

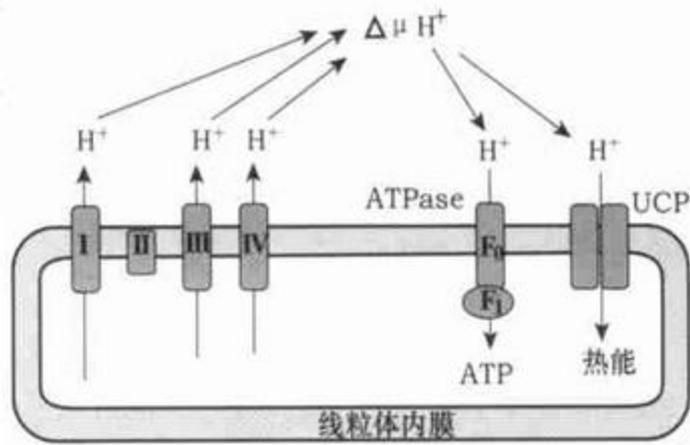
Bioinformatics analysis of UCP2

Group12

Gaomin Feng Dechao Wu Xiaoya Zhang

Outline

- Background
- Sequence analysis
- Structure and function
- Regulation

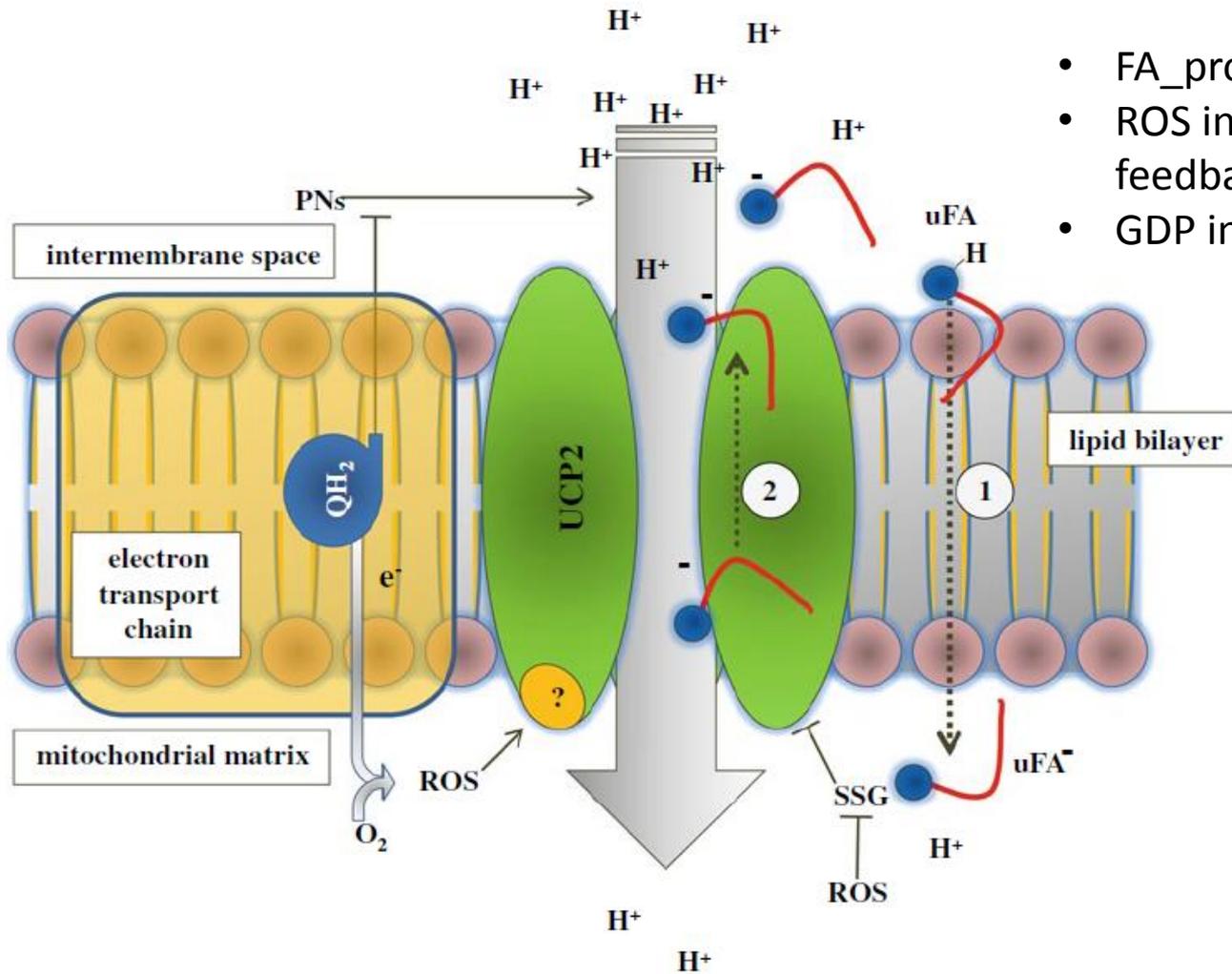


Mitochondrial uncoupling proteins(UCP)

Mitochondrial anion carrier protein family

- UCP1: mainly expressed in brown adipose tissue; Thermogenesis.
- UCP2 has been found in several tissues, such as liver, brain, pancreas, adipose tissue, immune cells, spleen, kidney, and the central nervous system.
- UCP3: mainly expressed in muscle and adipose tissues.
- UCP4 and UCP5, are expressed in a tissue-specific manner and are involved in mitochondrial membrane potential reduction.

Proton conductance activity of UCP2



- FA_proton conductance;
- ROS inducible: negative feedback of ROS production
- GDP inhibition

Function

GO - Biological processⁱ

- aging  Source: Ensembl
- cellular response to amino acid starvation  Source: Ensembl
- cellular response to glucose stimulus  Source: Ensembl
- cellular response to insulin stimulus  Source: Ensembl
- female pregnancy  Source: Ensembl
- liver regeneration  Source: Ensembl
- mitochondrial transport  Source: Ensembl
- negative regulation of apoptotic process  Source: Ensembl
- negative regulation of insulin secretion involved in cellular response to glucose stimulus  Source: Ensembl
- positive regulation of cell death  Source: Ensembl
- regulation of mitochondrial membrane potential  Source: ParkinsonsUK-UCL 
- response to fatty acid  Source: Ensembl
- response to hypoxia  Source: MGI
- response to superoxide  Source: Ensembl

Relationship between ucp2 polymorphisms and various diseases

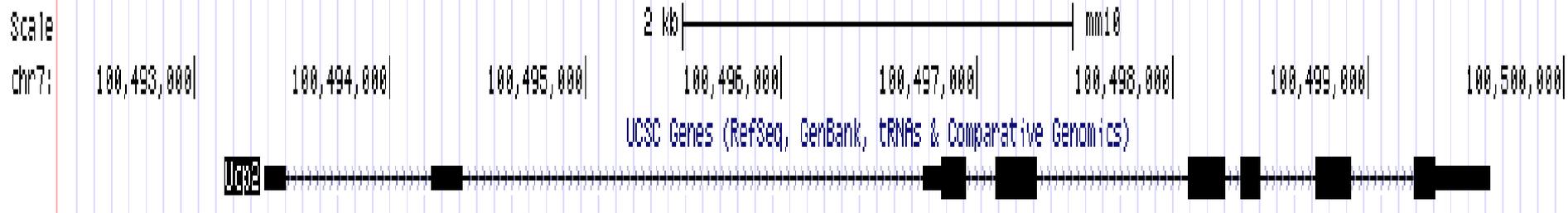
Table 1 Relationship between *UCP2* polymorphisms and various diseases

Polymorphism	Biological effect	Disease	Total subjects studied	References
-866G>A (rs659366)	Higher UCP2 mRNA expression	Abdominal obesity	2,367	[80]
		Obesity and hyperinsulinemia	440	[62]
		Obesity treated with sibutramine	131	[81]
		Diabetes and miocardial infraction	901	[67]
		Obesity and T2D	17,636	[63]
		Childhood obesity and metabolic disorders	200	[82]
		T2D treated with rosiglitazone	354	[61]
		T2D and high-sensitivity C reactive protein	383	[59]
		T2D and coronary artery disease	464	[83]
		Diabetic retinopathy	188	[84]
		Diabetic retinopathy	697	[85]
		Multiple sclerosis	1097	[86]
		Chronic inflammation	ND	[87]
		Hyperglycaemia in severe sepsis	120 + 103	[88]
		T2D and LTL	About 1,000	[89]
		Ala55Val (rs660339)	Lower degree of uncoupling	Stroke
Longevity	598			[74]
Abdominal obesity	2,367			[80]
T2D	1,406			[70]
Diabetic retinopathy	697			[85]
Weight regulation	234			[71]
Body fat and leptin levels	150			[73]
Morbid obesity	304			[72]
High acute insulin response to glucose	155			[69]
Longevity	598			[74]
-5331G>A	ND	T2D	1,393	[75]
Exon 8 deletion/deletion	ND	Fat tissue accumulation during PD	ND	[76]
		Fat tissue accumulation during PD	41	[91]
45 bp insertion/deletion in 3'UTR	ND	Obesity	988	[78]
		Neural tube defects	391	[92]

T2D type 2 diabetes, LTL leukocyte telomere length, PD peritoneal dialysis, ND not determined

Sequence analysis

Ucp2 (UCSC Genome Browser on Mouse)



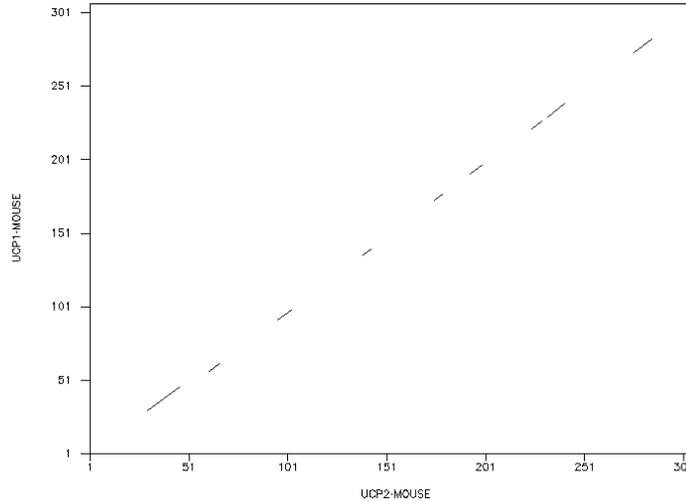
- The gene encoding Ucp2 is located on chromosome 7 in mice and chromosome 11 in humans and contains eight exons and seven introns, spanning an 8- and 6.3-kb region, respectively.
- The transcription unit of Ucp2 gene is composed of two non-coding exons followed by six exons encoding the UCP2 protein.

Protein Sequence analysis

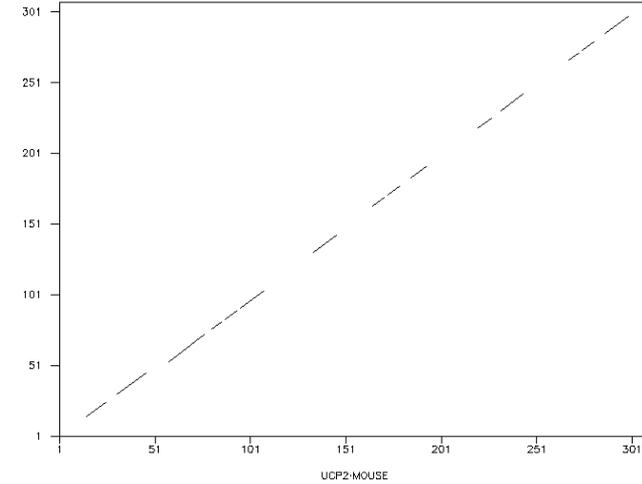
Needle(Identity)

Mouse	UCP2
UCP1	56.3%
UCP3	73.1%
UCP5	31.2%
ADT1	22.3%

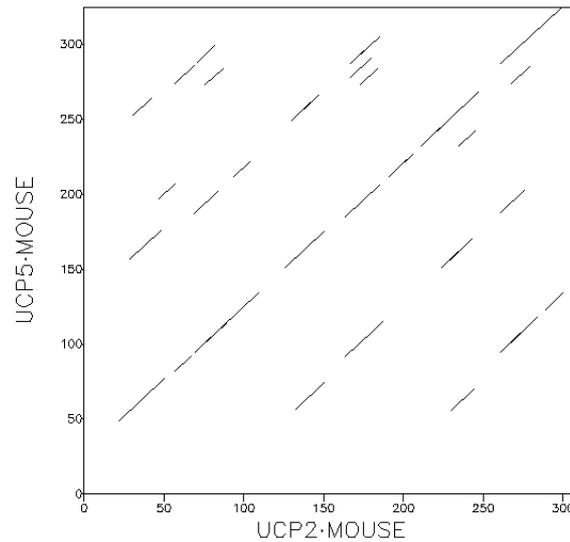
Dottup: fasta::851883:UCP2·MOUSE vs fasta::851860:UCP1·
Sat 27 Jun 2015 19:33:17



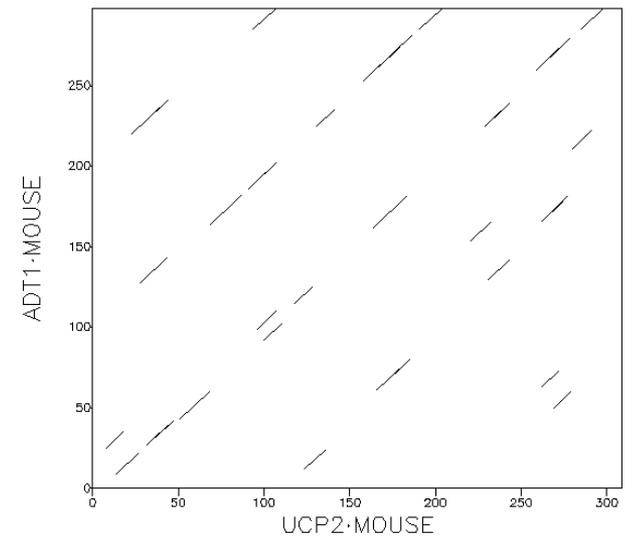
Dottup: fasta::851883:UCP2·MOUSE vs fasta::855650:UCP3·
Sat 27 Jun 2015 19:32:10



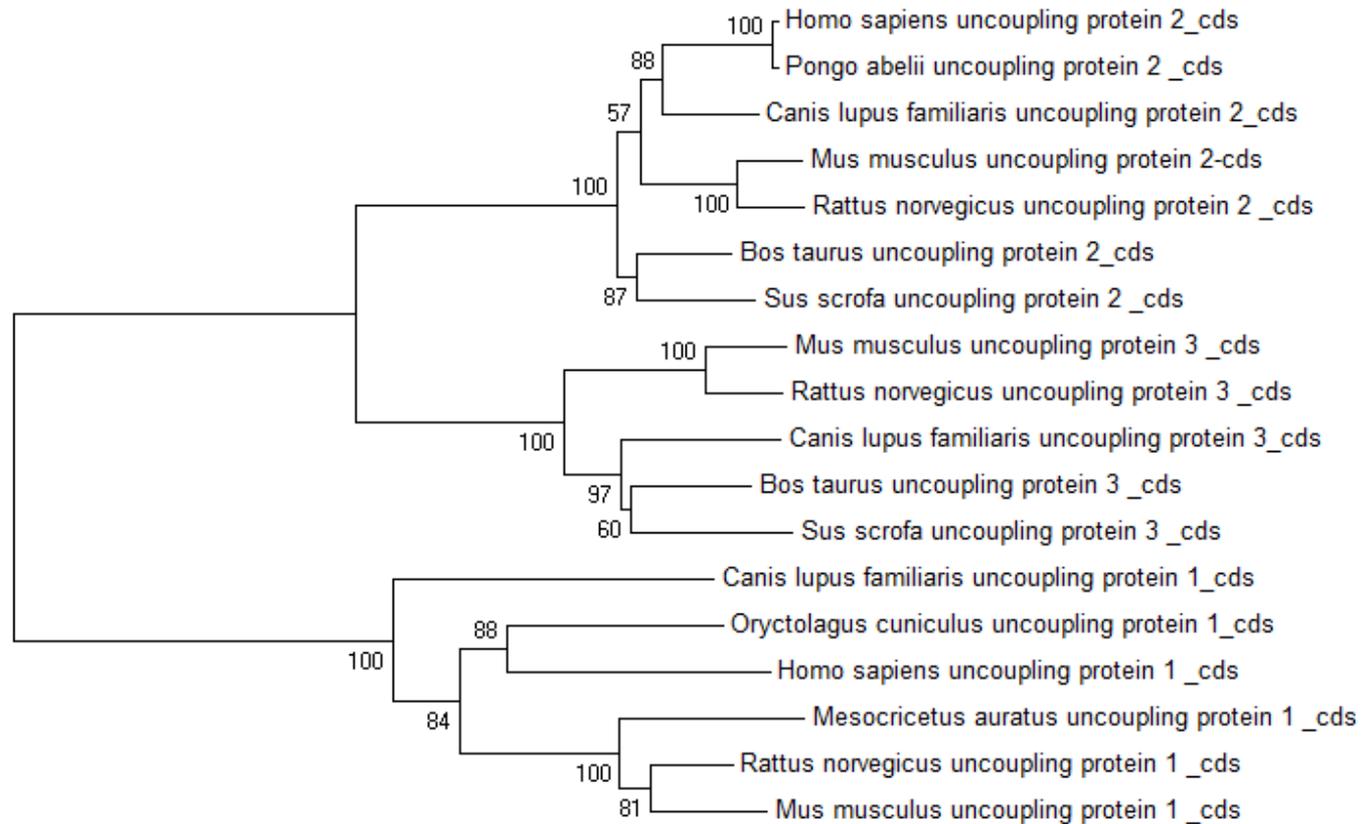
Dotmatcher: fasta::851883:UCP2·MOUSE vs
(windowsize = 10, threshold = 20.00 27/06/1)



Dotmatcher: fasta::851883:UCP2·MOUSE vs fast
(windowsize = 10, threshold = 20.00 27/06/15)



Phylogenetic tree



0.05

Motif discovery

DISCOVERED MOTIFS

	Logo	E-value ?	Sites ?	Width ?	More ?	Submit/Download ?
1.		3.1e-248	7	50	↓	→
2.		1.9e-238	7	50	↓	→
3.		8.5e-222	7	50	↓	→

MOTIF LOCATIONS

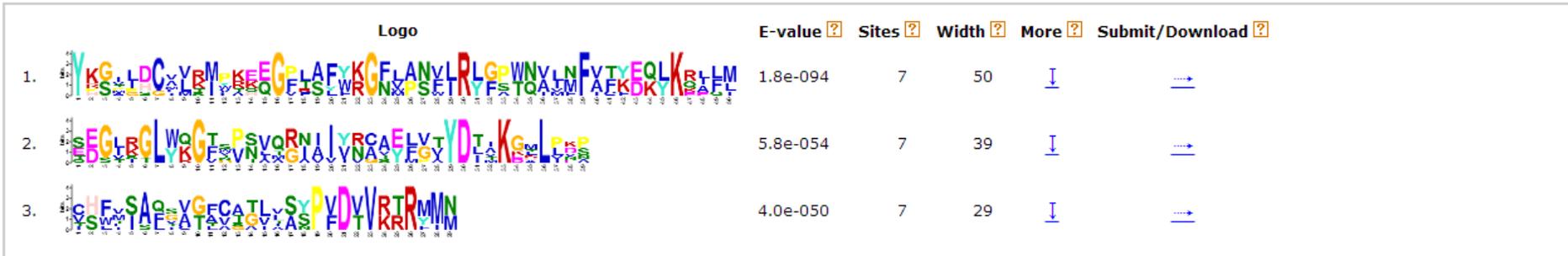
Only Motif Sites
 Motif Sites/Scan
 All Sequences

Name ?	p-value ?	Motif Location ?
1. sp P55851 UCP2_HUMAN	4.23e-179	
2. sp Q5R5A8 UCP2_PONAB	4.23e-179	
3. sp Q9N2J1 UCP2_CANFA	5.92e-177	
4. sp P70406 UCP2_MOUSE	8.26e-179	
5. sp Q3SZI5 UCP2_BOVIN	8.08e-176	
6. sp P56500 UCP2_RAT	4.75e-178	
7. sp O97562 UCP2_PIG	4.49e-172	

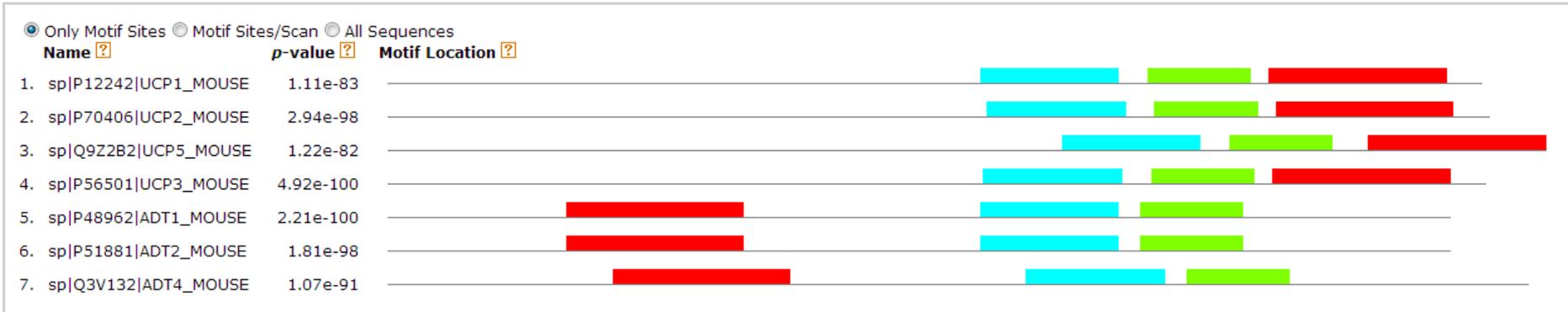
MEME

Motif discovery

DISCOVERED MOTIFS



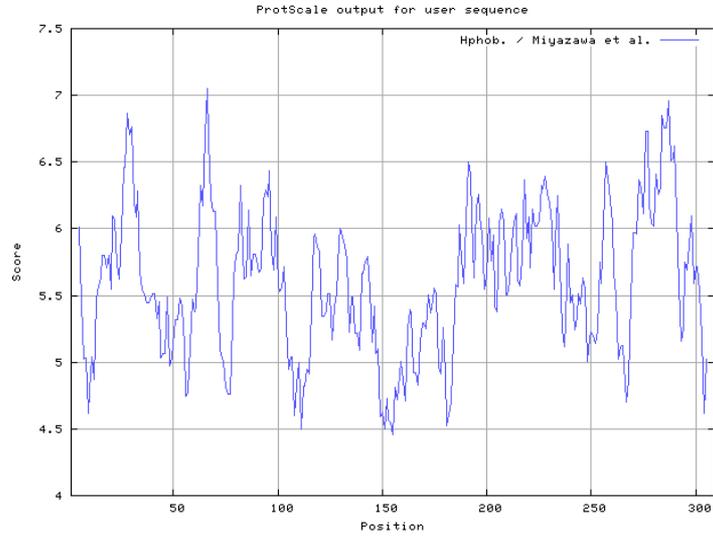
MOTIF LOCATIONS



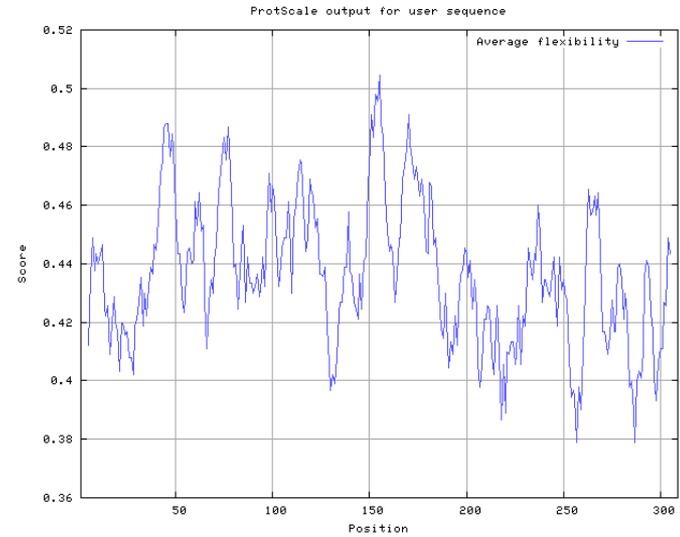
Structure and function

利用ExPASy网站的ProtScale分析UCP2氨基酸的序列特征:

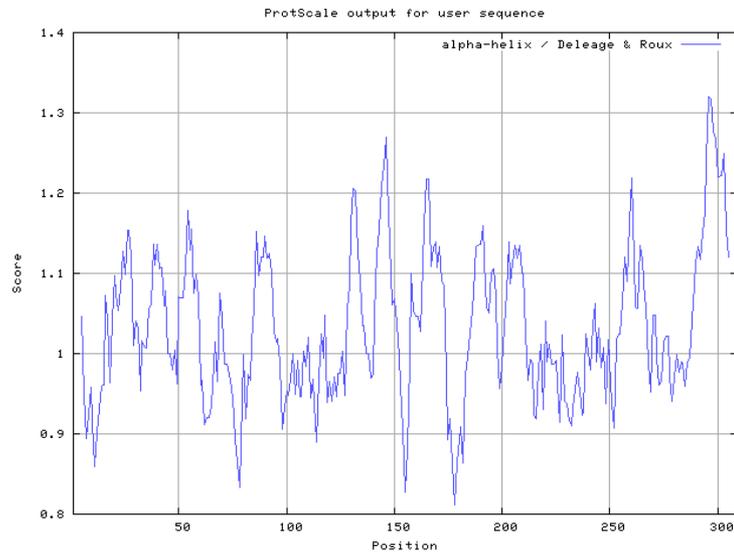
疏水和亲水: (Hphob. / Miyazawa et al)



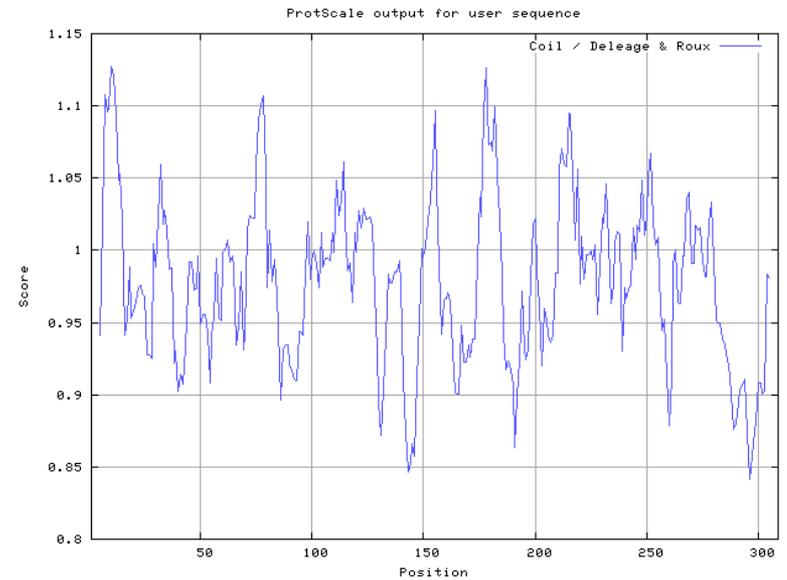
柔性和刚性 (Average flexibility)



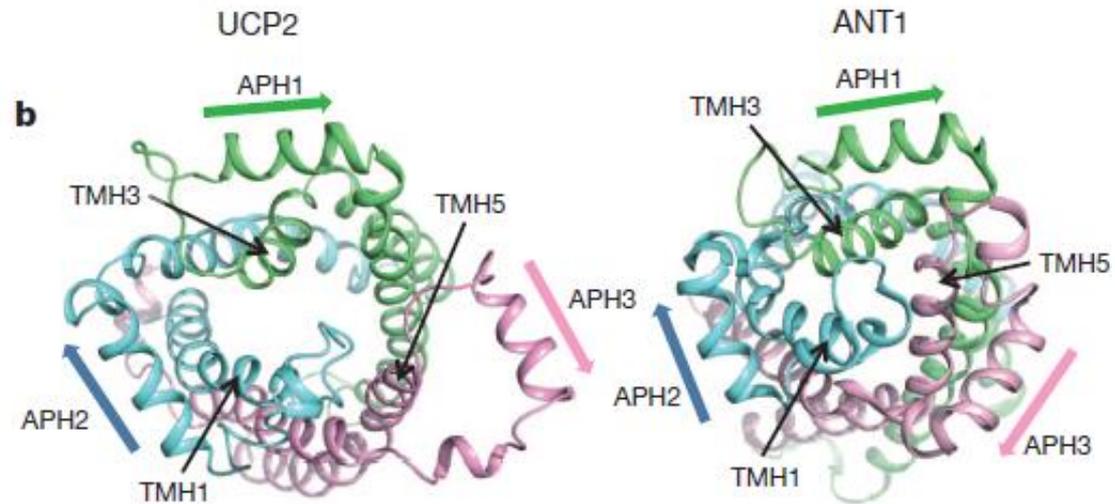
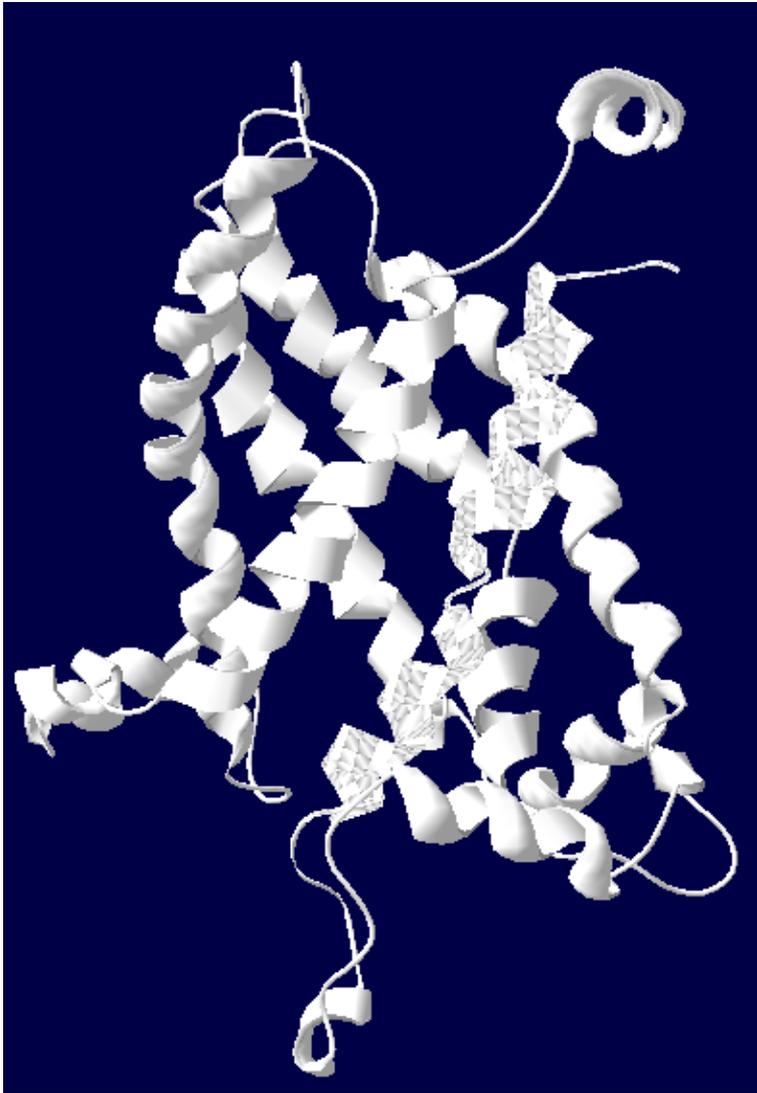
α -Helix (alpha-helix / Deleage & Roux)



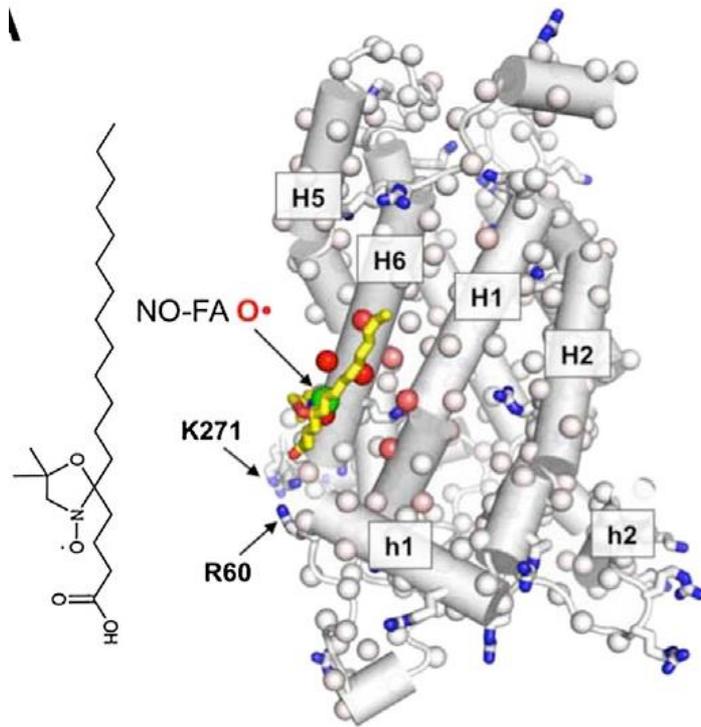
用weblab的Tmap预测可能的跨膜螺旋



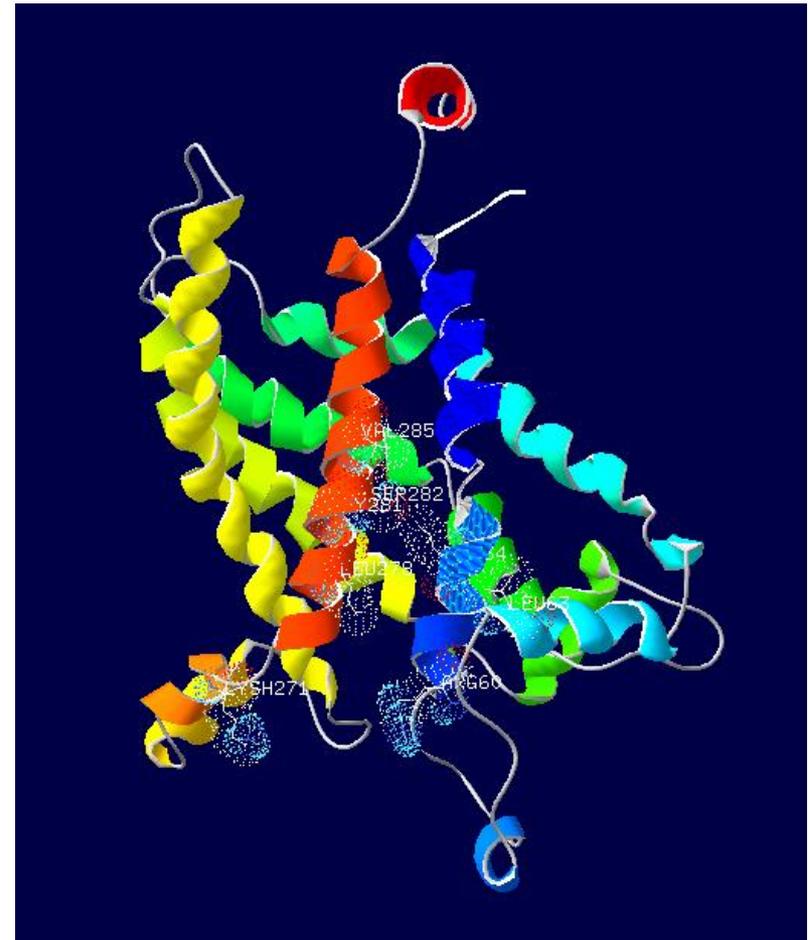
Structure of UCP2_mouse



The carboxylate group is close to the proximal basic residues Arg60 and Lys271, and the acyl chain leans against the hydrophobic groove between H1 and H6.

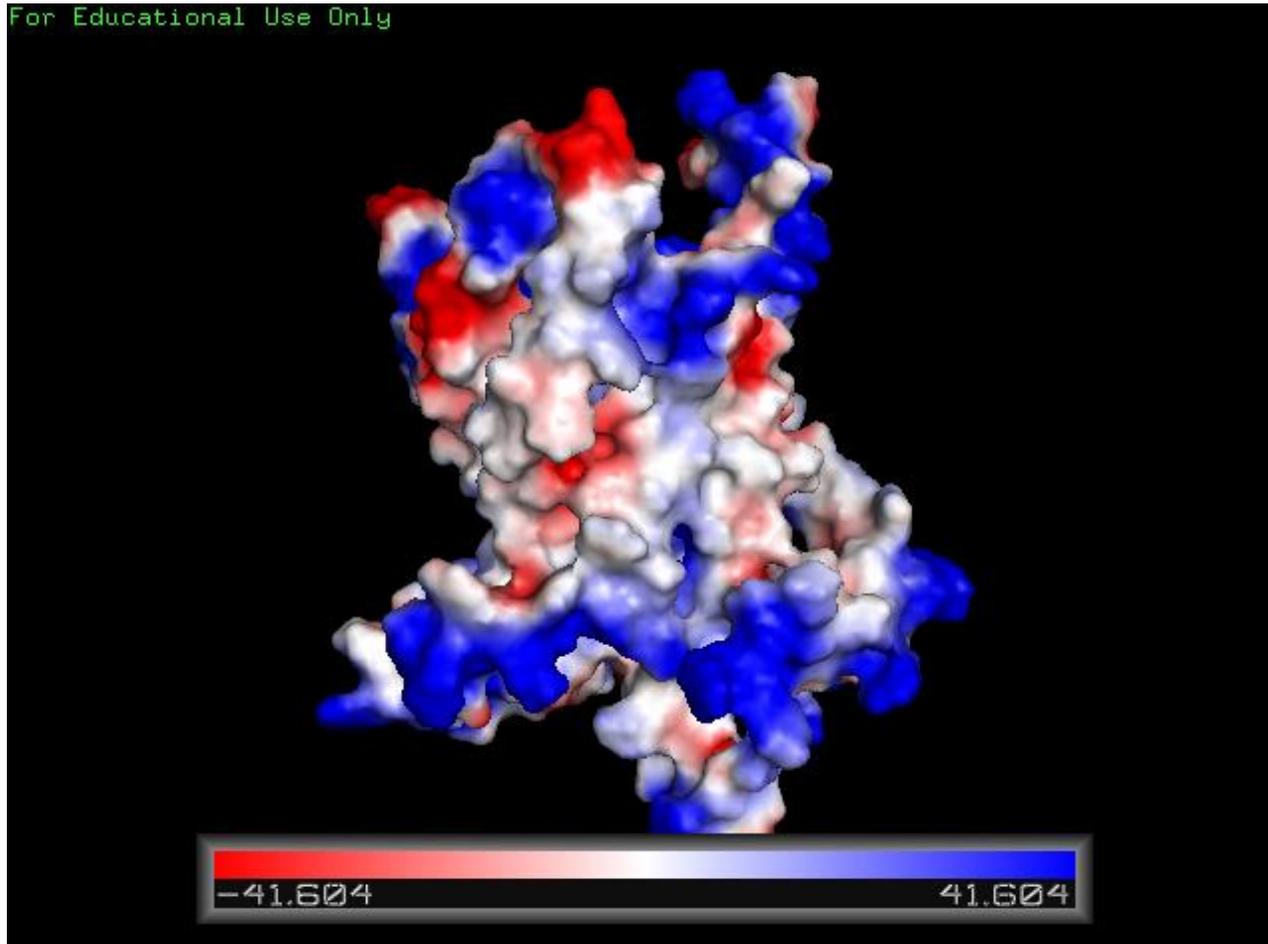


Marcelo J et al, Cell metabolism, 2014



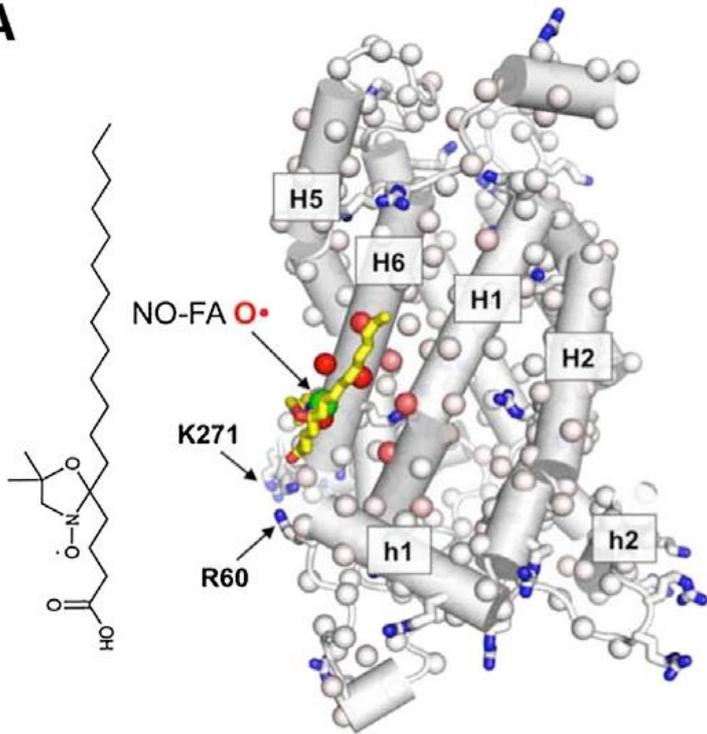
Swiss-PDB viewer

vaccum electrostatics (Pymol)

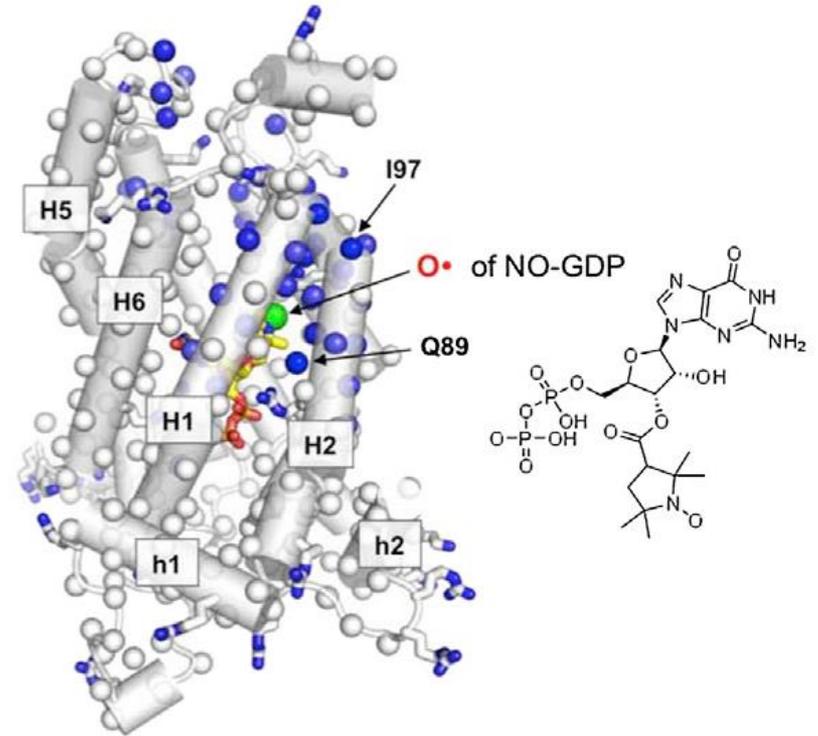


Structural Perturbation of FABound UCP2 by GDP

A

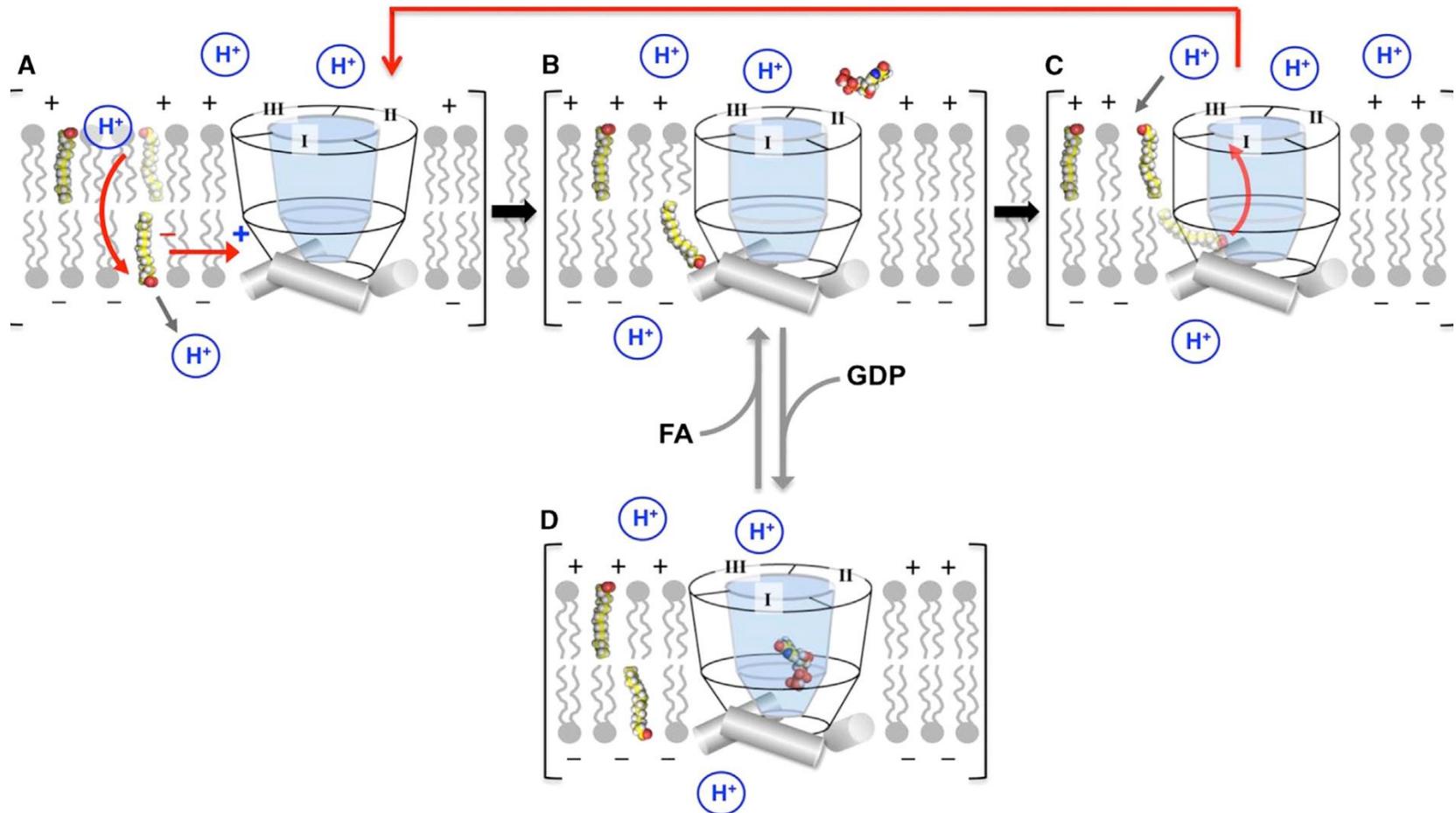


B

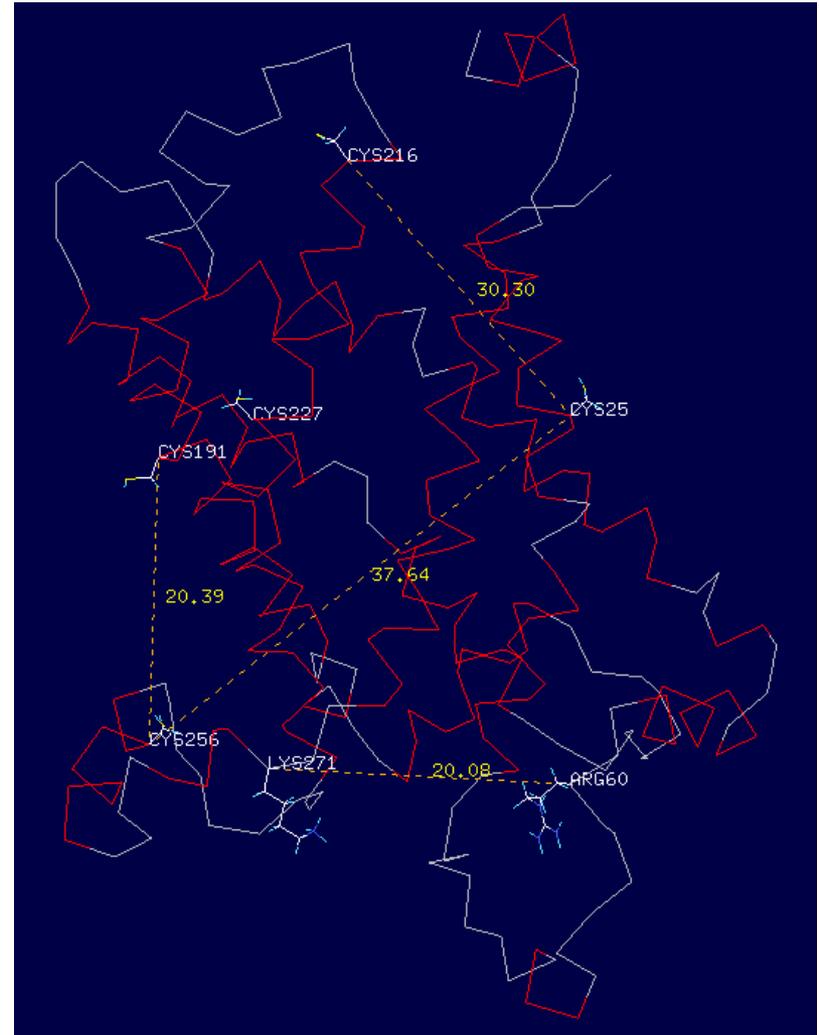


Marcelo J et al, Cell metabolism, 2014

A Model for the Interplay Among FA, UCP2, and GDP in Modulating H⁺ Translocation Across the Mitochondrial Inner Membrane

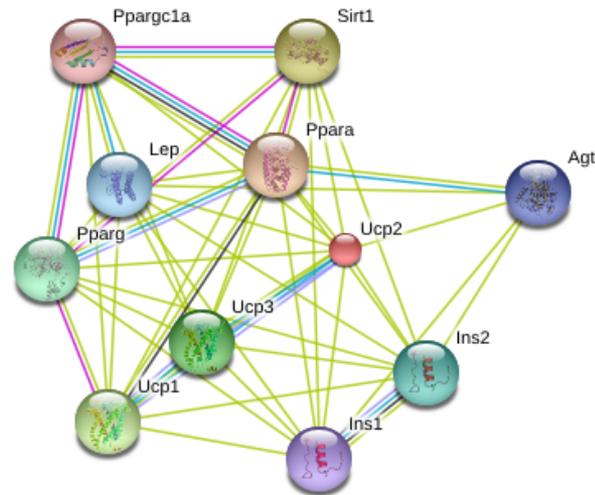


Possible ROS regulation sites

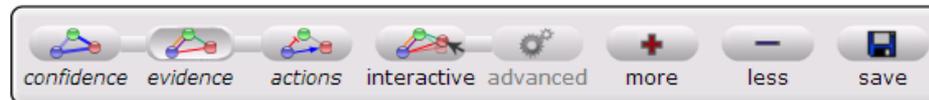


Regulation

Protein Interaction



This is the **evidence view**. Different line colors represent the types of evidence for the association.



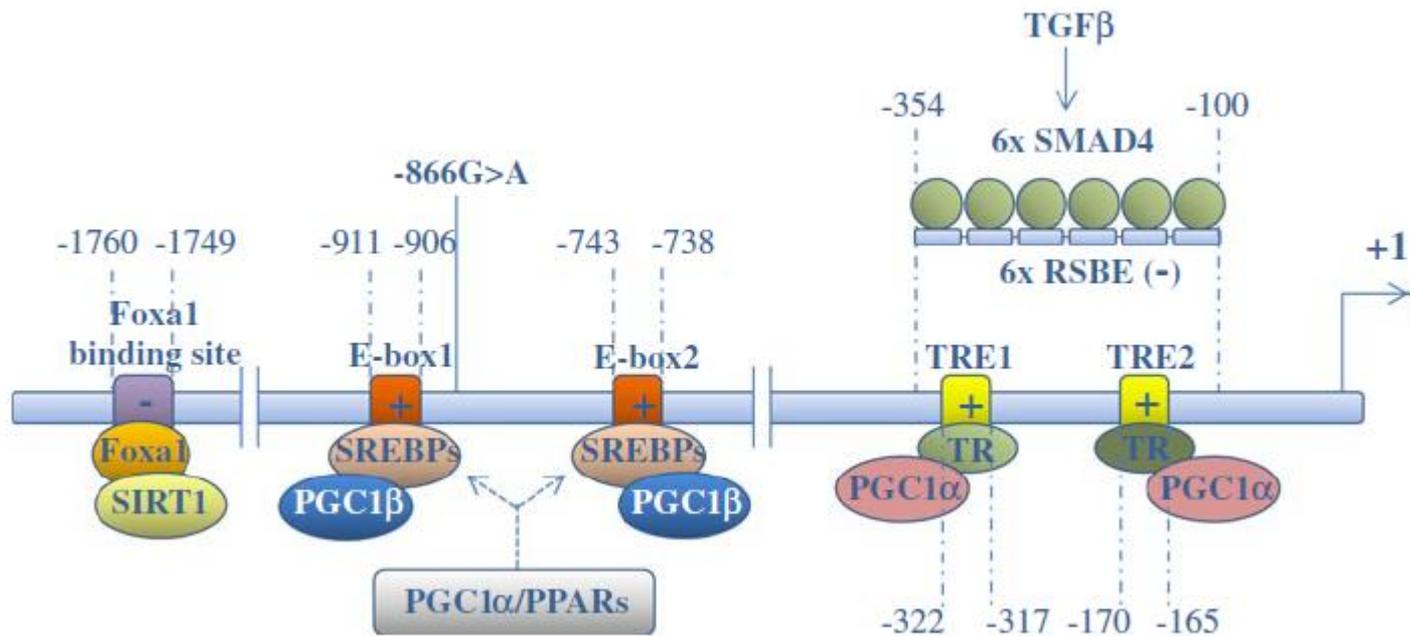
Your Input:

- Ucp2 uncoupling protein 2 (mitochondrial, proton carrier); UCP are mitochondrial transporter proteins that create proton leaks across the inner mitochondrial membrane, thus uncoupling oxidative phosphorylation from ATP synthesis. As a result, energy is dissipated in the form of heat (By similarity) (309 aa) (*Mus musculus*)

Predicted Functional Partners:

		Neighborhood	Gene Fusion	Cooccurrence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
● Ppara	peroxisome proliferator activated receptor alpha; Ligand-activated transcription factor. Key re [...]								●	0.911
● Sirt1	sirtuin 1 (silent mating type information regulation 2, homolog) 1 (<i>S. cerevisiae</i>); NAD-depende [...]								●	0.906
● Ucp1	uncoupling protein 1 (mitochondrial, proton carrier); UCP are mitochondrial transporter protein [...]								●	0.903
● Ucp3	uncoupling protein 3 (mitochondrial, proton carrier); UCP are mitochondrial transporter protein [...]								●	0.901
● Pparg	peroxisome proliferator activated receptor gamma; Receptor that binds peroxisome proliferators [...]								●	0.864
● Ins2	insulin II; Insulin decreases blood glucose concentration. It increases cell permeability to mo [...]								●	0.858
● Lep	leptin; May function as part of a signaling pathway that acts to regulate the size of the body [...]								●	0.833
● Agt	angiotensinogen (serpin peptidase inhibitor, clade A, member 8); Essential component of the ren [...]								●	0.826
● Ins1	insulin I; Insulin decreases blood glucose concentration. It increases cell permeability to mon [...]								●	0.804
● Ppargc1a	peroxisome proliferative activated receptor, gamma, coactivator 1 alpha; Transcriptional coacti [...]								●	0.782

Transcriptional regulation of human Ucp2 gene



The symbols plus or minus in the transcription factor binding sites indicate activation or repression of Ucp2 transcription, respectively.

Acknowledgements

- Professor Luo Jingchu
- Professor Cheng Heping
- Class PKU15S

Thank you!