Computational Prediction of Proteins Sumoylation: A Review on the Methods and Databases

Abstract

Protein is one of the biological macromolecules, which plays vital roles in the cell. There are numerous post-translational modifications (PTMs) that strongly affect proteins and their functionality. A PTM occurs when a chemical functional group is being added on or removed from a specific amino acid. A PTM may consist of both enzymatic and non-enzymatic changes. Recent studies have introduced more than 500 different PTM types. SUMOylation is one of the most important PTM; disruption in SUMOylation process affects the cell function and one of the consequences of this change is cell morphology disorder and leads to a variety of sever diseases such as Alzheimer’s disease and Parkinson’s disease. In this paper we have reviewed the current state-of-the-art in silico methods to predict SUMOylation as well as related databases.

Keywords: Post-transitional modification; PTM; SUMOylation; Predicted; Databases; Bioinformatics; Algorithms

Introduction

Being happened in the nucleus, cytoplasm and organelles of cells; PTM is considered as one of the most important processes in protein functionality [1]. Generally, mass spectrometry data are applied to identify the PTMs and their related sites [2]. However, the experimental data of PTMs are very limited due to the sophistication and high expenses of the experiments. Recently, the practice of applying the computational methods to predict the protein PTM has interested many researchers [3].

Post-translational modification by the Small Ubiquitin-like Modifier (SUMO) proteins, a process termed SUMOylation, is involved in many fundamental cellular processes. SUMOylation is a eukaryotic post-translational modification, which consists of a reversible attachment of members of the Small Ubiquitin-like Modifier (SUMO) protein family on a protein substrate resulting in the dynamic regulation of its biochemical properties [4]. Proteins involved in many fundamental cellular processes like DNA repair, transcriptional control, chromatin organization, macromolecular assembly and signal transduction are SUMOylated [5]. SUMOylation is also discovered to be involved in various diseases and disorders especially neural ones, such as Alzheimer’s disease and Parkinson’s disease [6-8].

The size of SUMO proteins is almost 10 kDa and three-dimensional structures of these proteins are similar to ubiquitin proteins. Interestingly, SUMO proteins have different distribution of surface charge and have less than 20% amino acid sequence similarity [10]. During SUMOylation, a SUMO protein is attached to the target protein, which has an acceptor lysine, through three enzymes and then makes the modification. Finally, SUMO is detached by sumo-specific protease [4] (Figure 2). SUMO proteins have been discovered in a wide range of eukaryotic organisms [9]. SUMO family has four isoforms in human, one isoform in yeast and eight isoforms in plants [10,11]. However, in most vertebrates family SUMO has three isoforms that are known as SUMO1 namely (sentrin-1, PIC1, GMP1, Ubl1, Smt3c) and SUMO2 namely (sentrin-2, Smt3b) and SUMO3 namely (sentrin-3, Smt3a) [11-15]. Figure 3 shows the number of papers that have reported experimentally verified SUMOylation in different years, these information are based on the PubMed IDs reported by dbPTM [16], recently published database about PTM data.

The SUMOylation prediction

Almost computational methods for SUMOylation prediction use sequence information in the neighborhood of the lysine amino acid. Specially considering sequence motifs that are recognized by SUMO. Although there are many lysine residues in a protein, but few of these residues in certain motifs are SUMOylation site [17]. Many SUMOylation sites contain a consensus sequence motif of WKXE, in which W represents aliphatic amino acids such as I, V, L, A, P or M; X represents each amino acid and E represents glutamic acid. However, the experimental data analysis demonstrates that nearly 23% of SUMOylation sites do not follow SUMOylation of this consensus motif [18,19]. In addition to the consensus motif, other SUMOylation motifs are reported such as SUMOylation negatively charged amino acid motif (NDSM: WKXE (D/E), SUMOylation dependent phosphorylation motif (PDSM: WKXEXXXP) and SUMO- Style motif (WKXEP) [20,21]. Generally, a computational method uses appropriate features of the potential SUMOylation sites considering the experimentally validated data to train a model for SUMOylation prediction. So, thee availability of the valid databases is crucial to construct accurate models. Then main databases for SUMOylation have been reviewed in Table 1 & 2.
Figure 1: Schematic drawing of the three Sumo proteins using software YASARA.
(A) 2MW5: Solution Structure of Human Small Ubiquitin-like Modifier protein-1 (SUMO-1) in Homo sapiens.
(B) 1L2N: Smt3 Solution Structure in Saccharomyces cerevisiae.
(C) 1W20: Solution Structure of Human SUMO-2 (SMT3B), a Ubiquitin-like Protein in Homo sapiens.
(D) 1U4A: Solution Structure of Human Small Ubiquitin like Modifier protein-3 (SUMO-3 C47S) in Homo sapiens.

Figure 2: Schematic drawing of the path of SUMOylation protein.
Computational Prediction of Proteins Sumoylation: A Review on the Methods and Databases

Copyright: ©2016 Ramazi et al.

Citation: Ramazi S, Zahiri J, Arab SS, Parandian Y (2016) Computational Prediction of Proteins Sumoylation: A Review on the Methods and Databases. J Nanomed Res 3(5): 00068. DOI: 10.15406/jnmr.2016.03.00068

Figure 3: Schematic drawing of the number of SUMOylation articles in different years.

Table 1: Information on database.

| Database                        | A Brief Description                                                                                                                                 |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Swiss-Prot/Uniprot database     | This database is one of the largest experimental sources for a variety of post-translational modifications of proteins. (www.ebi.ac.uk/uniprot/) |
| Tr EMBL database                | This database contains tools and extensive educational tools for both researchers and scholars. It also provides data about the different types of proteins PTMs and their related changes. |
| DbPTM database                  | This DB provides data on post-translational modifications of proteins. Using this database, protein-protein interactions and their specific protein binding positions with the domain could be identified. (http://dbPTM.mbc.nctu.edu.tw/) |
| HPRD database                   | This database is considered as a reference database. It contains data about the human proteins as well as protein PTM data. (http://www.ebi.ac.uk/RESID/) |
| Phospho site plus database      | Currently, the database contains information on a variety of protein post-translational modifications such as acetylation, methylation, SUMOylation and O- glycosylation. (http://www.phosphorylation.biochem.vt.edu/) |
Table 2: Information on predictions SUMOylation articles.

| Predictor         | Training Feature                          | AC   | SN   | SP   | MCC  | AUC   |
|-------------------|-------------------------------------------|------|------|------|------|-------|
| SUMO plot [22]    | Only sequence                             | 90%  | 80%  | 93%  | 48%  | -     |
| SUMOSP1 [19]      | Only sequence                             | 92.71%| 83.60%| 93.08%| 50.12%| 73%   |
| Boshulietal [23]  | Sequence and physicochemical properties   | 89.18%| 61%  | 61%  | 32%  | -     |
| Find SUMO [24]    | Only sequence                             | 87.40%| 86.40%| 87.50%| -    | -     |
| SUMO pre [10]     | Only sequence                             | 97.71%| 73.96%| 97.67%| 63.64%| -     |
| SUMOSP2 [25]      | Sequence and physicochemical properties   | 97.68%| 67.57%| 99.79%| 67.86%| 92%   |
| SUMO tr [26]      | Sequence and 3D structure and hydrophobicity | 85%  | 95%  | 75%  | 68%  | 85%   |
| See SUMO [21]     | Sequence and physicochemical properties   | 97.68%| 67.57%| 99.79%| 67.86%| 92%   |
| SUMO hydro [27]   | Sequence and physicochemical properties   | 58.30%| 94.40%| 93.30%| 41.90%| -     |
| SUMO hunt [28]    | Only sequence                             | 85%  | 95%  | 75%  | 68%  | -     |
| GPS – SUMO [7]    | Only sequence Hydrophobicity              | -    | -    | -    | -    | -     |

A review of articles from 2004 to 2015, predictions SUMOylation.

Assessing the Performance of the Sumoylation Prediction Methods

There are different assessment measures based the four following basic parameters:

A. “True positive” (TP): the experimentally validated SUMOylation sites that have been correctly predicted by the prediction method.

B. “True negative” (TN): the non-SUMOylation sites that have been correctly predicted.

C. “False positive” (FP): the non-SUMOylation sites that have been incorrectly predicted as SUMOylation sites.

D. “False negative” (FN): the experimentally validated SUMOylation sites that have been incorrectly predicted non-SUMOylation sites.

The most important assessment measures based on the above-mentioned parameters have been described in the following.

a. Sensitivity: sensitivity indicates the percentage of SUMOylation sites that have been predicted correctly.

Sensitivity = \( \frac{TP}{TP+FN} \) (Formula 1-1)

b. Specificity: shows the percentage of non-SUMOylation sites that have been predicted correctly as non-SUMOylation.

Specificity = \( \frac{TN}{TN+FP} \times 100 \) (Formula 1-2)

c. Accuracy: The percentage of the correct prediction.

\( \text{Accuracy} = \frac{TP+TN}{TP+FP+TN+FN} \times 100 \) (Formula 1-3)

d. Matthews correlation coefficient: Matthews correlation coefficient can be calculated using the formula defines [29].

\( \text{MCC} = \frac{(TP)(TN)-(FP)(FN)}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}} \) (Formula 1-4)

e. Area Under Curve: (AUC or “Area Under Curve”), is another measure of classification accuracy, the closer the AUC to one the more accurate the classification.

Conclusion

SUMOylation is one the most important PTM type, which a disruption in this PTM can lead to various diseases such as type 1 diabetes, Parkinson’s disease, Alzheimer’s disease, heart disease, cancer and brain failure. Considering the cost and limitations of the experimental methods, in the recent years, many studies devoted to computational detection of SUMOylation. In this paper, the databases of experimentally verified SUMOylation and the computational methods for the prediction of SUMOylation have been reviewed. While there are promising methods for the SUMOylation prediction, but considering the limited experimental SUMOylation data, there are considerable rooms to improve the SUMOylation prediction tools.

Citation: Ramazi S, Zahiri J, Arab SS, Parandian Y (2016) Computational Prediction of Proteins Sumoylation: A Review on the Methods and Databases. J Nanomed Res 3(5): 00068. DOI: 10.15406/jnmr.2016.03.00068
References

1. Nickle P, Jafari M, Kalantari S (2015) PEIMAN 1.0: Post-translational modification Enrichment, Integration and Matching ANalysis. Database 2015: bav037.

2. Lothrop AP, Torres MP, Fuchs SM (2013) Deciphering post-translational modification codes. FEBS letters 587(8): 1247-1257.

3. Kamath KS, Vasavada MS, Srivastava S (2011) Proteomic databases and tools to decipher post-translational modifications. J Proteomics 75(1): 127-144.

4. Song J, Durrin JK, Wilkinson TA, Krontris TG, Chen Y (2004) Identification of a SUMO-binding motif that recognizes SUMO-modified proteins. Proc Natl Acad Sci 101(40): 14373-14378.

5. Lomeli H, Vázquez M (2011) Emerging roles of the SUMO pathway in development. Cell Mol Life Sci 68(24): 4045-4064.

6. Lu L, Shi XH, Li SJ, Xie ZQ, Feng YL, et al. (2010) Protein sumoylation sites prediction based on two-stage feature selection. Mol Divers 14(1): 81-86.

7. Zhao Q, Xie Y, Zheng Y, Jiang S, Liu W, et al. (2014) GPS-SUMO: a tool for the prediction of sumoylation sites and SUMO-interaction motifs. Nucleic Acids Res 42(33): 9959-9969.

8. Müller S, Ledl A, Schmidt D (2004) SUMO: a regulator of gene expression and genome integrity. Oncogene 23(11): 1996-2008.

9. Seeler JS, Dejean A (2001) SUMO: of branched proteins and nuclear bodies. Oncogene 20(49): 7243-7247.

10. Xu J, He Y, Qiang B, Yuan J, Peng X, et al. (2008) A high accuracy sumoylation site prediction from protein sequences. BMC bioinformatics 9: 1.

11. Hong Y, Rogers R, Matunis MJ, Mayhew CN, Goodson ML, et al. (2001) Regulation of heat shock transcription factor 1 by stress-induced SUMO-1 modification. J Biol Chem 276(43): 40263-40267.

12. Saitoh H, Hinchey J (2000) Functional heterogeneity of small ubiquitin-related protein modifiers SUMO-1 versus SUMO-2/3. J Biol Chem 275(9): 6252-6258.

13. Tatham MH, Kim S, Yu B, Jaffray E, Song J, et al. (2003) Role of an N-terminal site of Ubc9 in SUMO-1,-2, and-3 binding and conjugation. Biochemistry 42(33): 9959-9969.

14. Guo D, Li M, Zhang Y, Yang P, Eckenrode S, et al. (2004) A functional variant of SUMO4, a new IκBα modifier, is associated with type 1 diabetes. Nat Genet 36(8): 837-841.

15. Mechkior F (2000) SUMO-nonclassical ubiquitin. Annual review of cell and developmental biology 16(1): 591-626.

16. Huang KY, Su MG, Kao HJ, Hsieh YC, Jhong JH, et al. (2016) dbPTM 2016: 10-year anniversary of a resource for post-translational modification of proteins. Nucleic Acids Res 44(D1): D435-D446.

17. Hay RT (2005) SUMO: a history of modification. Mol Cell 18(1): 1-12.

18. Mann M, Jensen ON (2003) Proteomic analysis of post-translational modifications. Nat Biotechnol 21(3): 255-261.

19. Xue Y, Zhou F, Fu C, Xu Y, Yao X, et al. (2006) SUMOsp: a web server for sumoylation site prediction. Nucleic Acids Res 34(suppl 2): W254-W257.

20. Martin S, Wilkinson KA, Nishimune A, Henley JM (2007) Emerging extranuclear roles of protein SUMOylation in neuronal function and dysfunction. Nat Rev Neurosci 8(12): 948-959.

21. Teng S, Luo H, Wang L (2012) Predicting protein sumoylation sites from sequence features. Amino Acids 43(1): 447-455.

22. Yu Xue, Fengfeng Z, Huaei L, Guoliang C, Xuebiao Y (2004) SUMO Substrates and Sites Prediction Combining Pattern Recognition and Phylogenetic Conservation. arXiv preprint q-bio/040901.

23. Liu B, Li S, Wang Y, Lu L, Li Y, et al. (2007) Predicting the protein SUMO modification sites based on Properties Sequential Forward Selection (PSFS). Biochem Biophys Res Commun 358(1): 136-139.

24. Friedline CJ, Zhang X, Zehner ZE, Zhao Z (2008) FindSUMO: a PSSM-based method for sumoylation site prediction. Advanced Intelligent Computing Theories and Applications. With Aspects of Artificial Intelligence pp. 1004-1011.

25. Ren J, Gao X, Jin C, Zhu M, Wang X (2009) Systematic study of protein sumoylation: Development of a site-specific predictor of SUMOsp 2.0. Proteomics 9(12): 3409-3412.

26. Yavuz AS, Sezerman U (2010) SUMOtr: SUMOylation site prediction based on 3D structure and hydrophobicity. in 2010 5th Int Symp Heal Informatics Bioinforma.

27. Chen YZ, Chen Z, Gong YA, Ying G (2012) SUMOhydro: a novel method for the prediction of sumoylation sites based on hydrophobic properties. PLoS One 7(6): e39195.

28. Ijaz A (2013) SUMOhunt: Combining spatial staging between lysine and SUMO with random forests to predict sumoylation. ISRN Bioinform.

29. Zahir J, Bozorgmehr JH, Masoudi-Nejad A (2013) Computational prediction of protein-protein interaction networks: algorithms and resources. Curr Genomics 14(6): 397-414.

Citation: Ramazi S, Zahir J, Arab SS, Parandian Y (2016) Computational Prediction of Proteins Sumoylation: A Review on the Methods and Databases. J Nanomed Res 3(5): 00068. DOI: 10.15406/jnmr.2016.03.00068