Correspondence

Meta-analysis of SUMO1
Brian J Wilson

Address: Molecular Oncology Group, Room H5-45, McGill University Health Centre, 687 Pine Avenue West, Montréal, Québec, H3A 1A1, Canada
Email: Brian J Wilson - brian.wilson2@mcgill.ca

Abstract
An abundantly growing body of literature implicates conjugation of SUMO in the regulation of many proteins and processes, yet the regulation of SUMO pathways is poorly understood. To gain insight into the players in the SUMO1 pathway I have performed an in-silico co-expression meta-analysis of SUMO1, comparing many different multi-microarray studies of various normal and human tumour tissues, from the Oncomine database. This serves as a data-driven predictor of pathway partners of SUMO1. While the data obtained need to be confirmed by future independent experiments and can currently only be considered a hypothesis, results implicate defender against cell death (DADI) and the anti-apoptotic DEK oncogene as new pathway partners of SUMO1.

Discussion

Oncomine [1] meta-analysis was performed as previously described [2,3]. Briefly, 15 multi-array studies were analyzed for common overlapping co-expressed genes of SUMO1, using muti-array studies within the Oncomine integrated cancer database. This technique gives insight into which pathways the searched gene (in this case SUMO1) are involved in, although it is impossible to tell if co-expressed gene products are complexed to SUMO1, act upstream of SUMO1 or downstream of SUMO1. Therefore, while limited, this technique is important for generating leads to assess both the pathways SUMO1 is important for, and regulation of SUMO1 itself.

After meta-analysis there were over 400 consistently co-expressed genes at the cutoff of 3 studies (Additional File 1). Table 1 shows the genes with the higher cutoff of 4 studies. This high number may be expected as SUMO1 is a general factor and involved in many processes. I note that the archetype SUMO1-modified promyelocytic leukemia (PML) was co-expressed with SUMO1, acting as validation of the results [4]. While the Ubc9 conjugation enzyme was not found to be co-expressed many other ubiquitin-conjugating enzymes were (UBE2N, UBE4A, UBE2G1, UBE2V2, UBE2E1, UBE2D2, UBE2A, UBE1C, CUL4A), as was the SUMO1 activating enzyme subunit 2 (UBA2). Transcription factors shown to be modified by SUMO were also co-expressed, such as HIF1α, Rb, YY1, and SMAD4 [5-9]. Interestingly RARα is also co-expressed and while it has never been shown to be a target of SUMO1 the PML-RARα fusion has been shown to be a target of SUMO1 mediated degradation [10]. It would be interesting to investigate if RARα itself is a SUMO1 target. Also co-expressed is the NF-κB subunit RelA. While RelA also is not a proven target of SUMO1 NF-κB is regulated indirectly by SUMO1 modification of IκB Kgamma/NEMO or IκB [11,12].

A similar meta-analysis was attempted for SUMO2 and SUMO3. However, SUMO2 was not expressed to levels that allowed for meta-analysis, and the results of SUMO3 meta-analysis gave fewer co-expressed genes than for SUMO1 (Additional File 2). There was a small overlap (37 genes) of co-expressed genes of SUMO1:SUMO3, but this does not necessarily imply that both are involved in completely distinct pathways. Rather, the meta-analysis tech-
### Table 1: Oncomine meta-analysis of SUMO1 co-expressed genes

| GENE      | %     | GENE NAME                                                                 |
|-----------|-------|---------------------------------------------------------------------------|
| SUMO1     | 100%  | SMT3 suppressor of mif two 3 homolog 1 (S. cerevisiae)                    |
| DAD1      | 67%   | defender against cell death 1                                             |
| DEK       | 53%   | DEK oncogene (DNA binding)                                                |
| UBE2N     | 47%   | ubiquitin-conjugating enzyme E2N (UBC13 homolog, yeast)                   |
| SET       | 47%   | SET translocation (myeloid leukemia-associated)                           |
| SLC25A5   | 40%   | solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5 |
| SFRS3     | 40%   | splicing factor, arginine/serine-rich 3                                   |
| RPA1      | 40%   | replication protein A1, 70 kDa                                            |
| RCN2      | 40%   | Reticulocalbin 2, EF-hand calcium binding domain                          |
| RB1       | 40%   | retinoblastoma 1 (including osteosarcoma)                                 |
| PSMD14    | 40%   | proteasome (prosome, macropain) 26S subunit, non-ATPase, 14               |
| PSMC2     | 40%   | proteasome (prosome, macropain) 26S subunit, ATPase, 2                   |
| PSMA2     | 40%   | proteasome (prosome, macropain) subunit, alpha type, 2                   |
| NUP153    | 40%   | nucleoporin 153 kDa                                                      |
| GLO1      | 40%   | glyoxalase 1                                                              |
| DPM1      | 40%   | dolichyl-phosphate mannosyltransferase polypeptide 1, catalytic subunit   |
| DARS      | 40%   | Aspartyl-tRNA synthetase                                                   |
| CD164     | 40%   | CD164 antigen, sialomucin                                                  |
| CCT8      | 40%   | chaperonin containing TCP1, subunit 8 (theta)                             |
| BNIp2     | 40%   | BCL2 adenovirus E1B 19 kDa interacting protein 2                           |
| YY1       | 33%   | YY1 transcription factor                                                   |
| VPS16     | 33%   | vacuolar protein sorting 16 (yeast)                                       |
| USP1      | 33%   | ubiquitin specific protease 1                                             |
| UBE4A     | 33%   | ubiquitination factor E4A (homologous to yeast UFD2)                      |
| UBE2G1    | 33%   | ubiquitin-conjugating enzyme E2G 1 (UBC7 homolog, C. elegans)            |
| TSNAx     | 33%   | translin-associated factor X                                              |
| SSBP1     | 33%   | single-stranded DNA-binding protein 1                                     |
| SMAD4     | 33%   | SMAD, mothers against DPP homolog 4 (Drosophila)                          |
| SIAHBP1   | 33%   | siah binding protein 1                                                     |
| SEC61B    | 33%   | Sec61 beta subunit                                                        |
| RFI       | 33%   | RAP1 interacting factor homolog (yeast)                                   |
| RBMX      | 33%   | RNA binding motif protein, X-linked                                       |
| PSMA3     | 33%   | proteasome (prosome, macropain) subunit, alpha type, 3                    |
| PPP6C     | 33%   | protein phosphatase 6, catalytic subunit                                  |
| POLD2     | 33%   | polymerase (DNA directed), delta 2, regulatory subunit 50 kDa             |
| NCBP2     | 33%   | nuclear cap binding protein subunit 2, 20 kDa                             |
| IRS1      | 33%   | insulin receptor substrate 1                                              |
| ILF3      | 33%   | interleukin enhancer binding factor 3, 90 kDa                            |
| HMGN4     | 33%   | high mobility group nucleosomal binding domain 4                          |
| H2AFV     | 33%   | H2A histone family, member V                                              |
| G22P1     | 33%   | thyroid autoantigen 70 kDa (Ku antigen)                                   |
| EIF253    | 33%   | eukaryotic translation initiation factor 2, subunit 3 gamma, 52 kDa       |
| CUL1      | 33%   | cullin 1                                                                  |
| C10orf7   | 33%   | chromosome 10 open reading frame 7                                         |
| B2W1      | 33%   | basic leucine zipper and W2 domains 1                                     |
| BRD2      | 33%   | bromodomain-containing 2                                                  |
| A TP6V0B   | 33%   | ATPase, H+ transporting, lysosomal 21 kDa, V0 subunit c’                  |
| A TP5J     | 33%   | ATP synthase, H+ transporting, mitochondrial F0 complex, subunit F6       |
| WEEI      | 27%   | WEEI homolog (S. pombe)                                                   |
| VBP1      | 27%   | von Hippel-Lindau binding protein 1 (prefoldin 3)                         |
| UQ CRC1    | 27%   | ubiquinol-cytochrome c reductase core protein 1                           |
| UB XD2     | 27%   | UBX domain containing 2                                                   |
| TSN       | 27%   | translin                                                                  |
| TNIIP1     | 27%   | TNFAIP3 interacting protein 1                                             |
| TEBP      | 27%   | unactive progesterone receptor, 23 kDa                                    |
| TAX1B P3   | 27%   | Tax1 (human T-cell leukemia virus type 1) binding protein 3               |
| TANK      | 27%   | TRAF family member-associated NFKB activator                             |
| SYPL      | 27%   | synaptophysin-like protein                                                |
| SUPT6H    | 27%   | suppressor of Ty 6 homolog (S. cerevisiae)                                |
| Gene     | Description                                      |
|----------|--------------------------------------------------|
| SUPT5H   | 27% suppressor of Ty 5 homolog (S. cerevisiae)   |
| SUCLG1   | 27% succinate-CoA ligase, GDP-forming, alpha subunit |
| SRI      | 27% sorcin                                      |
| SON      | 27% SON DNA binding protein                      |
| SNRPD3   | 27% small nuclear ribonucleoprotein D3 polypeptide 18 kDa |
| SNAP23   | 27% synaptosomal-associated protein, 23 kDa      |
| SMAP     | 27% small acidic protein                          |
| S100A1I  | 27% S100 calcium binding protein A1I (calgizzarin) |
| RW1      | 27% RW1 protein                                  |
| RSN      | 27% restin (Reed-Steinberg cell-expressed intermediate filament-associated protein) |
| RPL36AL  | 27% ribosomal protein L36a-like                   |
| RPA3     | 27% replication protein A3, 14 kDa               |
| RNF4     | 27% ring finger protein 4                         |
| RBL2     | 27% retinoblastoma-like 2 (p130)                 |
| RBBP4    | 27% retinoblastoma binding protein 4              |
| RARS     | 27% arginyl-tRNA synthetase                       |
| RANBP2   | 27% RAN binding protein 2                         |
| RAE1     | 27% RAE1 RNA export 1 homolog (S. pombe)         |
| RAB1A    | 27% RAB1A, member RAS oncogene family             |
| PXMP3    | 27% peroxisomal membrane protein 3, 35 kDa (Zellweger syndrome) |
| PTPN12   | 27% protein tyrosine phosphatase, non-receptor type 12 |
| PTMA     | 27% prothymosin, alpha (gene sequence 2B)        |
| PSMA5    | 27% proteasome (prosome, macropain) subunit, alpha type, 5 |
| PSMA4    | 27% proteasome (prosome, macropain) subunit, alpha type, 4 |
| PRKDC    | 27% protein kinase, DNA-activated, catalytic polypeptide |
| PML      | 27% promyelocytic leukemia                        |
| PHKB     | 27% phosphoflase kinase, beta                     |
| NOLC1    | 27% nucleolar and coiled-body phosphoprotein     |
| MUC2     | 27% mucin 2, intestinal/tracheal                  |
| MPI      | 27% mannose phosphate isomerase                   |
| MGAT1    | 27% mannosyl (alpha-1,3-)glycoprotein beta-1,2-N-acetylgalactosaminyltransferase |
| MCP      | 27% membrane cofactor protein (CD46, trophoblast-lymphocyte cross-reactive antigen) |
| MARK3    | 27% MAP/microtubule affinity-regulating kinase 3  |
| MARK2    | 27% MAP/microtubule affinity-regulating kinase 2  |
| MARCK5   | 27% myristoylated alanine-rich protein kinase C substrate |
| MAP2K3   | 27% mitogen-activated protein kinase kinase 3     |
| LIMK2    | 27% LIM domain kinase 2                           |
| LEREP04  | 27% likely ortholog of mouse immediate early response, erythropoietin 4 |
| KPN2     | 27% karyopherin alpha 2 (RAG cohort 1, importin alpha 1) |
| KIAA0092 | 27% translokin                                    |
| IL13RA1  | 27% interleukin 13 receptor, alpha 1             |
| HSPE1    | 27% heat shock 10 kDa protein 1 (chaperonin 10)  |
| HNRPA0   | 27% heterogeneous nuclear ribonucleoprotein A0   |
| HMGN3    | 27% high mobility group nucleosomal binding domain 3 |
| HLA-A    | 27% major histocompatibility complex, class I, A |
| HIF1A    | 27% hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor) |
| HAT1     | 27% histone acetyltransferase 1                   |
| HADHA    | 27% hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit |
| GTF3C2   | 27% general transcription factor IIIC, polypeptide 2, beta 110 kDa |
| GRSF1    | 27% G-rich RNA sequence binding factor 1          |
| GA17     | 27% dendritic cell protein                        |
| G3BP     | 27% Ras-GTPase-activating protein SH3-domain-binding protein |
| FUBP3    | 27% far upstream element (FUSE) binding protein 3 |
| FMRI     | 27% fragile X mental retardation 1                |
| FKBP1A   | 27% FK506 binding protein 1A, 12 kDa             |
| FDFT1    | 27% farnesyl-diphosphate farnesyltransferase 1    |
| FAM3C    | 27% family with sequence similarity 3, member C   |
| EWSR1    | 27% Ewing sarcoma breakpoint region 1             |
| EPS8     | 27% epidermal growth factor receptor pathway substrate 8 |
| EIF359   | 27% eukaryotic translation initiation factor 3, subunit 9 eta, 116 kDa |
| EFNA1    | 27% ephrin-A1                                    |
| DYRK1A   | 27% dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A |
Oncomine meta-analysis of SUMO1 co-expressed genes

| Gene         | Percent |
|--------------|---------|
| DLG1         | 27%     |
| DDOST        | 27%     |
| DCTN6        | 27%     |
| DBI          | 27%     |
| DAZAP2       | 27%     |
| DAG1         | 27%     |
| CUL4A        | 27%     |
| CSG6         | 27%     |
| COG2         | 27%     |
| CEBPD        | 27%     |
| CDC34        | 27%     |
| CD9          | 27%     |
| CCT6A        | 27%     |
| CBX3         | 27%     |
| CARS         | 27%     |
| C1D          | 27%     |
| C14orf32     | 27%     |
| BUB3         | 27%     |
| BSG          | 27%     |
| BLOC1S1      | 27%     |
| BIRC2        | 27%     |
| ARMC2        | 27%     |
| ANP32A       | 27%     |

Table 1: Oncomine meta-analysis of SUMO1 co-expressed genes (Continued)

The technique has a high false-negative rate meaning that while the co-expressed genes we see are significant we will never get full coverage of every co-expressed gene as the stringency level of analysis is high.

SUMO1 was also seen to be involved in cell death pathways. In 67% (10 out of 15) of the studies analyzed SUMO1 was co-expressed with the DAD1 gene. This was the highest co-expression with SUMO1 in the meta-analysis. As the name suggests DAD1 is anti-apoptotic and can be upregulated in cancer [13,14]. Other SUMO1 co-expressed genes involved in cell death pathways include RELA, FADD, BCL2A1, BAK1, TNFRSF1A. The high co-expression with DAD1 is a novel finding and may prove important to SUMO1 pathways.

DEK oncogene was the next highest co-expressed gene (53%) with SUMO1. The DEK protein is important for chromatin structure, and may also play a role in cell death pathways by inhibiting apoptosis [15-17].

While co-expression meta-analysis data has previously been shown to have a high correlation with known pathways in other studies [2,3], prudence should still be used when interpreting novel findings until they can be proven in a separate experimental system. For this reason the meta-analysis list is presented here only as a predictive data-driven hypothesis. The next step is experimental analysis of DEK and DAD1 proteins to assess whether they are targets of SUMO1 conjugation, protein-complex partners of SUMO1, or act upstream or downstream of SUMO1.

In summary, it is interesting that both of the highest co-expressed genes of SUMO1 are anti-apoptotic, and it is tempting to speculate that this may be an important pathway of SUMO1 regulation.

Conclusion

Using co-expression meta-analysis from the Oncomine database SUMO1 co-expressed with many gene products, some which are already known to be in SUMO1 pathways. Novel predicted pathway partners include the DEK oncogene and DAD1, both of which co-expressed in over half of all studies analyzed. However, in what regard they take part in SUMO1 pathways remains to be further investigated.

Competing interests
The author declares that they have no competing interests.

Authors’ contributions
BW conceived and designed the study, performed the meta-analysis, and wrote the manuscript.

Additional material

Additional file 1
SUMO1 meta-analysis. Oncomine meta-analysis of SUMO1 with cutoff of 3 studies (20%). Click here for file [http://www.biomedcentral.com/content/supplementary/1756-0500-1-60-S1.xls]
Acknowledgements

BW is funded by a McGill University Health Centre fellowship. I thank Annie Tremblay for helpful discussions.

References

1. Oncomine: [http://www.oncomine.org].
2. Wilson BJ, Giguere V: Identification of novel pathway partners of p68 and p72 RNA helicases through Oncomine meta-analysis. BMC Genomics 2007, 8:419.
3. Wilson BJ, Giguere V: Meta-analysis of human cancer microarrays reveals GATA3 is integral to the estrogen receptor alpha pathway. Mol Cancer 2008, 7:49.
4. Muller S, Matsunis MJ, Dejean A: Conjugation with the ubiquitin-related modifier SUMO-1 regulates the partitioning of PML within the nucleus. Emba J 1998, 17:61-70.
5. Bae SH, Jeong JW, Park JA, Kim SH, Bae MK, Choi SJ, Kim KW: Sumoylation increases HIF-1alpha stability and its transcriptional activity. Biochem Biophys Res Commun 2004, 324:394-400.
6. Ledl A, Schmidt D, Muller S: Viral oncoproteins E1A and E7 and cellular LxCxE proteins repress SUMO modification of the retinoblastoma tumor suppressor. Oncogene 2005, 24:3810-3818.
7. Deng Z, Yan M, Sui G: PIASy-mediated sumoylation of Yin Yang 1 depends on their interaction but not the RING finger. Mol Cell Biol 2007, 27:3780-3792.
8. Sternerdorf T, Jensen K, Will H: Evidence for covalent modification of the nuclear dot-associated proteins PML and Sp100 by PIC1/SUMO-1. J Cell Biol 1997, 139:1621-1634.
9. Lin X, Liang M, Liang YY, Bruniciardi FC, Melchior F, Feng XH: Activation of transforming growth factor-beta signaling by SUMO-1 modification of tumor suppressor Smad4/DPC4. J Biol Chem 2003, 278:18714-18719.
10. Duprez E, Saurin AJ, Desterro JM, Lallemand-Breitenbach V, Howe K, Boddy MN, Solomon E, de The H, Hay RT, Freemont PS: SUMO-1 modification of the acute promyelocytic leukaemia protein PML: implications for nuclear localisation. J Cell Sci 1999, 112(Pt 3):381-393.
11. Huang TT, Wueurzberger-Davis SM, Wu ZH, Miyamoto S: Sequential modification of NEMO/IKKgamma by SUMO-1 and ubiquitin mediates NF-kappaB activation by genotoxic stress. Cell 2003, 115:565-576.
12. Carbia-Nagashima A, Gerez J, Perez-Castro C, Paz-Pareda M, Silberstein S, Stalla GK, Hollo W, Arzt J: RSUME, a small RWD-containing protein, enhances SUMO conjugation and stabilizes HIF-1alpha during hypoxia. Cell 2007, 131:309-323.
13. Hong NA, Flannery M, Hsieh SN, Cado D, Pedersen R, Winsor A: Mice lacking DAD1, the defender against apoptotic death-1, express abnormal N-linked glycoproteins and undergo increased embryonic apoptosis. Dev Bio 2000, 220:76-84.
14. Tanaka K, Kondoh N, Shuda M, Matsubara O, Imazeki N, Ryo A, Nakatsuki T, Hada A, Goseki N, Igarashi T, Haszus K, Alhara T, Horiiuchi S, Yamanoto N, Yamanoto M: Enhanced expression of mRNAs of antisecretory factor-1, p96, DADI and CDC34 in human hepatocellular carcinomas. Biochem Biophys Acta 2001, 1536:1-12.
15. Waldmann T, Scholten I, Kappes F, Hu HG, Knippers R: The DEK protein – an abundant and ubiquitous constituent of mammalian chromatin. Gene 2004, 343:1-9.
16. Cleary J, Sittwala KV, Khodadoust MS, Kwok RP, Mor-Vaknin N, Cebat M, Cole PA, Markowitz DM: p300/CBP-associated factor drives DEK into interchromatin granule clusters. J Biol Chem 2005, 280:31760-31767.

17. Wise-Draper TM, Allen HV, Jones EE, Habash KB, Matsuo H, Wells SI: Apoptosis inhibition by the human DEK oncoprotein involves interference with p53 functions. Mol Cell Biol 2006, 26:7506-7519.