buttons (Figure 4, left side) and table headers, respectively, and be downloaded as tab-separated values (TSV).

Further, improvements to the ELM database include revising the experimental methods used for annotation by using a standardized methods vocabulary [in sync with PSI-MI ontology (16,17)].

A candidate page has been introduced to display novel ELM classes that have not yet been annotated in detail or are currently undergoing annotation. We invite researchers to send us their feedback and expert opinion on these classes and to contribute novel motif classes that will be added to the candidate page and ultimately be turned into full ELM classes (Figure 5). Minimum requirements are at least one literature reference as well as a short description. In addition, a draft regular expression or a 3D structure showing the relevant interaction would also be helpful. Currently, the number of possible ELM classes on this candidate list (awaiting further annotation) exceeds the number of completely annotated classes, indicating the great demand for further annotation.

Graphical representation of sequence search

The ELM motif detection pipeline scans protein sequences for matches to the regular expressions of annotated ELM classes (Figure 2). The query output combines these putative instances with information from the database (annotated ELM instances) as well as predictions from different algorithms/filters. The ELM resource employs a structural filter (18) to highlight and mask secondary structure elements, as well as SMART (19) to detect protein domains. Furthermore, an additional disorder prediction algorithm (IUPred) (20) has been included to predict ordered/disordered regions within the protein. IUPred uses a cutoff of 0.5 to classify a sequence region as either structured or disordered, with values above this threshold corresponding to disorder, highlighted in green background and lower values indicating structured regions, displayed in red background in the output graph. Disorder and domain information is combined by

Table 2. List of novel ELM classes

| Identifier          | Description                                                                                                                                 |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| LIG_Actin_WH2_1     | Motifs, present in proteins in several repeats, which mediate binding to the hydrophobic cleft created by subdomains 1 and 3 of G-actin     |
| LIG_Actin_WH2_2     |                                                                                                                                             |
| LIG_Actin_RPEL_3    |                                                                                                                                             |
| LIG_AGCK_PIF_1      | The AGCK docking motif mediates intramolecular interactions to the PDK1 Interacting Fragment (PIF) pocket, serving as a cis-activating module |
| LIG_AGCK_PIF_2      |                                                                                                                                             |
| LIG_AGCK_PIF_3      |                                                                                                                                             |
| LIG_BIR_I_1         | IAP-binding motifs are found in pro-apoptotic proteins and function in the abrogation of caspase inhibition by inhibitor of apoptosis proteins in apoptotic cells |
| LIG_BIR_I_1         |                                                                                                                                             |
| LIG_BIR_I_2         |                                                                                                                                             |
| LIG_BIR_I_3         |                                                                                                                                             |
| LIG_BIR_I_4         |                                                                                                                                             |
| LIG_eIF4E_1         | Motif binding to the dorsal surface of eIF4E                                                                                               |
| LIG_eIF4E_2         |                                                                                                                                             |
| LIG_EVH1_3          | A proline-rich motif binding to EVH1/WH1 domains of WASP and N-WASP proteins                                                              |
| LIG_HCF-1_HBM_1     | The DHxY Host Cell Factor-1 binding motif interacts with the N-terminal kelch propeller domain of the cell cycle regulator HCF-1          |
| LIG_Integrin_isoDGR_1| Present in proteins of extracellular matrix which upon deamidation forms biologically active isoDGR motif which binds to various members of integrin family |
| LIG_LYPX1_L_2       | The LYPxL motif binds the V-domain of Alix, a protein involved in endosomal sorting                                                        |
| LIG_LYPX1_S_1       |                                                                                                                                             |
| LIG_PAM2_1          | Peptide ligand motif that directly interacts with the MLLE/PABD domain found in poly(A) binding proteins and HYD E3 ubiquitin ligases     |
| LIG_PIKK_1          | Motif located in the C terminus of Nbs1 and its homologous interacting with PIKK family members                                             |
| LIG_Rb_pABgroove_1  | The LxxLF motif binds in a deep groove between pocket A and pocket B of the Retinoblastoma protein                                         |
| LIG_SCF_FBW7_1      | The TPxS phospho-dependent degron binds the FBW7 F box proteins of the SCF (Skp1-Cullin-Fbox) complex                                     |
| LIG_SCF_FBW7_2      |                                                                                                                                             |
| LIG_SPAK-OSR1_1     | SPAK/OSR1 kinase binding motif acts as a docking site which aids the interaction with their binding partners including the upstream activators and the phosphorylated substrates |

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The conservation of linear motifs can help in assessing the functional relevance of putative instances, with functional instances showing higher overall sequence conservation than non-functional ones (21). Therefore, sequence conservation of the query protein is calculated using a tree-based conservation scoring method (22) and highlighted in the graphical output. Here, lighter shades of blue represent low conservation while dark blue shading corresponds to high-sequence conservation. The actual conservation score can be inspected by moving the mouse over the respective ELM instance (Figure 2).

The functionality of linear motifs can be modulated by modifications such as phosphorylation (23,24). To enable the user to investigate phosphorylation data in the context of putative linear motif instances, phosphorylation annotations from the Phospho.ELM resource (25) have been added to the graphical output (Figure 2, top row).
The phosphorylated residues are highlighted in different colors (serine: green, threonine: blue, tyrosine: red); each phosphorylation site is linked to a page showing detailed information about the respective modification site from the manually curated data set of the Phospho.ELM resource.

VIRAL INSTANCES

The importance of the short linear motifs in virus–host interactions makes the ELM resource an important tool for the viral research community. For example, Cruz et al. (26) analyzed a protein phosphatase 1 (PP1) docking motif in ‘protein 7’ of transmissible gastroenteritis virus using the ELM class LIG_PP1. This conserved sequence motif mediates binding to the PP1 catalytic subunit, a key regulator of the cellular antiviral defense mechanisms, and is also found in other viral proteomes, suggesting that it might be a recurring strategy to counteract the hosts’ defense against RNA viruses by dephosphorylating eukaryotic translation initiation factor 2a and ultimately ribonuclease L.

To reflect our increasing awareness of viral motifs (8), special focus has been attributed to the annotation of viral instances in the ELM database: in the latest release, more than 200 novel ELM instances found in 84 different viral taxons have been added. The notion of viruses abusing existing SLiMs in their hosts is demonstrated by viral instances being annotated alongside instances in their hosts’ proteins. For example, the ELM class LIG_PDZ_Class_1 contains 12 instances in human proteins but has recently been expanded with 5 instances from 5 different human pathogenic virus proteins.
of these interactions results in myofibrillar myopathies (32). Additionally, ELM annotations can contribute to high-throughput screenings (33) as well as development of novel algorithms (34–36), methods (37) and databases (38). Furthermore, the highly curated data of the ELM resource are used as a benchmarking data set to evaluate the accuracy of prediction algorithms (21,39,40).

For any such analysis, the user should be aware that many matches to ELM regular expressions are false positives. Before conducting experiments based on ELM results, it is strongly advisable to check if a motif match is conserved, exposed in a cell compartment in which the motif is known to be functional. The ELM resource applies several filters to provide the user with such information that should ideally also be supported by the experimental evidence.

**SUMMARY**

The importance of SLiMs is highlighted by the growing number of instances with relevance to diseases or viruses. Yet, despite their importance and abundance, our understanding of linear motifs is still limited. This is mainly owing to the fact that they are still quite difficult to predict computationally and to investigate experimentally (3,41,42). By better understanding the biology of linear motifs, we hope to increase our insight into diseases and viruses (and vice versa). The ELM resource tries to aid the researcher in the search for putative SLiM instances by providing a feature-rich toolset for sequence analysis. Consequently, with the aforementioned additions and changes, we hope that the ELM resource continues to be a valuable asset to the community.

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