Posttranslační modifikace a jejich význam

C2138 Pokročilá bioinformatika, jaro 2023

Lenka Malinovská

Proteom a proteomika

- **Proteom – soubor všech forem proteinů existujících v buňce (organismu, biologickém vzorku) v určitém čase a za určitých podmínek.**

- **Proteomika – studium proteomů.**
- **Proteomika – věda zabývající se komplexní analýzou proteinů (identifikace, exprese, charakterizace).**
- **Proteomika – analýza proteinů ve velkém rozsahu (struktura, funkce, interakce).**

- **Proteomika – vyžaduje separační techniky, hmotnostní spektrometrii, bioinformatiku, databáze genů a proteinů.**

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  Množství kovalentních forem proteinů přesahuje množství proteinů predikovaných z DNA (genom).

  Proteomy jsou složitější než genomy.

  1 genom – mnoho proteomů.

- **1 gen může být exprimován ve více než 20 různých variantách proteinu. Například α1-antitrypsin se může vyskytovat ve 22 různých formách.**

- **25 000 genů – 0,5 - 1 milion proteinů.**

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  Množství kovalentních forem proteinů přesahuje množství proteinů predikovaných z DNA (genom).

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- **Navýšení kódovací kapacity genomu: alternativní sestřih, posttranslační modifikace (PTM).**

Posttranslační modifikace

- **Posttranslační modifikace – kovalentní modifikace proteinů po transkripci DNA a translaci RNA.**

  Posttranslační modifikace – probíhají i u prokaryot

  Posttranslační modifikace jsou prováděny enzymy. Enzymy rozeznávají specifické signály – aminokyselinové sekvence v proteinech. Identifikace těchto sekvenčních motivů umožňuje predikci PTM.

  Člověk: 500 proteinkinas, 150 proteinfosfatas, 500 proteas.

  5 % genomu vyšších eukaryot – zapojení do PTM.

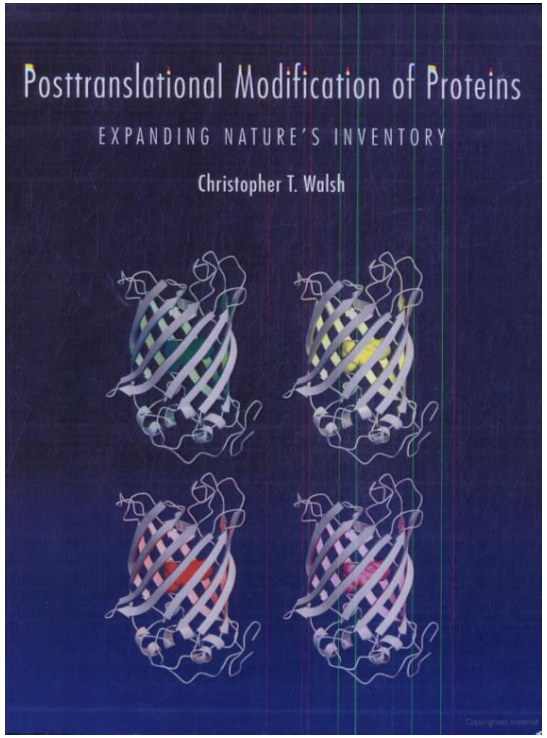
- **Klasifikace posttranslačních modifikací – typ modifikované aminokyseliny, podle modifikujícího enzymu, reverzibilita modifikací.**

Posttranslační modifikace - typy

Table 1: Posttranslational protein modifications at the side chains.[a]

Residue	Reaction	Example
Asp	phosphorylation	protein tyrosine phosphatases; response regulators in two-component systems
	isomerization to isoAsp	
Glu	methylation	chemotaxis receptor proteins
	carboxylation	Gla residues in blood coagulation
	polyglycination	tubulin
	polyglutamylation	tubulin
Ser	phosphorylation	protein serine kinases and phosphatases
	O-glycosylation	notch O-glycosylation
	phosphopantetheinylation	fatty acid synthase
	autocleavages	pyruvamidyl enzyme formation
Thr	phosphorylation	protein threonine kinases/phosphatases
	O-glycosylation	
Tyr	phosphorylation	tyrosine kinases/phosphatases
	sulfation	CCR5 receptor maturation
	ortho-nitration	inflammatory responses
	TOPA quinone	amine oxidase maturation
His	phosphorylation	sensor protein kinases in two-component regulatory systems
	aminocarboxypropylation	diphthamide formation
	N-methylation	methyl CoM reductase
Lys	N-methylation	histone methylation
	N-acylation by acetyl, biotinyl, lipoyl, ubiquityl groups	histone acetylation; swinging-arm prosthetic groups; ubiquitin; SUMO (small ubiquitin-like modifier) tagging of proteins
	C-hydroxylation	collagen maturation
Cys	S-hydroxylation (S-OH)	sulfenate intermediates
	disulfide bond formation	protein in oxidizing environments
	phosphorylation	PTPases
	S-acylation	Ras
	S-prenylation	Ras
	protein splicing	intein excisions
Met	oxidation to sulfoxide	Met sulfoxide reductase
Arg	N-methylation	histones
	N-ADP-ribosylation	$G_{s\alpha}$
Asn	N-glycosylation	N-glycoproteins
	N-ADP-ribosylation	eEF-2
	protein splicing	intein excision step
Gln	transglutamination	protein cross-linking
Trp	C-mannosylation	plasma-membrane proteins
Pro	C-hydroxylation	collagen; HIF-1α
Gly	C-hydroxylation	C-terminal amide formation

[a] No modifications of Leu, Ile, Val, Ala, Phe side chains are known. A more extensive list can be found in reference [3].



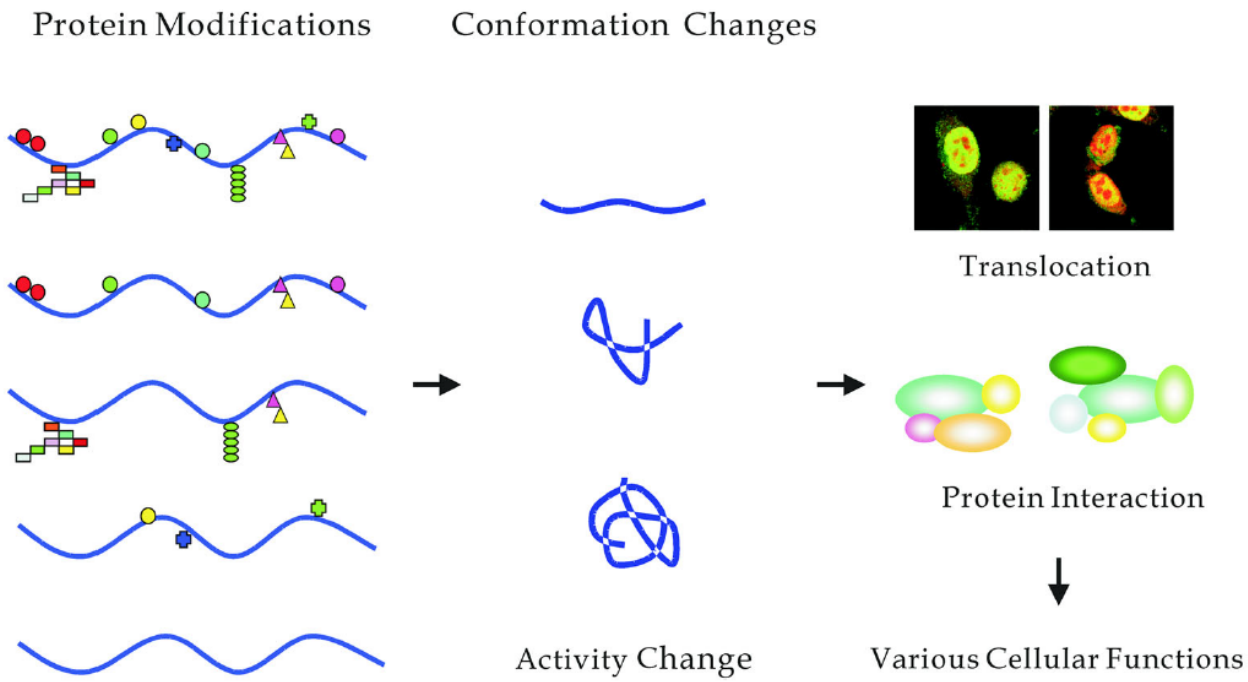
Protein Posttranslational Modifications: The Chemistry of Proteome Diversifications

Christopher T. Walsh, Sylvie Garneau-Tsodikova, and Gregory J. Gatto, Jr.*

DOI: 10.1002/anie.200501023

Posttranslační modifikace - význam

- Ovlivňují 3D a 4D strukturu proteinů, aktivitu a funkci (rozpustnost, stabilita, interakce, vypnuto/zapnuto).
- Mohou ovlivňovat lokalizaci proteinu v buňce (prenylace a jiné – připojení hydrofobní skupiny umožňuje lokalizaci do membrány).
- Tvorba disulfidických můstků může být nezbytná pro správné sbalení proteinů.
- Význam pro imunitní systém – glykosylace.



Post-translational Modifications and Their Biological Functions: Proteomic Analysis and Systematic Approaches

Jawon Seo and Kong-Joo Lee*

Posttranslační modifikace - příklady

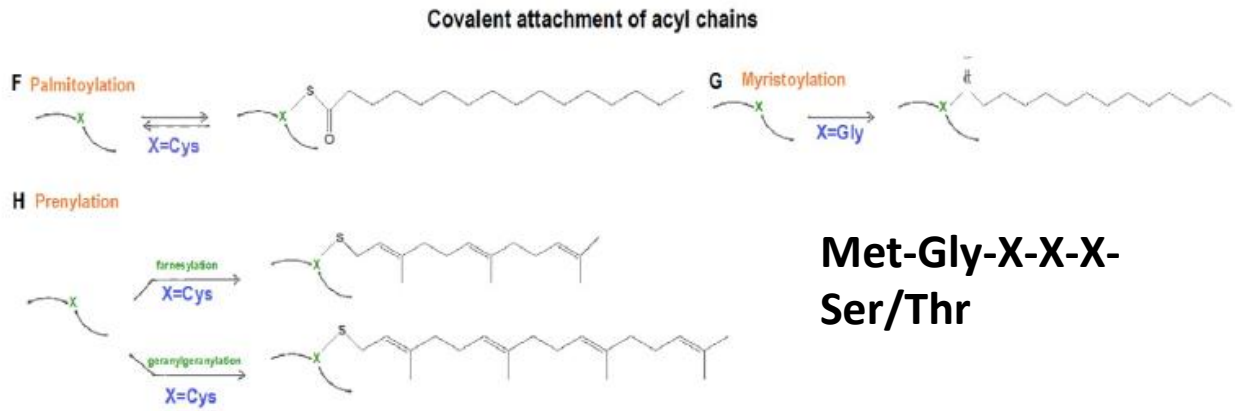
- **Kovalentní připojení malé molekuly (funkční skupiny):**

- **Fosforylace (serin, threonin, tyrosin, histidin, arginin, lysin), aktivace/inhibice enzymů. Nejstudovanější PTM.**

- **Glykosylace (*N*-glykosylace, *O*-glykosylace, GPI kotva, C-mannosylace).**

- **S-nitrosylace (cystein). Neenzymatické připojení NO. Vazba je labilní, náročná experimentální identifikace!**

- **Kovalentní připojení acylových řetězců:**



Met-Gly-X-X-X-Ser/Thr

- **Kovalentní připojení malých proteinů:**
- **Ubikvitinace (lysin). Regulace odbourávání proteinů, regulace funkce proteinů.**

Protein post-translational modifications: *In silico* prediction tools and molecular modeling

Martina Audagnotto *, Matteo Dal Peraro *

Institute of Bioengineering, School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
Swiss Institute of Bioinformatics (SIB), Lausanne, Switzerland

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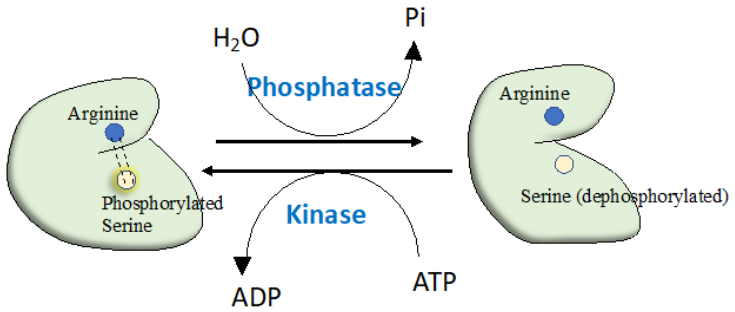

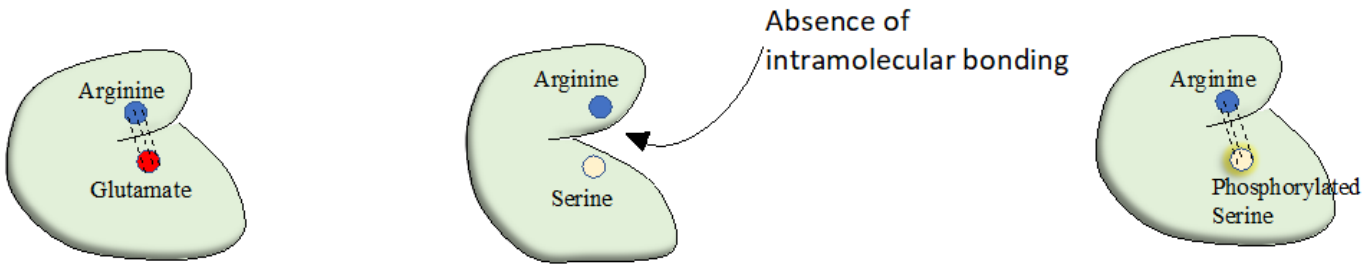

1
Ion pair formation between Arginine and Glutamate stabilizes the fold

2
Substitution of Glutamate with Serine leads to loss of intra-molecular bonding and loss of functional fold

3
Phosphorylated Serine can substitute for Glutamate and ion pair forms again stabilizing the proteins conformation

https://info.gbiosciences.com/blog/protein-phosphorylation-natures-favorite-way-of-decorating-proteins

Posttranslační modifikace - význam

Table 1 Golgi PTMs and associated diseases. This table summarizes all the human disorders linked to Golgi PTMs presented in this review

Affected gene	Protein	Affected PTM	Disease	Major clinical manifestations	Gene OMIM entry	Disease OMIM entry
MAN1B1	α 1,2 mannosidase	glycosylation	MAN1B1-CDG	severe mental retardation, delayed speech	604346	614202
SLC35A1	CMP-sialic acid transporter	glycosylation	SLC35A1-CDG	seizures, intellectual disability, ataxia, bleeding	605634	603585
SLC35A2	UDP-galactose transporter	glycosylation	SLC35A2-CDG	intellectual disability, seizures, skeletal abnormalities	314375	300896
SLC35A3	UDP-GlcNAc transporter	glycosylation	Arthrogryposis, mental retardation and seizures	autism spectrum disorder, hypotonia, epilepsy, and arthrogryposis	605632	615553
SEC23B	Sec23 homolog B	glycosylation	Dyserythropoietic anemia, congenital, type II	erythroblastic anemia: splenomegaly, gallstones, and iron overload potentially with liver cirrhosis or cardiac failure.	610512	224100
TRIP11	Golgi microtubule associated protein 210	glycosylation	Achondrogenesis type 1A	severe chondrodysplasia, lethal before or shortly after birth	604505	200600
UBE3A	Ubiquitin ligase E3A	glycosylation	Angelman syndrome	intellectual disability, seizures, lack of speech, and characteristic abnormal behavior	601623	105830
COG2	Component of oligomeric Golgi complex 2	glycosylation	COG2-CDG	microcephaly, developmental delay, intellectual disability, seizures, facial dysmorphism, liver dysfunction	606974	no entry yet
SLC33A1	Solute carrier family 33 (acetyl-CoA transporter), member 1	acetylation	Spastic paraplegia-42	spastic gait, increased lower limb tone, weakness and atrophy of the lower limb muscles, pes cavus	603690	612539
CHST3	Chondroitin 6-O-sulfotransferase	sulfation	Spondylo-epiphyseal dysplasia with joint dislocations	unusual skeletal dysplasia	603799	143095
CHST6	Corneal N-acetylglucosamine-6-O-sulfotransferase	sulfation	Macular corneal distrophy type II	progressive corneal opacification and reduced corneal sensitivity	605294	217800
CHST8	GalNAc-4-O sulfotransferase I	sulfation	Peeling skin syndrome	general skin peeling	610190	270300
CHST14	Dermatan sulfate GalNAc-4-O sulfotransferase I	sulfation	Ehlers-Danlos syndrome musculocontractural type 1	craniofacial dysmorphism, congenital contractures of thumbs and fingers, clubfeet, severe kyphoscoliosis	608429	601776
ARSE	Arylsulfatase E	sulfation	Chondrodysplasia punctata 1	stippled epiphyses, brachytelephalangy, nasomaxillary hypoplasia	300180	302950
PAPPS2	PAPS synthase	sulfation	Brachyolmia type 4	short-trunk stature, rectangular vertebral bodies, precocious calcification of rib cartilages, short femoral neck. Early death for severe cases.	603005	612847
SLA26A2	Sulfate anion transporter	sulfation	Achondrogenesis type 1B	severe chondrodysplasia, early death of respiratory failure	606718	600972
			Atelosteogenesis type 2	pulmonary hypoplasia, lethal in infants	606718	256050
			Epiphyseal dysplasia multiple 4	joint pain, scoliosis, malformations of the hands, feet, and knees	606718	226900
			Diastrophic dysplasia	scoliosis, clubfeet, malformed pinnae with calcification of the cartilage, cleft palate in some cases	606718	222600
GNTPG	N-acetylglucosamine-1-phosphotransferase gamma subunit	phosphorylation	Mucolipidosis III gamma	short stature, skeletal abnormalities, cardiomegaly, and developmental delay	607838	252605

Golgi post-translational modifications and associated diseases

Sven Potelle[1] · André Klein[2] · François Foulquier[1]

DOI 10.1007/s10545-015-9851-7

Posttranslační modifikace - význam

Table 1 (continued)

Affected gene	Protein	Affected PTM	Disease	Major clinical manifestations	Gene OMIM entry	Disease OMIM entry
GNTPAB	N-acetylglucosamine-1-phosphotransferase alpha and beta subunits	phosphorylation	Mucolipidosis II and III	Hip dislocation, gingival hyperplasian, thoracic deformities and hernia soon after birth. Delayed psychomotor development. Same clinical features for mucolipidosis III as described just above.	607840	252500 252600
IMPAD1	Golgi-resident PAP phosphatase	phosphorylation	Chondrodysplasia with joint dislocations	short stature, chondrodysplasia with brachydactyly, congenital joint dislocations, micrognathia, cleft palate, and facial dysmorphism	614010	614078
INPP5E	Inositol polyphosphate-5-phosphatase	phosphorylation	Morm syndrome	Mental retardation, truncal obesity, retinal dystrophy, and micropenis	613037	610156
		phosphorylation	Joubert syndrome 1	Heterogenous: hypoplasia of the cerebellar vermis with the characteristic neuroradiologic molar tooth sign , dysregulation of breathing pattern and developmental delay.	613037	213300
AKAP9	A-kinase anchor protein 9	phosphorylation	Long QT syndrome-11	recurrent syncope, seizure, or sudden death	604001	611820
FAM20C	Golgi kinase (family with sequence similarity 20, member C)	phosphorylation	Raine syndrome	neonatal osteosclerotic bone dysplasia, increased ossification of the skull	611061	259775
CAMKMT	Calmodulin-lysine N-methyltransferase	methylation	2p21 deletion syndrome	cystinuria, neonatal seizures, hypotonia, severe somatic and developmental delay, facial dysmorphism	609559	606407
MBTPS2	Site-2 protease	proteolytic cleavage	IFAP syndrome with or without BRESHECK syndrome	ichthyosis follicularis, atrichia, and photophobia	300294	308205
			Olmsted syndrome, X-linked	periorificial keratotic plaques and bilateral palmoplantar transgredient keratoderma	300294	300918
			keratosis follicularis spinulosa decalvans, X-linked	keratosis pilaris, progressive cicatricial alopecia of the scalp, eyebrows, and eyelashes	300294	308800
ZDHHC8	Zinc finger, DHHC-type containing 8	palmitoylation	Schizophrenia susceptibility	hallucinations and delusions, inappropriate emotional responses, disordered thinking and concentration, erratic behavior	608784	181500
ZDHHC9	Zinc finger, DHHC-type containing 9	palmitoylation	X-linked mental retardation (Raymond type)	general intellectual limitations associated with impairments in adaptive behavior	300646	300799
ZDHHC15	Zinc finger, DHHC-type containing 15	palmitoylation	X-linked mental retardation-91	general intellectual limitations associated with impairments in adaptive behavior	300576	300577
PPT1	Palmitoyl-protein thioesterase 1	palmitoylation	Neuronal ceroid lipofuscinosis 1	Heterogenous: progressive dementia, seizures, and progressive visual deficiency. The cellular phenotype includes intracellular accumulation of autofluorescent lipopigment storage material.	600722	256730

Golgi post-translational modifications and associated diseases

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OMIM® - Online Mendelian Inheritance in Man®

Welcome to OMIM®, Online Mendelian Inheritance in Man®. OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 15,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.

This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). Twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985 by a collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. It was made generally available on the internet starting in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh.

NLM's Profiles in Science -- The McKusick Papers

Searching Online Mendelian Inheritance in Man (OMIM): A Knowledgebase of Human Genes and Genetic Phenotypes

Joanna S. Amberger[1] and **Ada Hamosh**
McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287, Tel. 410-955-0313, Fax. 410-955-4999

Abstract

Online Mendelian Inheritance in Man (OMIM) at OMIM.org is the primary repository of comprehensive, curated information on genes and genetic phenotypes and the relationships between them. This unit provides an overview of the types of information in OMIM and optimal strategies for searching and retrieving the information. OMIM.org has links to many related and complementary databases providing easy access to exploring more information on a topic. The relationship between genes and genetic disorders is highlighted in this unit. The basic protocol explains searching OMIM both from a gene then clinical features perspective. Two alternate protocols provide strategies for viewing gene-phenotype relationships as a gene map table and clinical features as a Quick View or Side-by-Side format. OMIM.org is updated nightly and the MIMmatch service, described in the Support Protocol, provides a convenient way to follow updates to entries, gene-phenotype relationships, and collaborate with other researchers.

OMIM databáze – geny a geneticky podmíněné choroby

50 YEARS OMIM
Human Genetics Knowledge for the World

https://omim.org

https://omim.org

Posttranslační modifikace - význam

603585

CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IIf; CDG2F

Alternative titles; symbols

CDG IIf; CDGIIf

Clinical Features

Willig et al. (2001) reported a 4-month-old boy who presented with a spontaneous massive bleed in the posterior chamber of the right eye along with cutaneous hemorrhages. Laboratory studies showed marked thrombocytopenia and neutropenia. The patient experienced multiple episodes of bleeding over the next 30 months, including severe pulmonary hemorrhage. He also had multiple recurrent bacterial infections. Bone marrow transplantation was performed at age 34 months, but the patient died of complications at age 37 months.

Macrothrombocytopenia with abnormal demarcation membranes in megakaryocytes and neutropenia with a complete lack of sialyl-Lewis-X antigen in leukocytes--a new syndrome?

Willig TB, Breton-Gorius J, Elbim C, Mignotte V, Kaplan C, Mollicone R, Pasquier C, Filipe A, Miélot F, Cartron JP, Gougerot-Pocidalo MA, Debili N, Guichard J, Dommergues JP, Mohandas N, Tchernia G.

Blood. 2001 Feb 1;97(3):826-8. doi: 10.1182/blood.v97.3.826.

PMID: 11157507 Free article.

PubMed.gov

50 YEARS OMIM Human Genetics Knowledge for the World

* 606672

GLYCOPROTEIN Ib, PLATELET, ALPHA POLYPEPTIDE; GP1BA

Alternative titles; symbols

GP Ib, ALPHA SUBUNIT
PLATELET GLYCOPROTEIN Ib, ALPHA POLYPEPTIDE
CD42B

Biochemical Features

By detailed laboratory analysis of a patient with thrombocytopenia and recurrent infections, Willig et al. (2001) found markedly decreased amounts of platelet membrane GP Ib (see GP1BA, 606672) and undetectable sialyl-Lewis-X on the surface of neutrophils, suggesting a defect in the posttranslational modification of glycoproteins. Martinez-Duncker et al. (2005) noted that the plasma of the patient reported by Willig et al. (2001) showed a normal sialylation pattern of transferrin (TF; 190000) and other major serum glycoproteins. The phenotype was due to the lack of sialyl-Lewis-X, which has considerable roles in cell-to-cell interactions, such as infections and megakaryocytic immaturity, that were defective in this patient.

Molecular Genetics

In a patient originally described by Willig et al. (2001), Martinez-Duncker et al. (2005) identified compound heterozygosity for 2 mutations in the SLC35A1 gene (605634.0001; 605634.0002). Martinez-Duncker et al. (2005) referred to this disorder as CDG type IIf.

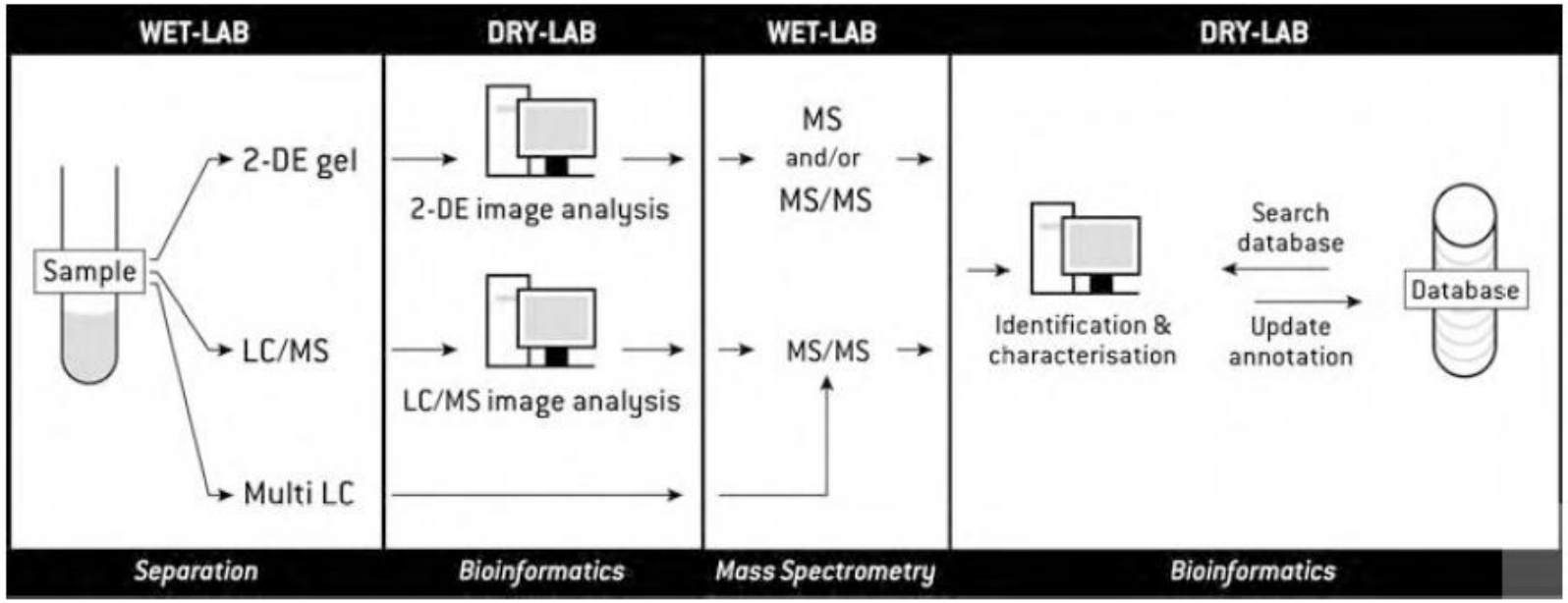
* 605634

SOLUTE CARRIER FAMILY 35 (CMP-SIALIC ACID TRANSPORTER), MEMBER 1; SLC35A1

The SLC35A1 gene encodes a CMP-sialic acid transporter located within the membrane of the Golgi apparatus. The transporter moves nucleotide sugars across the membrane for use in glycosylation reactions that take place within the Golgi department (Eckhardt et al., 1996).

Posttranslační modifikace a proteomika

- **Proteomika – vyžaduje separační techniky, hmotnostní spektrometrii, bioinformatiku, databáze genů a proteinů.**
- **Proteomika – diagnostika (markery), „drug targets“, zkoumání vlivu léčiv na organismus. Podmíněno schopností identifikovat, charakterizovat a kvantifikovat výskyt jednotlivých proteinů v komplexním vzorku.**



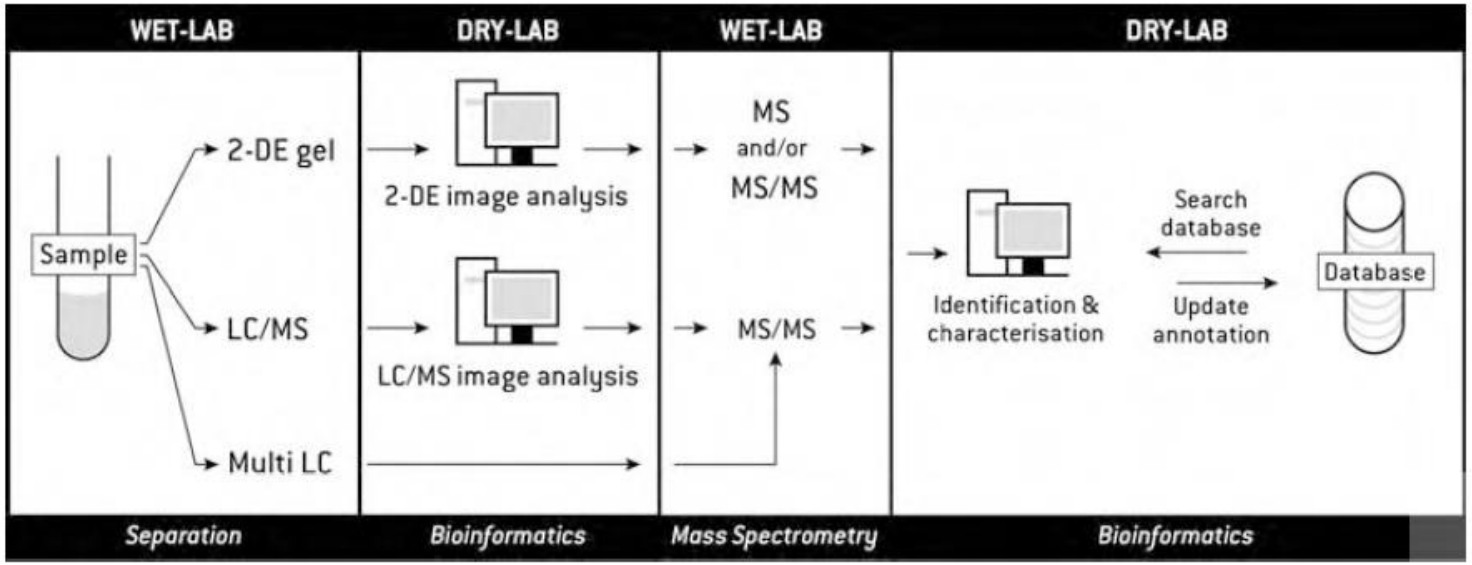
Bioinformatics-From Genomes to Therapies. **Editors(s):Prof. Dr. Thomas Lengauer**

Posttranslační modifikace
Experimentální identifikace

- **Problémy při identifikaci posttranslačních modifikací:**

  modifikovaná je jen frakce proteinu (nízká koncentrace, nutné citlivé metody), kovalentní vazba PTM je labilní – nemusí vydržet zpracování vzorku a analýzu.

- **Identifikace a analýza PTM: kombinace separační metody a MS analýzy.**



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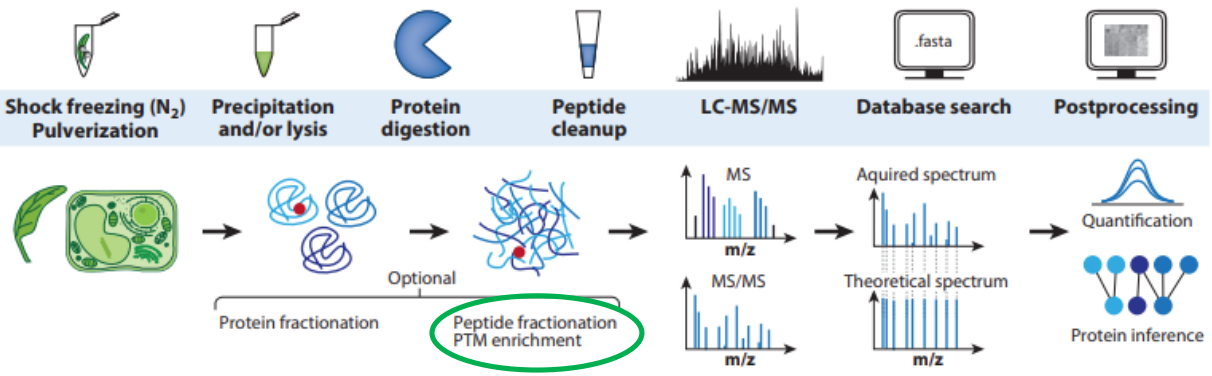

Figure 2

Generic workflow for proteomic sample preparation, data acquisition, and analysis. Proteins are extracted from whole-plant samples or enriched subfractions using optimized homogenization and protein extraction methods. Proteins are digested into peptides and measured on an LC-MS/MS system. Peptides are identified from MS/MS spectra by database matching and quantified based on the peak areas of intact peptide (survey MS spectra) or fragment ion signals (tandem MS spectra) provided by the mass spectrometer along the chromatographic time scale. Protein identity and quantity are then inferred based on peptide sequence assignments. Abbreviations: LC-MS/MS, liquid chromatography–coupled tandem mass spectrometry; MS, mass spectrometry; MS/MS, tandem mass spectrometry; m/z, mass-to-charge ratio; PTM, posttranslational modification.

Annual Review of Plant Biology

Plant Proteome Dynamics

Julia Mergner[1,2] and Bernhard Kuster[2,3]

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The *Annual Review of Plant Biology* is online at plant.annualreviews.org

https://doi.org/10.1146/annurev-arplant-102620-031308

Posttranslační modifikace
Predikce

- **Posttranslační modifikace jsou prováděny enzymy. Enzymy rozeznávají specifické signály – aminokyselinové sekvence v proteinech. Identifikace těchto sekvenčních motivů umožňuje predikci PTM.**

- **Problémy predikce:**

- **Může být těžké vytvořit „průměrný“ sekvenční motiv vhodný pro predikci.**
- **Proteiny jsou modifikovány různými enzymy s různou specifitou.**
- **Vliv okolních aminokyselin – ovlivnění náboje, hydrofility části proteinu v kontaktu s enzymem.**
- **Vliv 3D/4D struktury.**

Prediction of Posttranslational Modification of Proteins from Their Amino Acid Sequence

Birgit Eisenhaber and Frank Eisenhaber

Post-translational modifications of proteins

DictyOGlyc	*O-(alpha)-GlcNAc glycosylation sites (trained on Dictyostelium discoideum proteins)*
NetAcet	*N-terminal acetylation in eukaryotic proteins*
NetCGlyc	*C-mannosylation sites in mammalian proteins*
NetCorona	*Coronavirus 3C-like proteinase cleavage sites in proteins*
NetGPI	*GPI Anchor predictions*
NetNGlyc	*N-linked glycosylation sites in human proteins*
NetOGlyc	*O-GalNAc (mucin type) glycosylation sites in mammalian proteins*
NetPhorest	*Linear motif atlas for phosphorylation-dependent signaling*
NetPhos	*Generic phosphorylation sites in eukaryotic proteins*
NetPhosBac	*Generic phosphorylation sites in bacterial proteins*
NetPhosYeast	*Serine and threonine phosphorylation sites in yeast proteins*
NetPhospan	*Prediction of phosphorylation using convolutional neural networks (CNNs).*
NetworKIN	*In vivo kinase-substrate relationships*
ProP	*Arginine and lysine propeptide cleavage sites in eukaryotic protein sequences*

DTU Health Tech

DTU - Technical University of Denmark

https://services.healthtech.dtu.dk/

Expasy

Swiss Bioinformatics Resource Portal

PeptideCutter

Potential cleavage sites in a protein

GlycoMod

Possible oligosaccharide structures on proteins from masses

Sulfinator

Predict tyrosine sulfation sites in protein sequences

The Sulfinator is a software tool able to predict tyrosine sulfation sites in protein sequences. It employs four different Hidden Markov Models that were built to recognise sulfated tyrosine residues located N-terminally, within sequence windows of more than 25 amino acids and C-terminally, as well as sulfated tyrosines clustered within 25 amino acid windows, respectively. All four HMMs contain the distilled information from one multiple sequence alignment.

FindMod

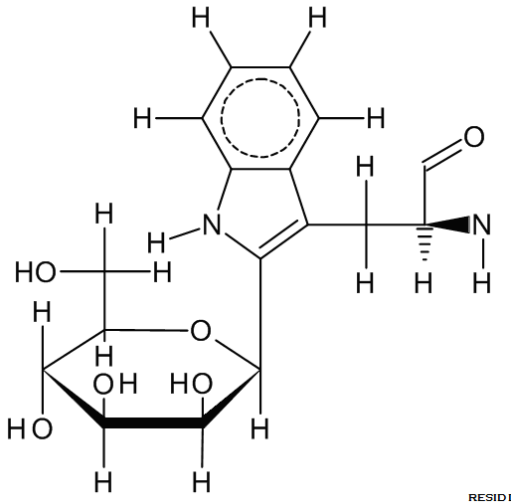
Potential PTMs and single amino acid substitutions

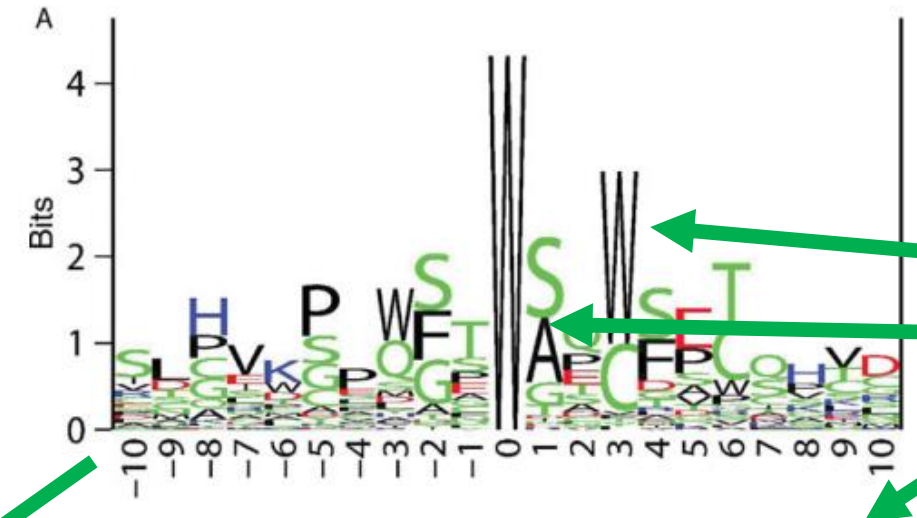
Myristoylator

N-terminal myristoylation of proteins by neural networks.

Expert Protein Analysis System
http://www.expasy.org

[Annotation | Image | Model]





C-mannosylation is the attachment of an α-mannopyranose to a tryptophan via a C–C linkage. The sequence WXXW, in which the first Trp becomes mannosylated, has been suggested as a consensus motif for the modification, but only two-thirds of known sites follow this rule. We have gathered a data set of 69 experimentally verified C-mannosylation sites from the literature. We analyzed these for sequence context and found that apart from Trp in position +3, Cys is accepted in the same position. We also find a clear preference in position +1, where a small and/or polar residue (Ser, Ala, Gly, and Thr) is preferred and a Phe or a Leu residue discriminated against. The Protein Data Bank was searched for structural information, and five structures of C-mannosylated proteins were obtained. We showed that modified tryptophan residues are at least partly solvent exposed. A method predicting the location of C-mannosylation sites in proteins was developed using a neural network approach. The best overall network used a 21-residue sequence input window and information on the presence/absence of the WXXW motif. NetCGlyc 1.0 correctly predicts 93% of both positive and negative C-mannosylation sites. This is a significant improvement over the WXXW consensus motif itself, which only identifies 67% of positive sites. NetCGlyc 1.0 is available at http://www.cbs.dtu.dk/services/NetCGlyc/. Using NetCGlyc 1.0, we scanned the human genome and found 2573 exported or transmembrane transcripts with at least one predicted C-mannosylation site.

Unfortunately, no structure was found for the only protein where the C-mannosylation sites are completely unrelated to the WXXW motif, lens fiber membrane intrinsic protein.

NetCGlyc - 1.0

C-mannosylation sites in mammalian proteins

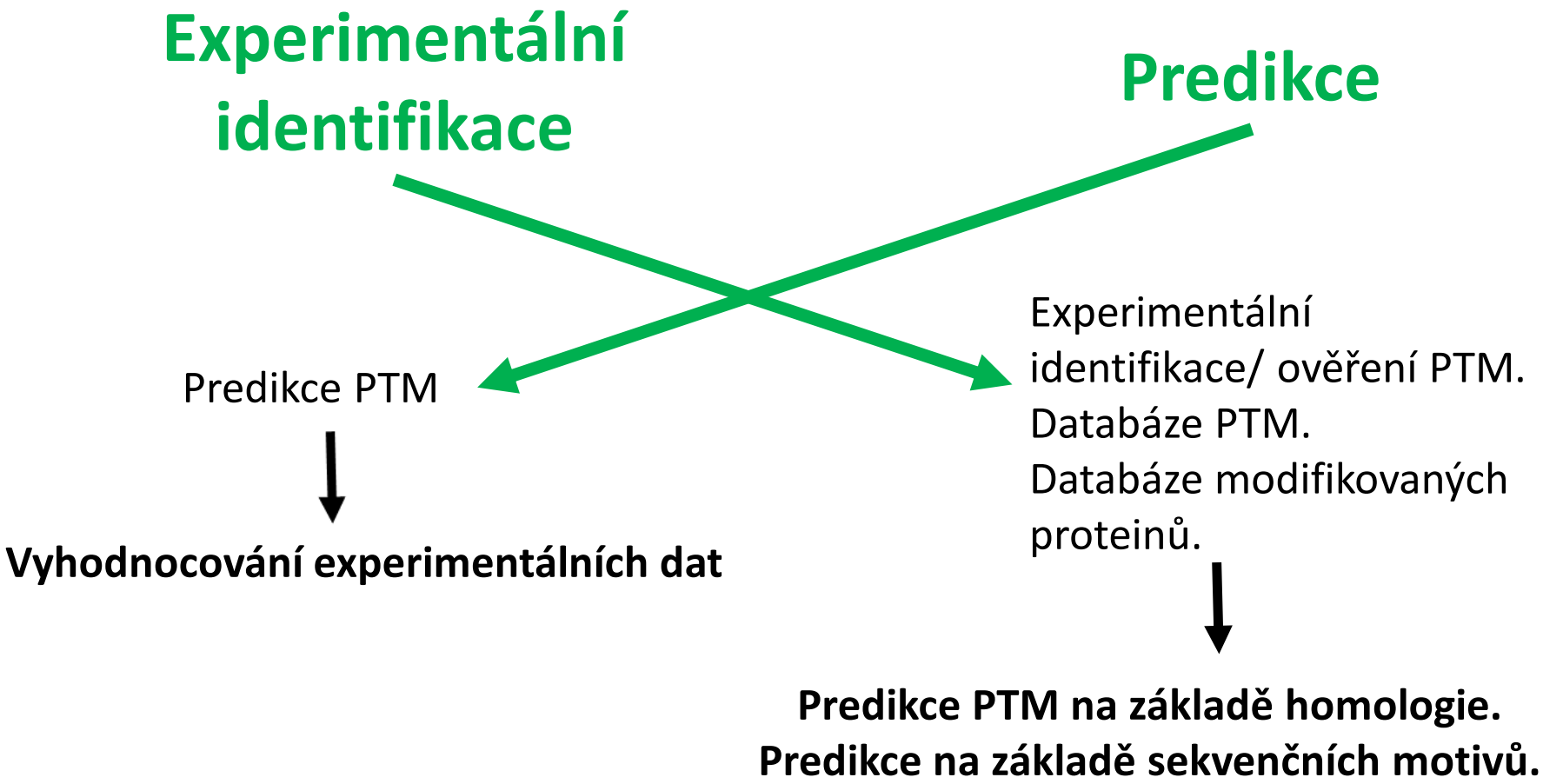
The NetCGlyc 1.0 produces neural network predictions of C-mannosylation sites in mammalian proteins.

```
##gff-version 2
##source-version netCglyc-1.0b
##date 2007-03-14
##Type Protein
# seqname                source         feature  start    end    score +/-  ?
# ------------------------------------------------------------------------------
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno     21     21    0.269  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno     38     38    0.459  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno     41     41    0.639  .   W
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno     44     44    0.484  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno     72     72    0.221  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno    115    115    0.285  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno    207    207    0.228  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno    244    244    0.246  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno    299    299    0.160  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno    317    317    0.203  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno    410    410    0.243  .   .
Q6ZMM2_ATL5_HUMAN        netCglyc-1.0b  C-manno    454    454    0.227  .   .
# ------------------------------------------------------------------------------
```

Only the residues with scores higher than **0.5**, marked with **"W"** are predicted as C-mannosylated.

https://services.healthtech.dtu.dk/services/NetCGlyc-1.0/

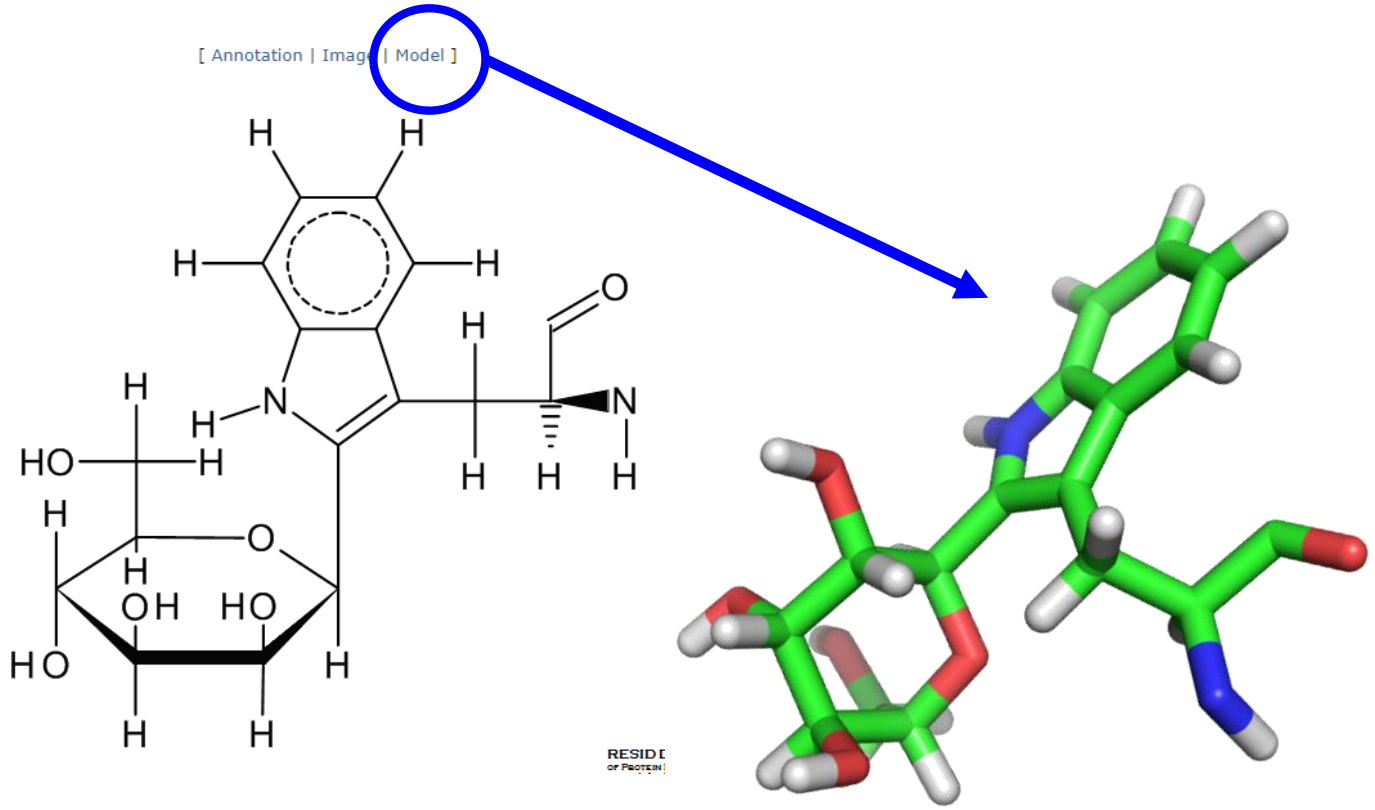
Posttranslační modifikace



Posttranslační modifikace - databáze

List of SequenceSpecs

- L-alanine
- L-arginine
- L-asparagine
- L-aspartic acid
- L-cysteine
- L-glutamic acid
- L-glutamine
- glycine
- L-histidine
- L-isoleucine
- L-leucine
- L-lysine
- L-methionine
- L-phenylalanine
- L-proline
- L-pyrrolysine
- L-selenocysteine
- L-serine
- L-threonine
- L-tryptophan
- L-tyrosine
- L-valine



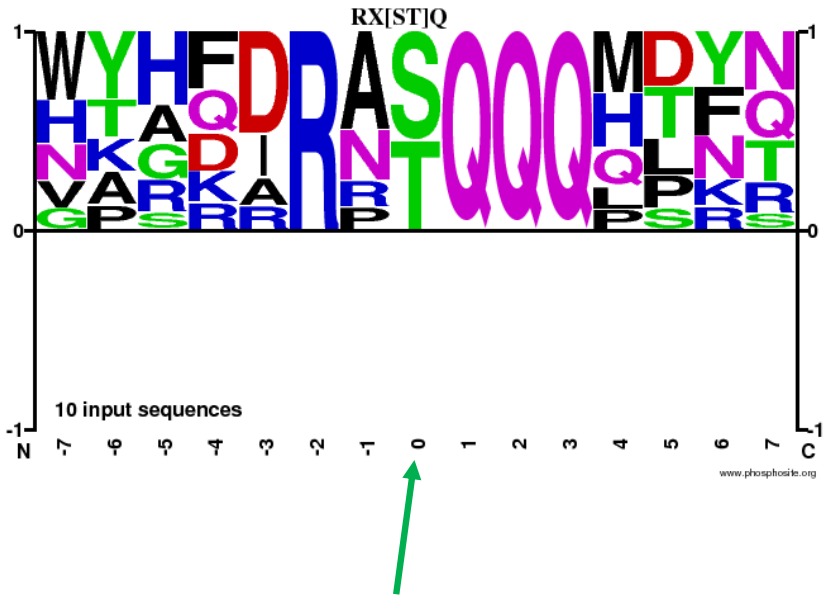
RESID Database at PIR https://pir.georgetown.edu/resid/

RESID Database *Release 76.00 31-May-2018*
Search version Beta-02

Posttranslační modifikace - databáze

PhosphoSitePlus® v6.7.1.1

https://www.phosphosite.org/homeAction



MODIFICATION SITE STATISTICS, NON-REDUNDANT:

Acetylation:	38,343
Caspase cleavage:	484
Di-Methylation:	2,888
Methylation:	296
Mono-Methylation:	15,196
N-Glycosylation:	6,399
O-Galnac:	2,111
O-Glcnac:	1,763
Phospho-Ser:	177,033
Phospho-Thr:	72,726
Phospho-Tyr:	44,927
Succinylation:	4,634
Sumoylation:	8,688
Tri-Methylation:	348
Ubiquitylation:	110,312

Show Sequence Logo Launch Motif Analysis

You searched for: **Sequence or motif:** RX[ST]Q(3)

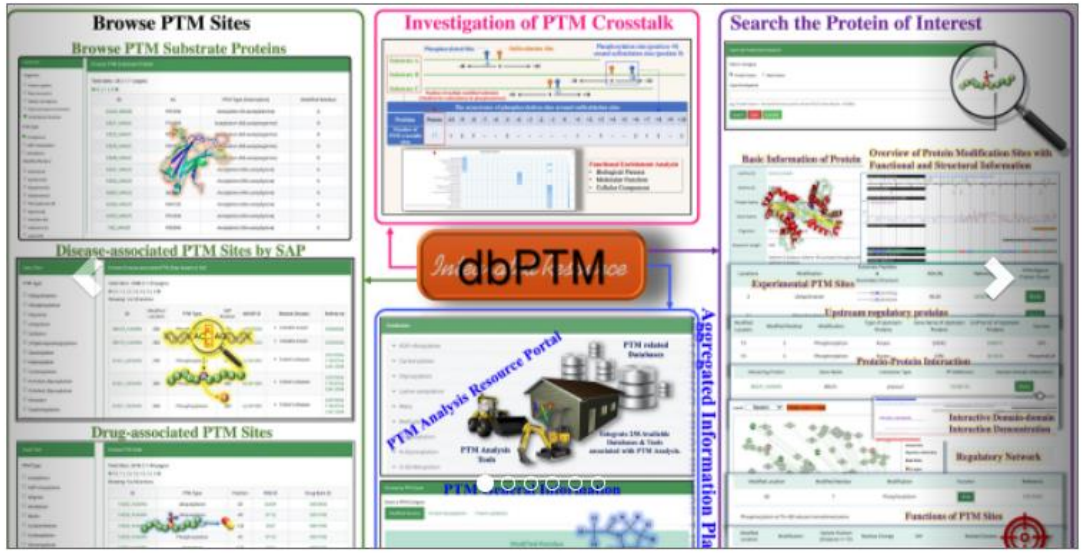
Download

30 6 records found. Displaying 1 of 1 Pages. << First < Previous | Next > Last >>

GENE	PROTEIN	ACC_ID	ORGANISM	MW_(DA)	RSD	SITE_GRP_ID	SITE_+/-7_AA
ABRAXAS2	ABRAXAS2	Q15018	human	46,901	T101-p	23104841	WYRFRRNtQQQMSYR
CRTC2	TORC2	Q53ET0	human	73,302	S447-p	23154638	GPADARRsQQQLPkQ
CSNK1G1	CK1G1	Q9HCP0	human	48,511	S361-p	4270552	HTHRDRPsQQQPLRN
NBN	NBS1	O60934	human	84,959	S447-p	36128582	NksKDRAsQQQQTNS
PRKDC	DNAPK	P78527	human	469,089	T2638-p	448712	VAGQIRAtQQQHDFt
PRKDC	DNAPK	P97313	mouse	471,471	T2634-p	448712	KPGQVRAtQQQYDFT

30 6 records found. Displaying 1 of 1 Pages. << First < Previous | Next > Last >>

Posttranslační modifikace - databáze



dbPTM: an information repository of protein post-translational modification

Tzong-Yi Lee[1], Hsien-Da Huang[1,2,*], Jui-Hung Hung[1], Hsi-Yuan Huang[1], Yuh-Shyong Yang[2,3] and Tzu-Hao Wang[4]

https://awi.cuhk.edu.cn/dbPTM/index.php

dbPTM

Search Results

Search : ricinus

ID	Organism	Protein Name	PTM
2SS_RICCO	Ricinus communis (Castor bean).	2S albumin	Show

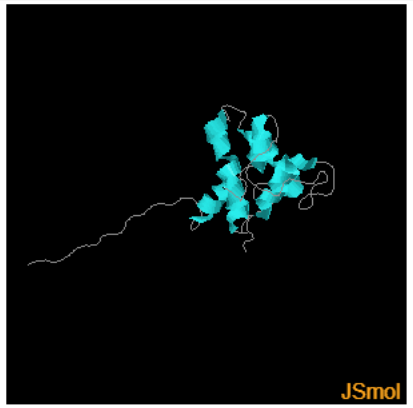
Showing 1 to 1 of 1 entries (filtered from 117 total entries)

2SS_RICCO - PTM Information in dbPTM

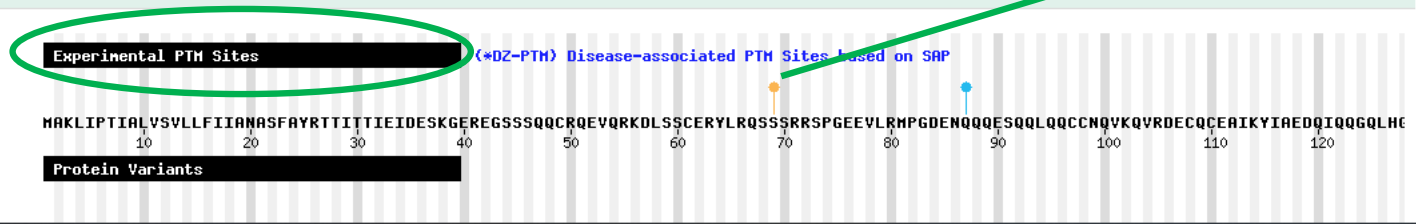
Information | Experimental PTM Sites | Upstream Regulatory Proteins | Interacting Proteins | Disease-associated PTM Sites by SAP | Drug & Disease Associations | Literatures

Basic Information of Protein

UniProt ID	2SS_RICCO
UniProt AC	P01089
Protein Name	2S albumin
Gene Name	
Organism	Ricinus communis (Castor bean).
Sequence Length	258
Subcellular Localization	
Protein Description	2S seed storage proteins..
Protein Sequence	MAKLIPTIALVSVLLFIIANASFAYRTTITTIEIDESKGEREGSSSQQCRQEVQRKDLSSCERYLRQSSSRRSPGEEVLRMPGDENQQQESQQLQQCCNQVKQVRD ECQCEAIKYIAEDQIQQGQLHGEESERVAQRAGEIVSSCGVRCMRQTRTNPSQQGCRGQIQEQQNLRQCQEYIKQQVSGQGPRRSDNQERSLRGCCDHLKQ MQSQCRCEGLRQAIEQQQSQGQLQGQDVFEAFRTAANLPSMCGVSPTECRF



Overview of Protein Modification Sites with Functional and Structural Information



Search by Protein/Gene Keyword

Select a Category

(•) Protein Name ( ) Gene Name

Input the Keyword

albumin

(eg. Protein Name = Serine/threonine-protein kinase Chk2 / Gene Name = CHEK2)

Search | Clear | Example

Purification and sequencing of napin-like protein small and large chains from Momordica charantia and Ricinus communis seeds and determination of sites phosphorylated by plant Ca(2+)-dependent protein kinase

G M Neumann [1], R Condron, G M Polya

https://awi.cuhk.edu.cn/dbPTM/index.php

Posttranslační modifikace – „crosstalk“

The next level of complexity: Crosstalk of posttranslational modifications

A. Saskia Venne, Laxmikanth Kollipara* and René P. Zahedi*

Leibniz-Institut für Analytische Wissenschaften – ISAS – e.V., Dortmund, Germany

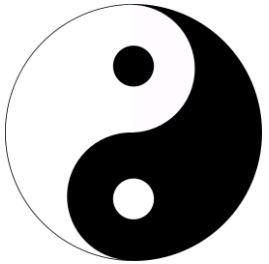
Beside gene expression and translational control, which are relatively slow, PTM of proteins represents the major level of regulation, from very fast and reversible to slow or irreversible processes. PTMs affect protein structure and act as molecular switches, which regulate the interaction of proteins with DNA, cofactors, lipids, and other proteins. In the past few years, evidence for extensive crosstalk between PTMs has accumulated. The combination of different PTMs on protein surfaces can create a "PTM code," which can be recognized by specific effectors to initiate/inhibit downstream events, only inducing/retaining a signal once the complementary incoming signals are present at the same time and place. Although MS-based proteomics has substantially improved our knowledge about PTMs, currently sensitive and dedicated analytical strategies are available only for few different types of PTM. Several recent studies focused on the combinatorial analysis of PTMs, but preferentially utilized peptide-centric bottom-up strategies might be too restricted to decipher complex PTM codes. Here, we discuss the current state of PTM crosstalk research and how proteomics may contribute to understanding PTM codes, representing the next level of complexity and one of the biggest challenges for future proteomics research.

Keywords:
Cell biology / Crosstalk / Interplay / Phosphorylation / PTM code / Ubiquitination

Pozitivní

Negativní

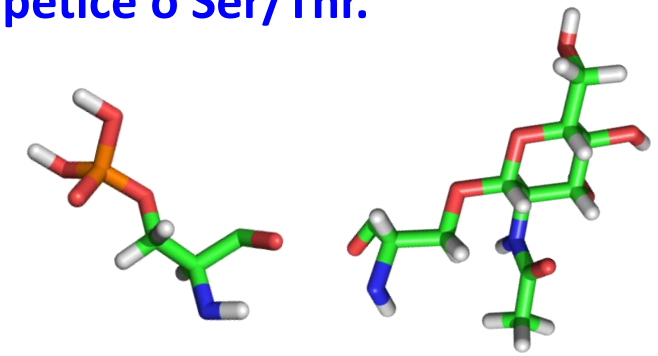
- **Pozitivní – první PTM slouží jako signál pro připojení (odstranění) jiné PTM.**
- **Negativní – přímá kompetice dvou PTM o stejnou aminokyselinu, případně první PTM „maskuje“ místo pro druhou PTM a zabrání jejímu připojení/odstranění.**



Hart *et al.* - *“yin-yang hypothesis”*

O*-fosforylace/*O*-glykosylace *(O-GlcNAc)

Kompetice o Ser/Thr.



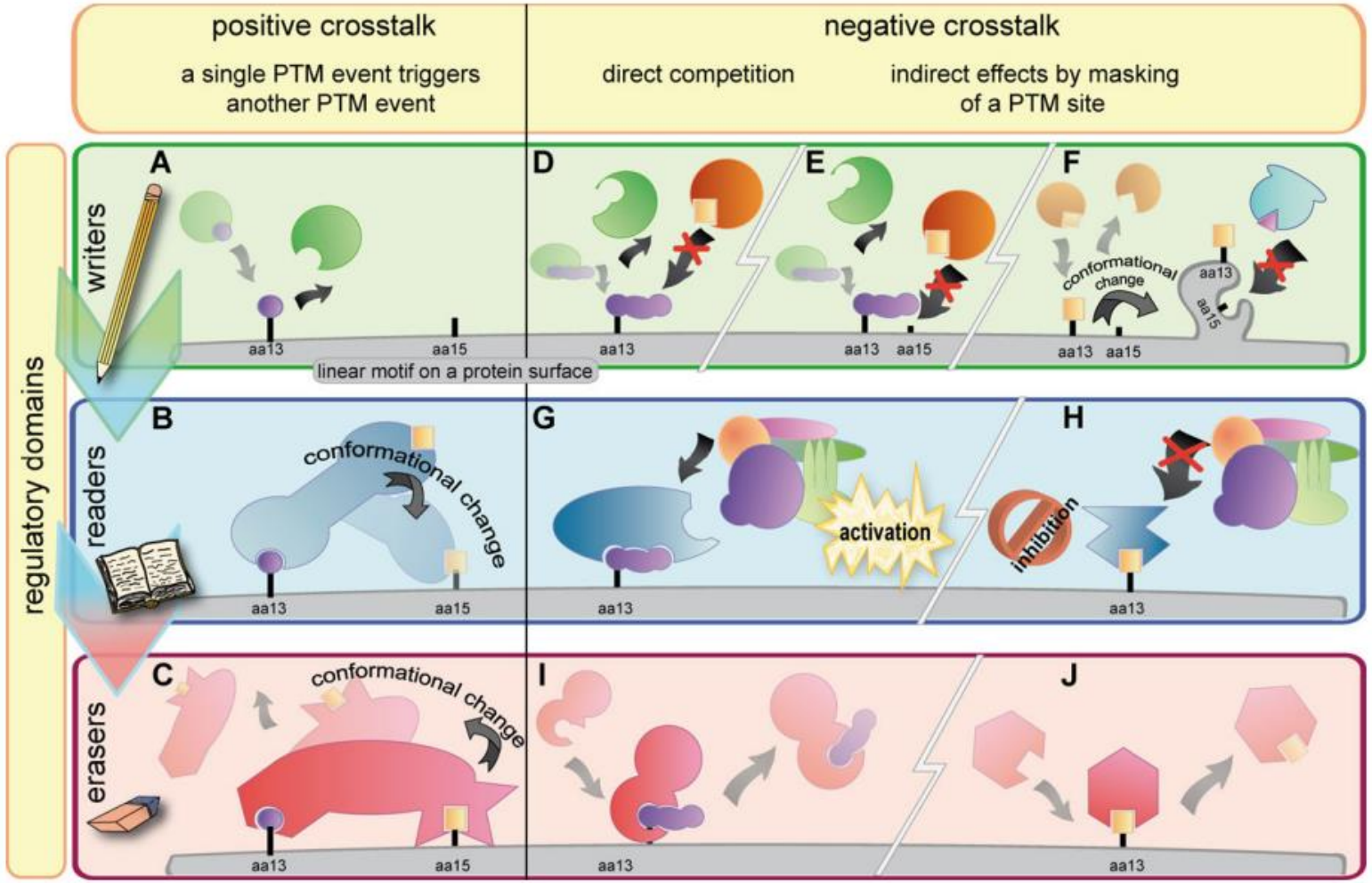


Figure 1. Classification of PTM crosstalk. Short linear motifs on protein surfaces enable protein–protein interaction and can be processed by different regulatory domains. Depending on their function they are classified as writers, readers, and erasers (green, blue, and red rows). In general, positive and negative crosstalk can be distinguished. (A) A writer attaches a PTM to an amino acid (aa) on a target protein. (B) This PTM can attract a reader and trigger the addition of a second PTM, e.g. by recruitment of another writer, or induced by a conformational change of the reader protein itself. (C) Vice versa, a PTM can be read and removed by an eraser protein. Negative crosstalk can be subdivided in direct competition and indirect effects. (D) Two different PTM compete for the same residue. (E) Two PTM have different binding sites but upon initial attachment of the first PTM, the second binding site is indirectly masked. (F) The first PTM leads to a conformational change, which conceals the second PTM binding site from its writer. (G) Depending on which PTM is bound to the respective site different downstream events are initiated: After PTM of the target protein, a protein complex is recruited and the corresponding pathway is triggered. (H) Another PTM can block the respective site such that the pathway is inhibited instead. (I, J) Attached PTM can be removed by an eraser.

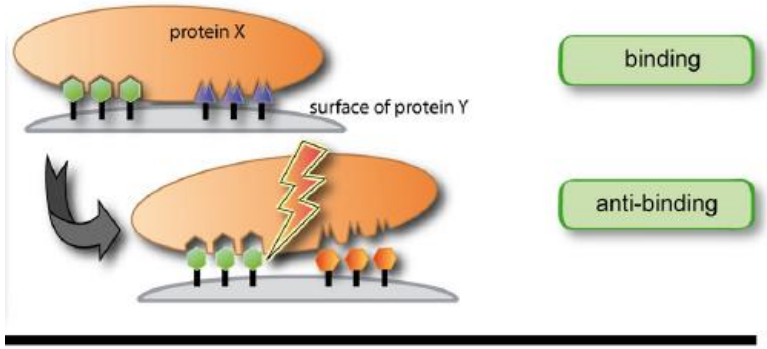
- **Pozitivní – první PTM slouží jako signál pro připojení (odstranění) jiné PTM.**
- **Negativní – přímá kompetice dvou PTM o stejnou aminokyselinu, případně první PTM „maskuje“ místo pro druhou PTM a zabrání jejímu připojení/odstranění.**

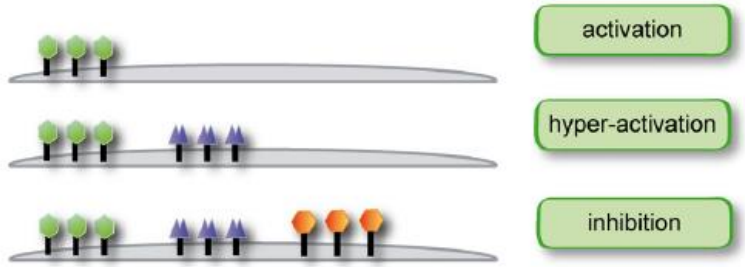
The next level of complexity: Crosstalk of posttranslational modifications

A. Saskia Venne, Laxmikanth Kollipara* and René P. Zahedi*

Posttranslační modifikace – „crosstalk“

- **„Crosstalks“ – vyšší úroveň regulace aktivity proteinů, prevence „chybných“ aktivací/inaktivací. Složitější regulace při zachování stejného množství PTM – různé kombinace, různé efekty, případně různé úrovně odezvy.**
- **Různé proteiny s různou funkcí – nohou podléhat stejným „crosstalk“ mechanismům.**
- **Histon H3 a protein p53 – specifická methylace konkrétního lysinu vyvolá acetylaci druhého lysinu, ve vzdálenosti deset aminokyselin od prvního.**
- **Existuje obecný „PTM kód“ sloužící k lepší regulaci aktivity proteinů???**





Posttranslační modifikace – „crosstalk“

PTMcode: a database of known and predicted functional associations between post-translational modifications in proteins

Pablo Minguez[1], Ivica Letunic[2], Luca Parca[3] and Peer Bork[1,4,*]

[1]European Molecular Biology Laboratory, Meyerhofstrasse 1, 69117 Heidelberg, [2]Biobyte solutions GmbH, Bothestrasse 142, 69126 Heidelberg, Germany, [3]Department of Biology, Centre for Molecular Bioinformatics, University of Rome ‘Tor Vergata’, Via della Ricerca Scientifica snc, 00133 Rome, Italy and [4]Max-Delbruck-Centre for Molecular Medicine, Berlin-Buch, Germany

Received September 15, 2012; Revised October 16, 2012; Accepted October 31, 2012

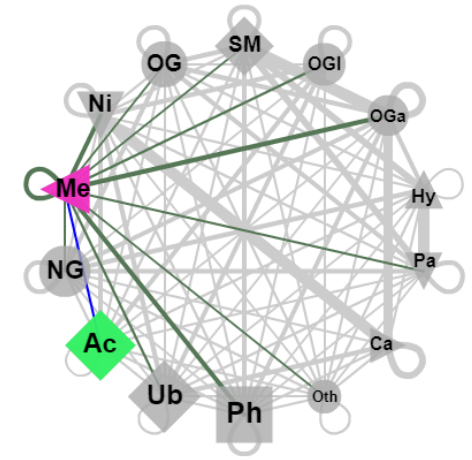
PTMcode v2: a resource for functional associations of post-translational modifications within and between proteins

Pablo Minguez[1], Ivica Letunic[2], Luca Parca[1], Luz Garcia-Alonso[3], Joaquin Dopazo[3], Jaime Huerta-Cepas[1] and Peer Bork[1,4,*]

[1]European Molecular Biology Laboratory (EMBL), Meyerhofstrasse 1, 69117 Heidelberg, Germany, [2]Biobyte solutions GmbH, Bothestr 142, 69117 Heidelberg, Germany, [3]Computational Genomics Department, Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain and [4]Max-Delbruck-Centre for Molecular Medicine, Berlin-Buch, Germany

Received September 15, 2014; Revised October 13, 2014; Accepted October 16, 2014

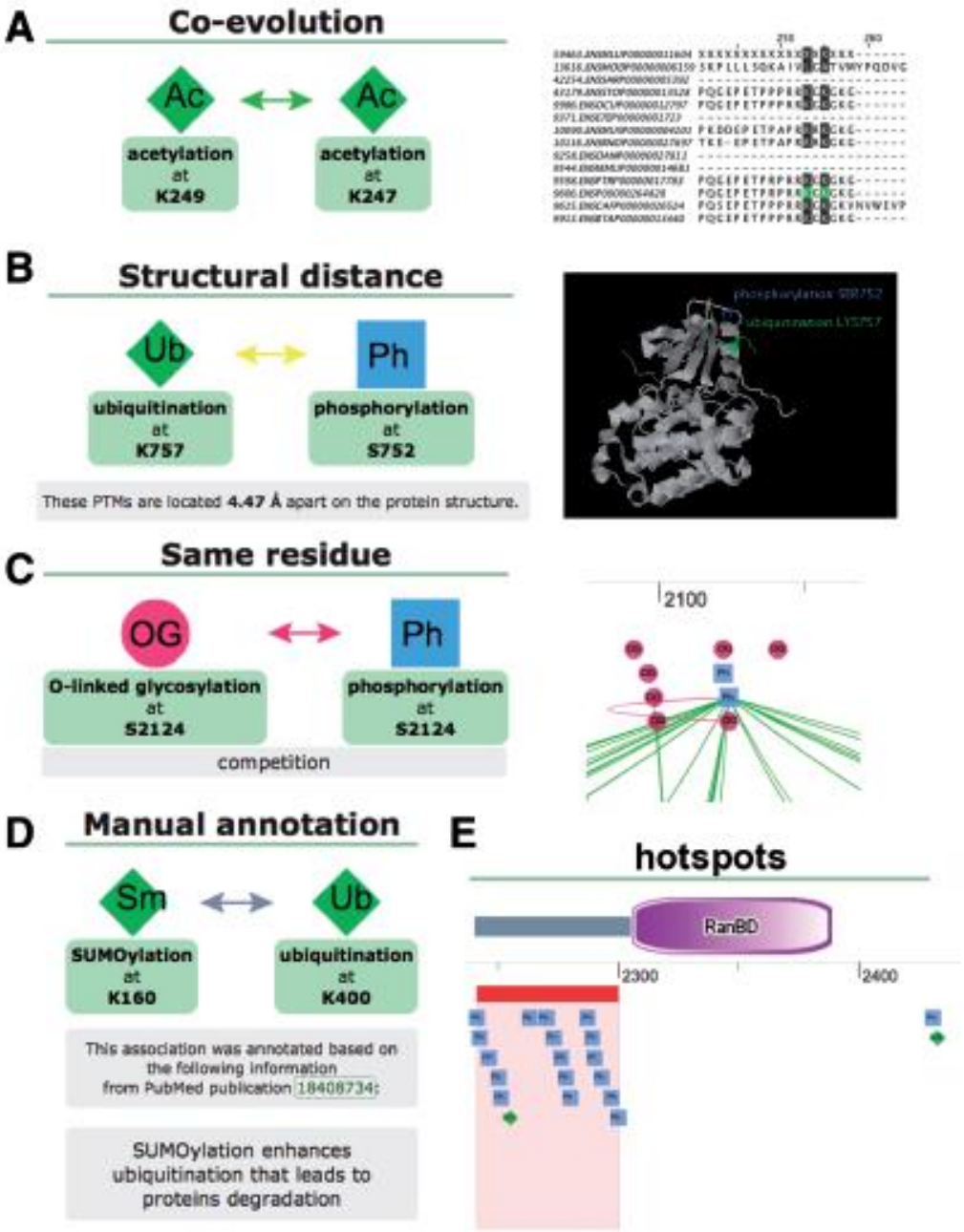
PTMcode 2



http://ptmcode.embl.de/

Known and predicted PTM functional associations

PTMCode is a resource of known and predicted functional associations between protein post-translational modifications (PTMs) within and between interacting proteins. It currently contains 316,546 modified sites from 69 different PTM types which are also propagated through ortholgs between 19 different eukaryotic species. A total of 1.6 million sites and 17 million functional associations more than 100,000 proteins can currently be explored.



PTMcode 2

PTMcode: a database of known and predicted functional associations between post-translational modifications in proteins

A: Dvě modifikovaná rezidua jsou evolučně konzervovaná.

B: Dvě modifikovaná rezidua jsou blíž, než je pro PTM typické.

C: Dvě PTM probíhají ve stejném místě.

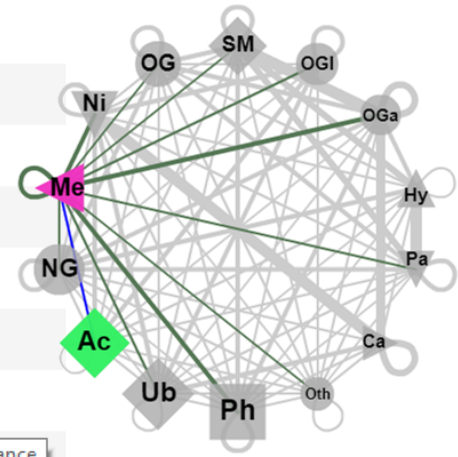
D: Manuální anotace (publikace). Známé experimentální „crosstalks“.

E: „Hotspots“ – oblasti proteinu s vysokým výskytem modifikací.

Functional associations between acetylation and methylation

The table below lists all proteins in our database where a functional association between acetylation (Ac) and methylation (Me) was predictied. The evidence supporting the prediction is listed in the last column. Click on any evidence type box to display more details about it. To explore any protein in detail, click on it to pre-fill the input form above.

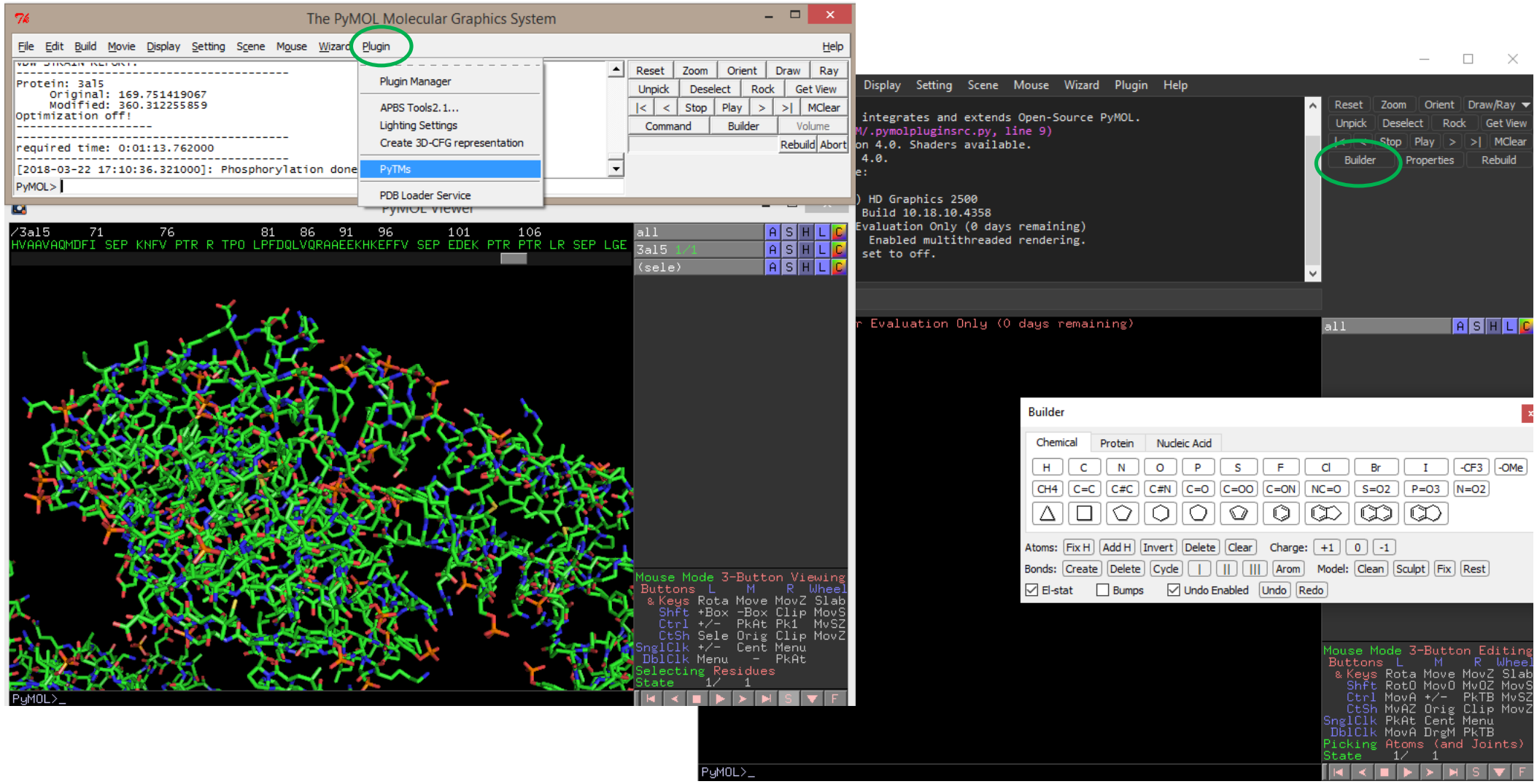
Akap8	Mus musculus	Ac	K301	87	Me	R188	86	
AKAP8L	Homo sapiens	Ac	K257	55	Me	R237	86	
ALB	Homo sapiens	Ac	K198	88	Me	K75	86	
ALB	Homo sapiens	Ac	K183	41	Me	K75	86	
ALB	Homo sapiens	Ac	K558	93	Me	K558	93	
ALB	Homo sapiens	Ac	K75	86	Me	K75	86	
ALB	Homo sapiens	Ac	K569	92	Me	K558	93	
ALB	Homo sapiens	Ac	K524	81	Me	K558	93	
ALDH1A1	Homo sapiens	Ac	K367	59	Me	R68	79	
ALDH1A1	Homo sapiens	Ac	K128	64	Me	R68	79	
ALDH1A1	Homo sapiens	Ac	K419	37	Me	R68	79	
ALDH1A1	Homo sapiens	Ac	K412	54	Me	R68	79	
Aldoa	Mus musculus	Ac	K200	68	Me	K322	77	
ALS2	Homo sapiens	Ac	K1281	84	Me	R481	89	
ANKRD12	Homo sapiens	Ac	K1036	67	Me	K1036	67	
ANKRD12	Homo sapiens	Ac	K1034	75	Me	K1034	75	
ANKZF1	Homo sapiens	Ac	K310	77	Me	K599	97	



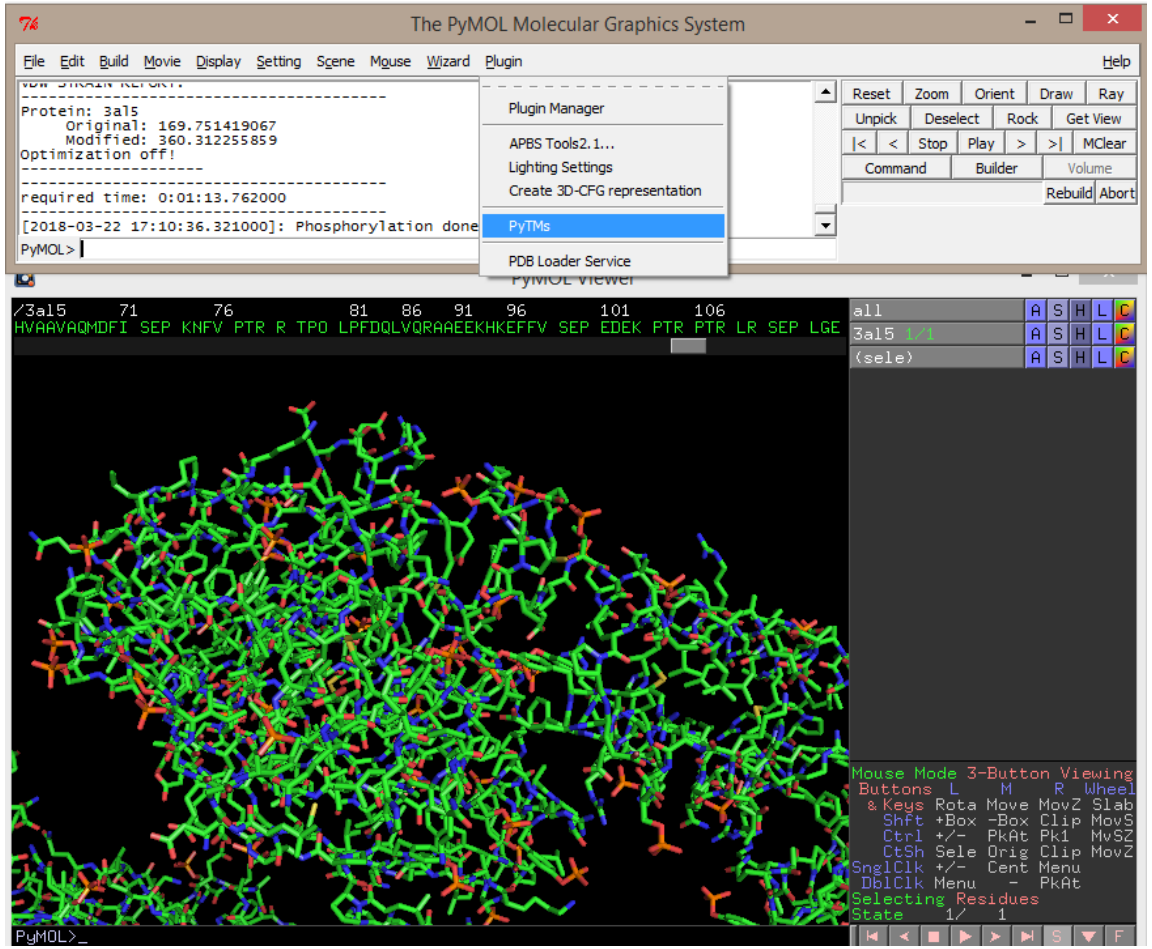
Browse PTMs

PTMcode requires Adobe Flash Player version **11.1.0** or greater. Since 2021, Flash is no longer supported by Adobe. You can still access PTMcode using an older plugin version (e.g. v 11.9.900), and possibly an older browser version (Firefox 58 works fine with this plugin).

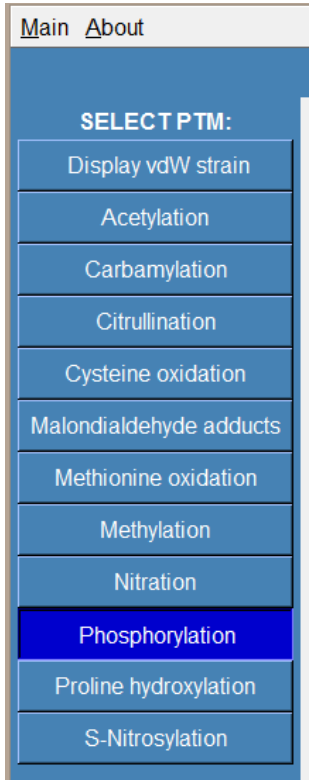
Posttranslační modifikace - vizualizace



Posttranslační modifikace - vizualizace



PyTMs



https://pymolwiki.org/index.php/Pytms

SOFTWARE Open Access

PyTMs: a useful PyMOL plugin for modeling common post-translational modifications

Andreas Warnecke[1*], Tatyana Sandalova[2], Adnane Achour[2] and Robert A Harris[1*]

Abstract

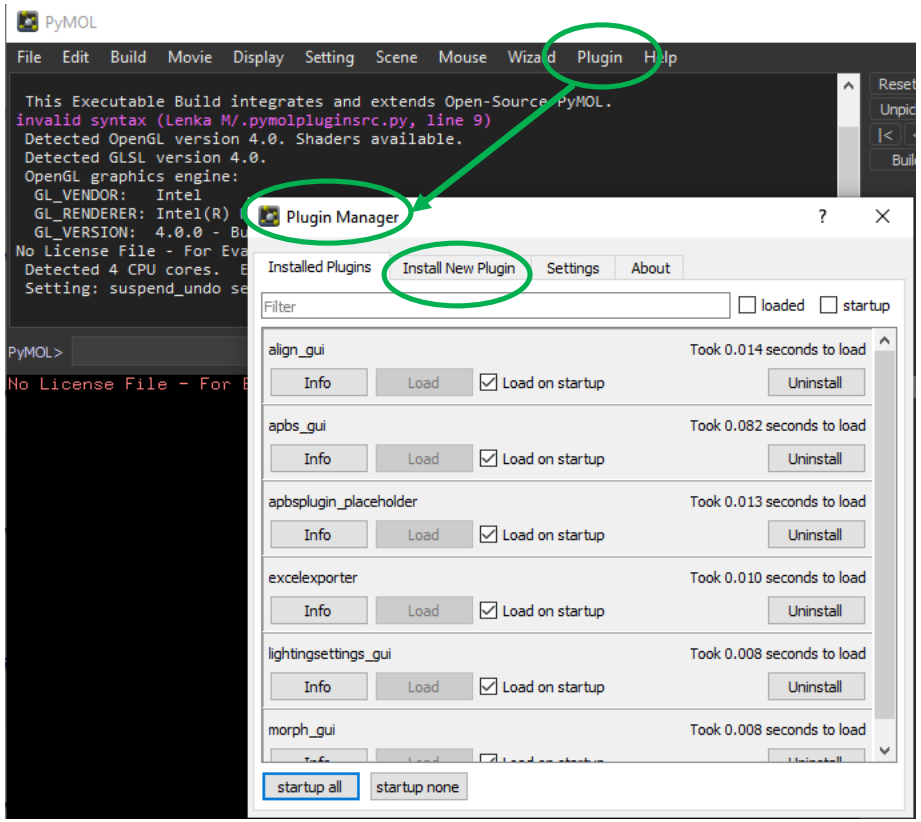
Background: Post-translational modifications (PTMs) constitute a major aspect of protein biology, particularly signaling events. Conversely, several different pathophysiological PTMs are hallmarks of oxidative imbalance or inflammatory states and are strongly associated with pathogenesis of autoimmune diseases or cancers. Accordingly, it is of interest to assess both the biological and structural effects of modification. For the latter, computer-based modeling offers an attractive option. We thus identified the need for easily applicable modeling options for PTMs.

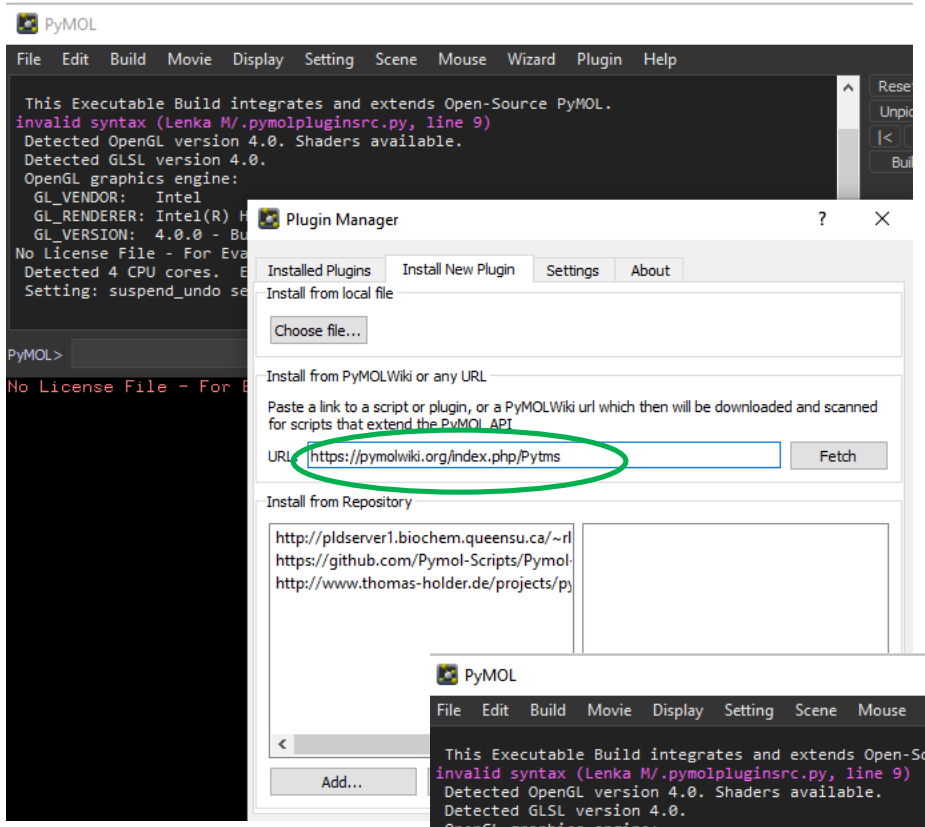
Results: We developed PyTMs, a plugin implemented with the commonly used visualization software PyMOL. PyTMs enables users to introduce a set of common PTMs into protein/peptide models and can be used to address research questions related to PTMs. Ten types of modification are currently supported, including acetylation, carbamylation, citrullination, cysteine oxidation, malondialdehyde adducts, methionine oxidation, methylation, nitration, proline hydroxylation and phosphorylation. Furthermore, advanced settings integrate the pre-selection of surface-exposed atoms, define stereochemical alternatives and allow for basic structure optimization of the newly modified residues.

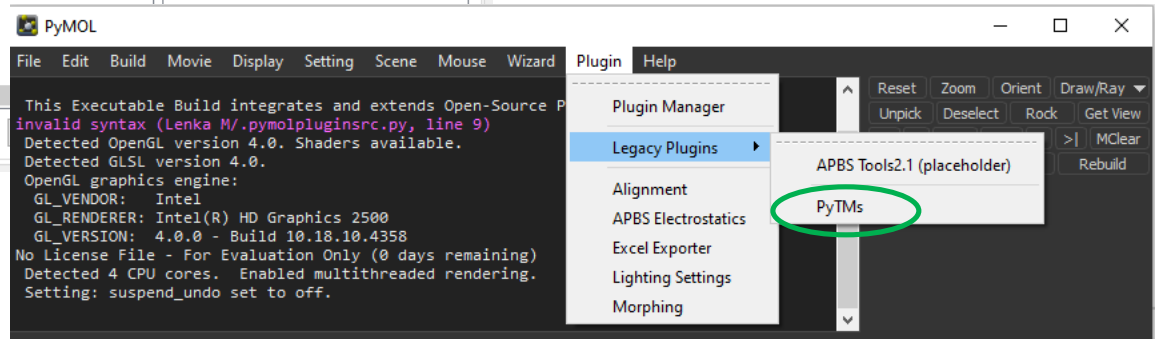
Conclusion: PyTMs is a useful, user-friendly modelling plugin for PyMOL. Advantages of PyTMs include standardized generation of PTMs, rapid time-to-result and facilitated user control. Although modeling cannot substitute for conventional structure determination it constitutes a convenient tool that allows uncomplicated exploration of potential implications prior to experimental investments and basic explanation of experimental data. PyTMs is freely available as part of the PyMOL script repository project on GitHub and will further evolve.

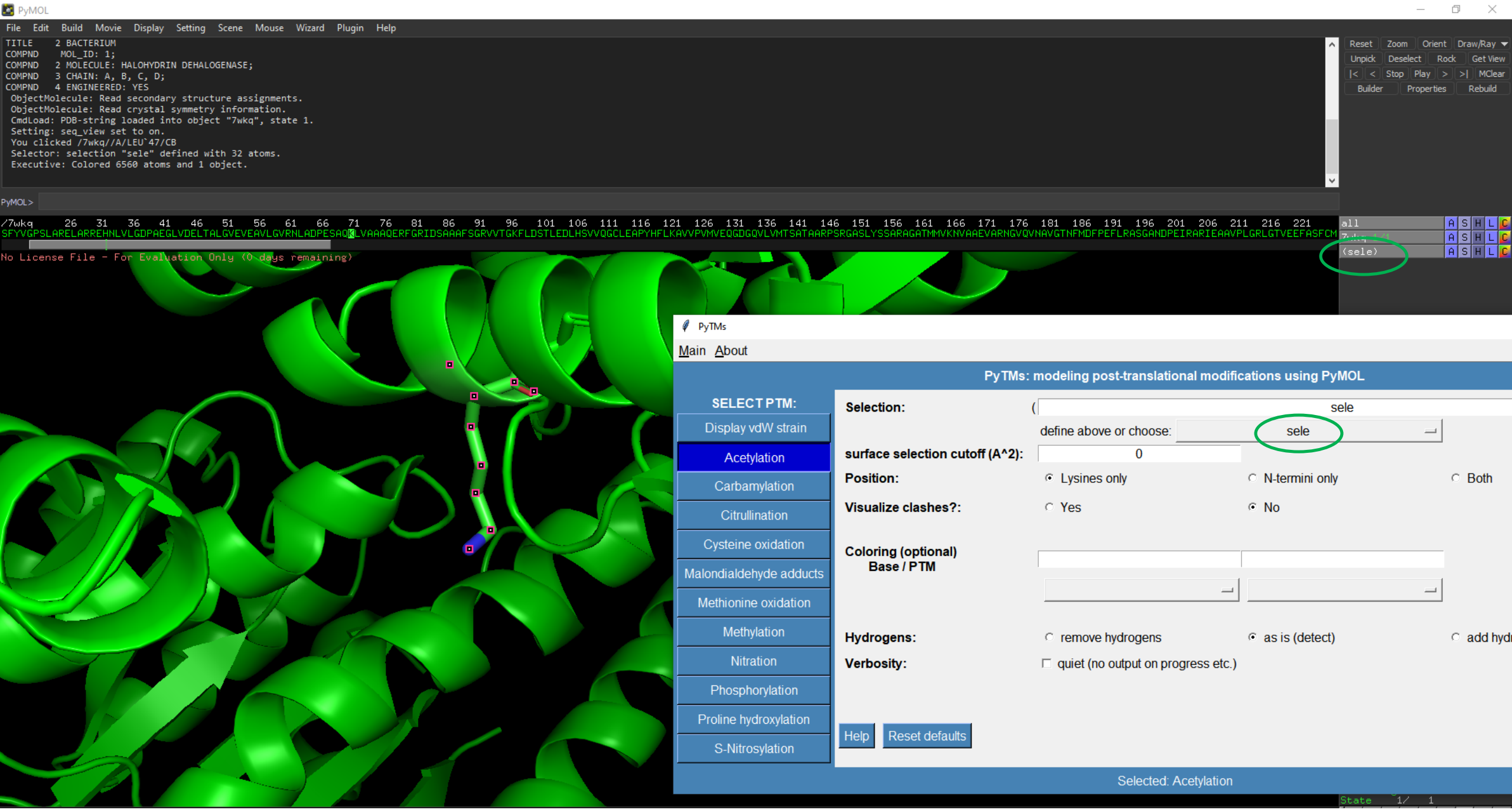
Keywords: Post-translational modifications, PyMOL plugin, Structural bioinformatics, Modeling, Acetylation, Carbamylation, Citrullination, Oxidations, Malondialdehyde adducts, Nitration

Posttranslační modifikace - vizualizace








PyMOL
File Edit Build Movie Display Setting Scene Mouse Wizard Plugin Help
TITLE 2 BACTERIUM
COMPND MOL_ID: 1;
COMPND 2 MOLECULE: HALOHYDRIN DEHALOGENASE;
COMPND 3 CHAIN: A, B, C, D;
COMPND 4 ENGINEERED: YES
ObjectMolecule: Read secondary structure assignments.
ObjectMolecule: Read crystal symmetry information.
CmdLoad: PDB-string loaded into object "7wkq", state 1.
Setting: seq_view set to on.
You clicked /7wkq//A/LEU`47/CB
Selector: selection "sele" defined with 32 atoms.
Executive: Colored 6560 atoms and 1 object.
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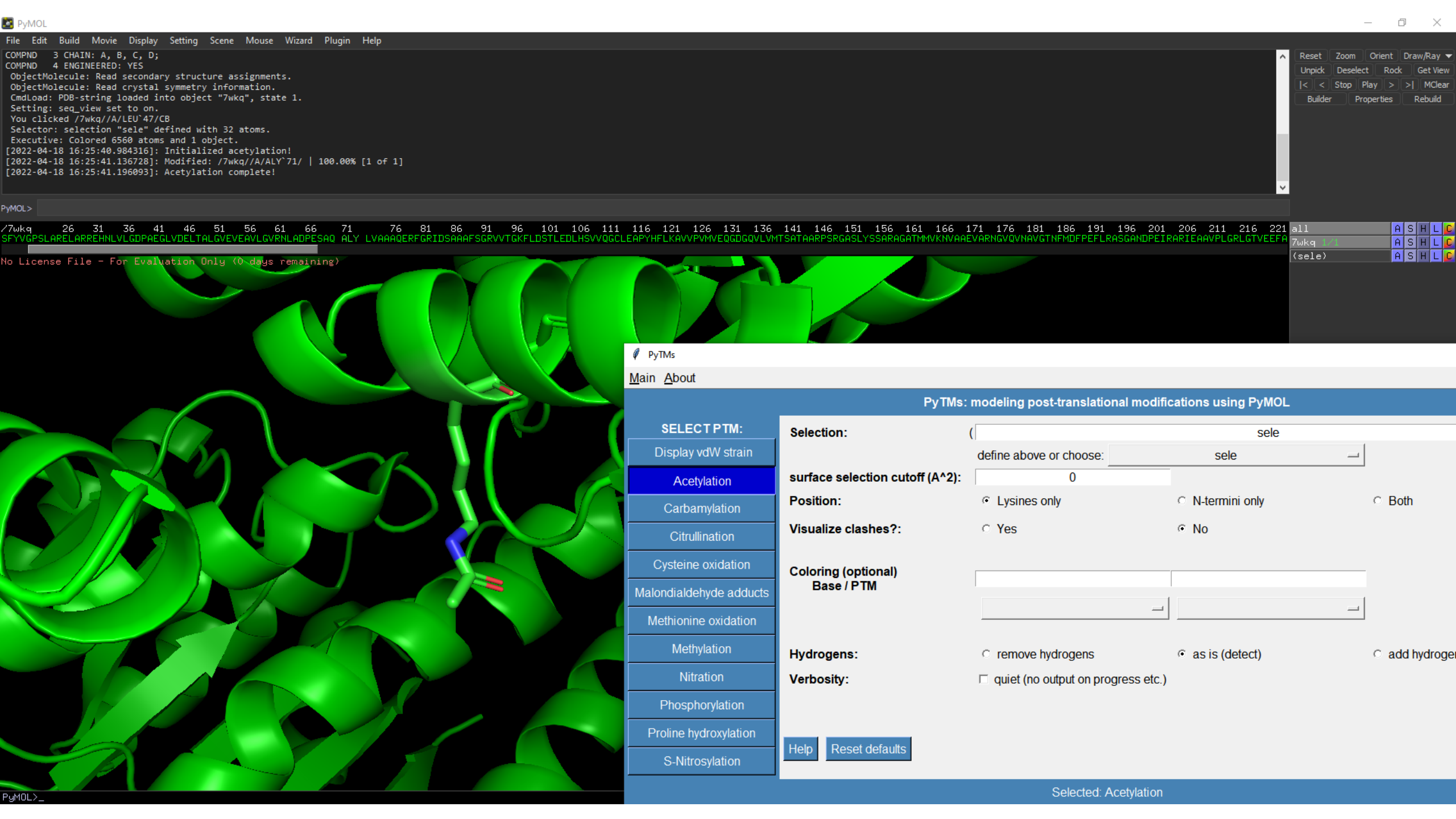
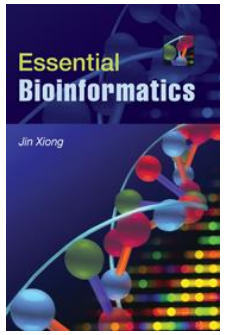
Unpick Deselect Rock Get View
Stop Play MClear
Builder Properties Rebuild
PyMOL>
all
(sele)
No License File - For Evaluation Only (0 days remaining)
PyTMs
Main About
PyTMs: modeling post-translational modifications using PyMOL
SELECT PTM:
Display vdW strain
Acetylation
Carbamylation
Citrullination
Cysteine oxidation
Malondialdehyde adducts
Methionine oxidation
Methylation
Nitration
Phosphorylation
Proline hydroxylation
S-Nitrosylation
Selection:
sele
define above or choose:
surface selection cutoff (A^2):
0
Position:
Lysines only
N-termini only
Both
Visualize clashes?:
Yes
No
Coloring (optional)
Base / PTM
Hydrogens:
remove hydrogens
as is (detect)
Verbosity:
quiet (no output on progress etc.)
Help
Reset defaults
Selected: Acetylation

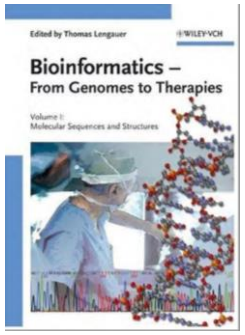

PyMOL
File Edit Build Movie Display Setting Scene Mouse Wizard Plugin Help
COMPND 3 CHAIN: A, B, C, D;
COMPND 4 ENGINEERED: YES
ObjectMolecule: Read secondary structure assignments.
ObjectMolecule: Read crystal symmetry information.
CmdLoad: PDB-string loaded into object "7wkq", state 1.
Setting: seq_view set to on.
You clicked /7wkq//A/LEU`47/CB
Selector: selection "sele" defined with 32 atoms.
Executive: Colored 6560 atoms and 1 object.
[2022-04-18 16:25:40.984316]: Initialized acetylation!
[2022-04-18 16:25:41.136728]: Modified: /7wkq//A/ALY`71/ | 100.00% [1 of 1]
[2022-04-18 16:25:41.196093]: Acetylation complete!
PyMOL>
Reset Zoom Orient Draw/Ray
Unpick Deselect Rock Get View
|< < Stop Play > >| MClear
Builder Properties Rebuild
/7wkq 26 31 36 41 46 51 56 61 66 71 76 81 86 91 96 101 106 111 116 121 126 131 136 141 146 151 156 161 166 171 176 181 186 191 196 201 206 211 216 221
SFYVGPSLARELARREHNLVLGDPAEGLVDELTALGVEVEAVLGVRNLADPESAQ ALY LVAAAQERFGRIDSAAAFSGRVVTGKFLDSTLEDLHSVVQGCLEAPYHFLKAVVPVMVEQGDGQVLVMTSATAARPSRGASLYSSARAGATMMVKNVAAEVARNGVQVNAVGTNFMDFPEFLRASGANDPEIRARIEAAVPLGRLGTVEEFA
all A S H L C
7wkq 1/1 A S H L C
(sele) A S H L C
No License File - For Evaluation Only (0 days remaining)
PyMOL>_
PyTMs
Main About
PyTMs: modeling post-translational modifications using PyMOL
SELECT PTM:
Display vdW strain
Acetylation
Carbamylation
Citrullination
Cysteine oxidation
Malondialdehyde adducts
Methionine oxidation
Methylation
Nitration
Phosphorylation
Proline hydroxylation
S-Nitrosylation
Selection: (sele
define above or choose: sele
surface selection cutoff (A^2): 0
Position: Lysines only N-termini only Both
Visualize clashes?: Yes No
Coloring (optional)
Base / PTM
Hydrogens: remove hydrogens as is (detect) add hydroge
Verbosity: quiet (no output on progress etc.)
Help Reset defaults
Selected: Acetylation

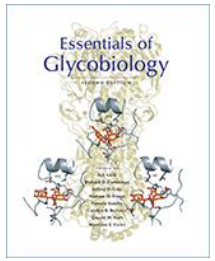
Použitá a doporučená literatura

Bioinformatics-From Genomes to Therapies.
Editors(s):Prof. Dr. Thomas Lengauer.

Jin Xiong. Essential Bioinformatics.







Essentials of Glycobiology, 2nd edition
Chapter 42 Genetic Disorders of Glycosylation

Protein Posttranslational Modifications: The Chemistry of Proteome Diversifications

Christopher T. Walsh, Sylvie Garneau-Tsodikova, and Gregory J. Gatto, Jr.*

Post-translational Modifications and Their Biological Functions: Proteomic Analysis and Systematic Approaches

Jawon Seo and Kong-Joo Lee*

Prediction of Posttranslational Modification of Proteins from Their Amino Acid Sequence

Birgit Eisenhaber and Frank Eisenhaber

Golgi post-translational modifications and associated diseases

Sven Potelle[1] · André Klein[2] · François Foulquier[1]

The next level of complexity: Crosstalk of posttranslational modifications

A. Saskia Venne, Laxmikanth Kollipara* and René P. Zahedi*

Leibniz-Institut für Analytische Wissenschaften – ISAS – e.V., Dortmund, Germany

PTMcode v2: a resource for functional associations of post-translational modifications within and between proteins

Pablo Minguez[1], Ivica Letunic[2], Luca Parca[1], Luz Garcia-Alonso[3], Joaquin Dopazo[3], Jaime Huerta-Cepas[1] and Peer Bork[1,4,*]

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PTMcode: a database of known and predicted functional associations between post-translational modifications in proteins

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dbPTM: an information repository of protein post-translational modification

Tzong-Yi Lee[1], Hsien-Da Huang[1,2,*], Jui-Hung Hung[1], Hsi-Yuan Huang[1], Yuh-Shyong Yang[2,3] and Tzu-Hao Wang[4]

Protein post-translational modifications: *In silico* prediction tools and molecular modeling

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Swiss Institute of Bioinformatics (SIB), Lausanne, Switzerland