



Linking biological pathways, networks and disease

Robin Haw
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COMBINE 2014 Meeting



Ministry of Research and
Innovation



www.reactome.org



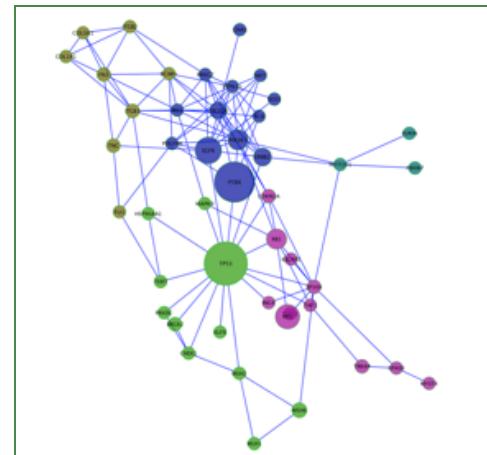
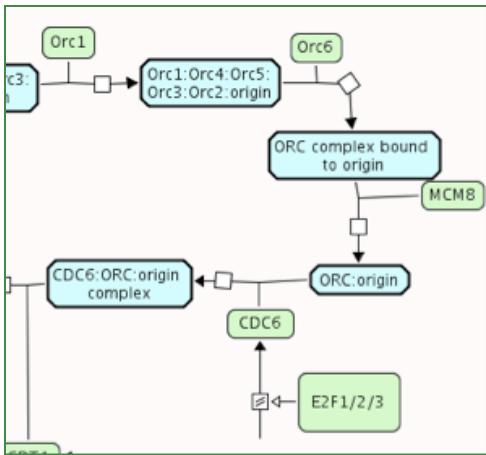
Overview

- Content
 - Controlled Vocabularies
 - Disease Pathway Curation
- Visualization and Analysis
 - New Pathway Browser
- Exchange
 - SBML, SBGN, BioPAX, PSIQUIC

What is Reactome?



- Open source and open access pathway database
- 1500+ pathway modules encompassing many areas of human biology.
 - V49 has annotations for 7684 human proteins, 7332 reactions, and 1462 small molecules, based on data from 16900 literature references.
- Provides tools and datasets for browsing and visualizing pathway data.



www.reactome.org

Controlled vocabularies for entities and events

- Created unique, unambiguous names for pathway events and molecular entities.
- Significantly improves consistency and readability of names.
- Benefits for searching and data mining within and between databases.
- Reduced curation burden.

Peptide CV Names

- Gene Symbol Core - HGNC approved gene symbols
- Peptide coordinates suffix
 - Refers to UniProt ‘Chain’ Feature
 - e.g. large and small subunits of CASP9 - **CASP9(1-315)** and **CASP9(316-416)**
- Post-translational modification (PTM) prefixes
 - Abbreviated from PSI-MOD
 - Includes coordinate of PTM (if known)
- Phosphorylation subtypes grouped as one class, ordered by coordinate.
 - DAPP1 phosphorylated on tyrosine-139 = **p-Y139-DAPP1**
 - WASF2 phosphorylated on tyrosine-150, serine-343 and threonine-346 = **p-Y150,S343,T346-WASF2**
 - GAB2 tyrosine-phosphorylated at unknown coordinate = **p-Y-GAB2**
 - GLI3 phosphorylated, unknown residue = **p-GLI3**

Complex and set CV names

- Concatenated string of component or set member names.
- Comma separator for sets, colon for complexes.
 - G protein-activated inward rectifier potassium channels = **KCNJ3, KCNJ5, KCNJ6, KCNJ9**
 - Complex of IL3, IL3RA, IL3RB, and JAK2 = **IL3:IL3RA:IL3RB:JAK2**
- Entity occurs more than once, name is preceded by *nx*
 - Complex of 2 molecules of PPOX and one of FAD = **2xPPOX:FAD**
 - *n*mer names e.g. dimer, hexamer allowed for homomers
- ‘Candidates’ (possible members) named in round brackets
 - Set of HRH2, HRH3, plus possible ‘candidate’ members HRH6 and HRH8 = **HRH2, HRH3, (HRH6, HRH8)**
- Precedence or hierarchical structure indicated with square brackets
 - Complex ABC1:ABC2 binds complex ABC3:ABC4 = **[ABC1:ABC2]: [ABC3:ABC4]**

Small molecule (chemical) CV names

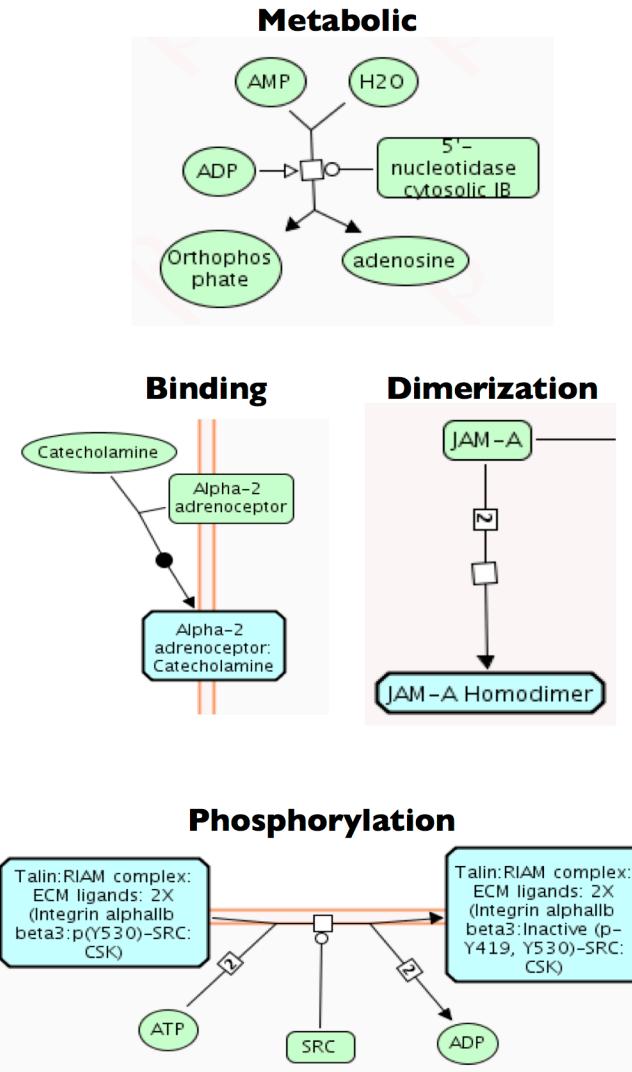
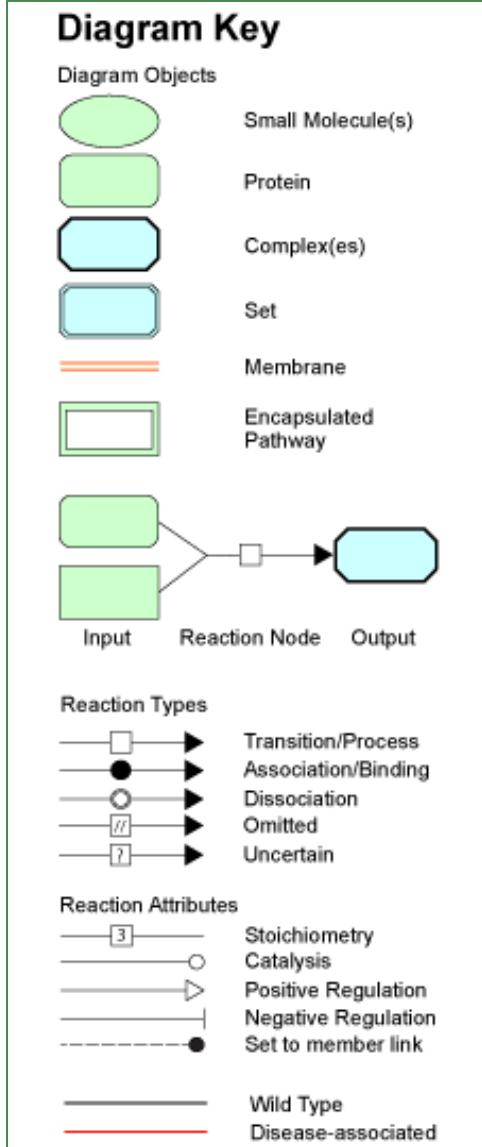
- Standardised abbreviation for >1400 small molecules in Reactome
- Sourced from ChEBI, KEGG Compounds, PubChem, or literature
- Checked for precedence/ambiguity at <http://www.allacronyms.com>
- e.g. Calcium ion = **Ca2+**
- adenosine triphosphate = **ATP**
- Diacylglycerol = **DAG**
- 4-(4-(dimethylamino)styryl)-N-methylpyridinium = **4-Di-2-ASP**
- D-Glyceraldehyde 3-phosphate = **GA3P**

Pathway event (reaction) CV names

- A small set of CV terms - can be applied automatically using simple rules:
 - Transformation (default) a (,b and c) **TRANSFORMS TO** d (,e and f)
 - Binding, Dissociation a BINDS b forming c, c **DISSOCIATES TO** a AND b
 - Polymerization a (,b and c) **POLYMERIZE TO** x
 - Transfer reactions a **TRANSFERS** b **TO** c1 (**TO FORM** c2)
 - Passive transport a **TRANSLOCATES FROM** [x] **TO** [y]
 - Active transport a **TRANSPORTS** b (**FROM** x **TO** y)
 - Antiporter a **EXCHANGES** b **FOR** c (across x membrane)
 - Cotransporter a **COTRANSPORTS** b (,c) **WITH** d (,e)
 - Activation (conformational) a (,b) **IS (ARE) ACTIVATED**
 - Catalysis* (default) a **CATALYZES** b (,c and d) **TO** e (,f and g)

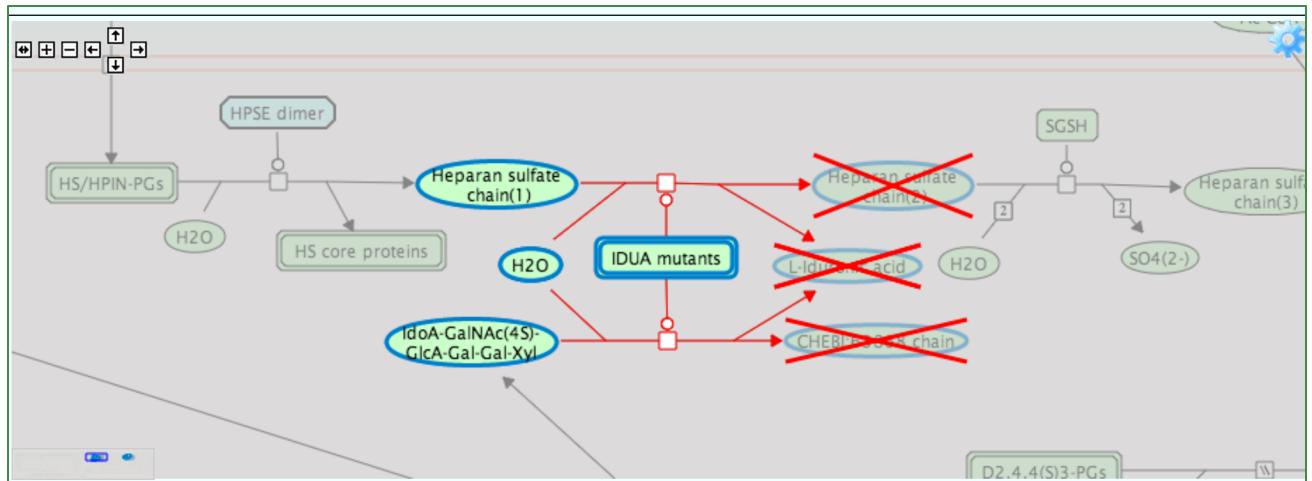
*Catalyst with defined GO molecular function

Reactome supports minimal SBGN PD glyphs

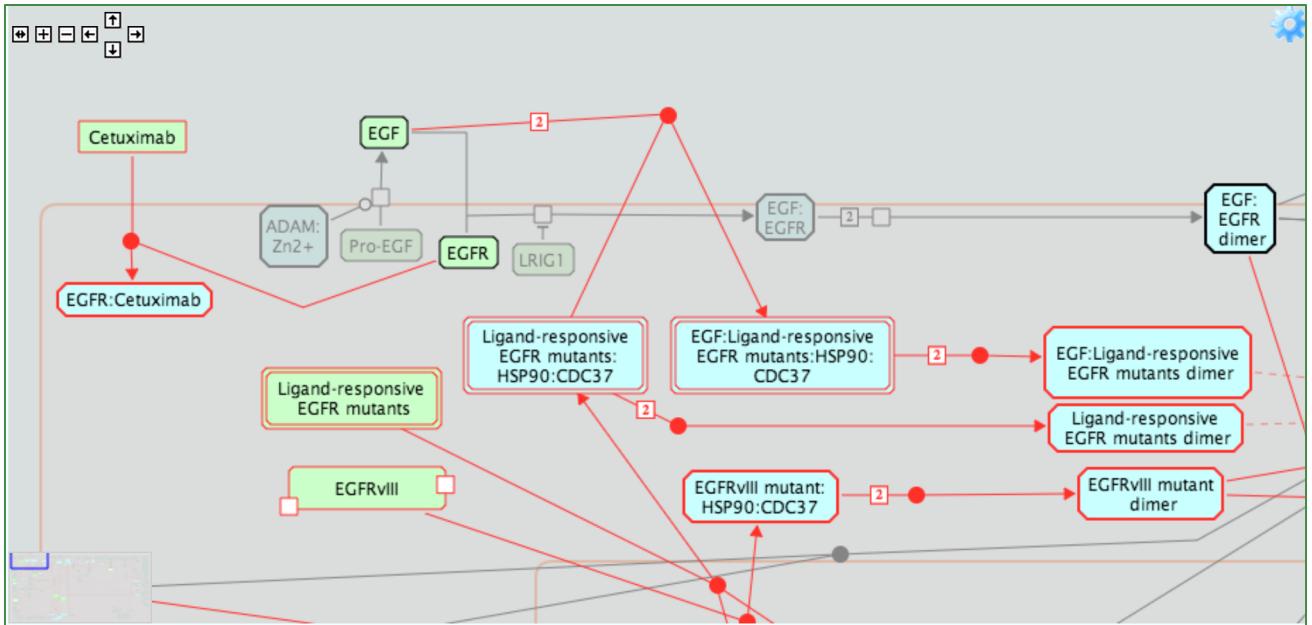


Disease Pathway Curation

Monofactorial genetic disease

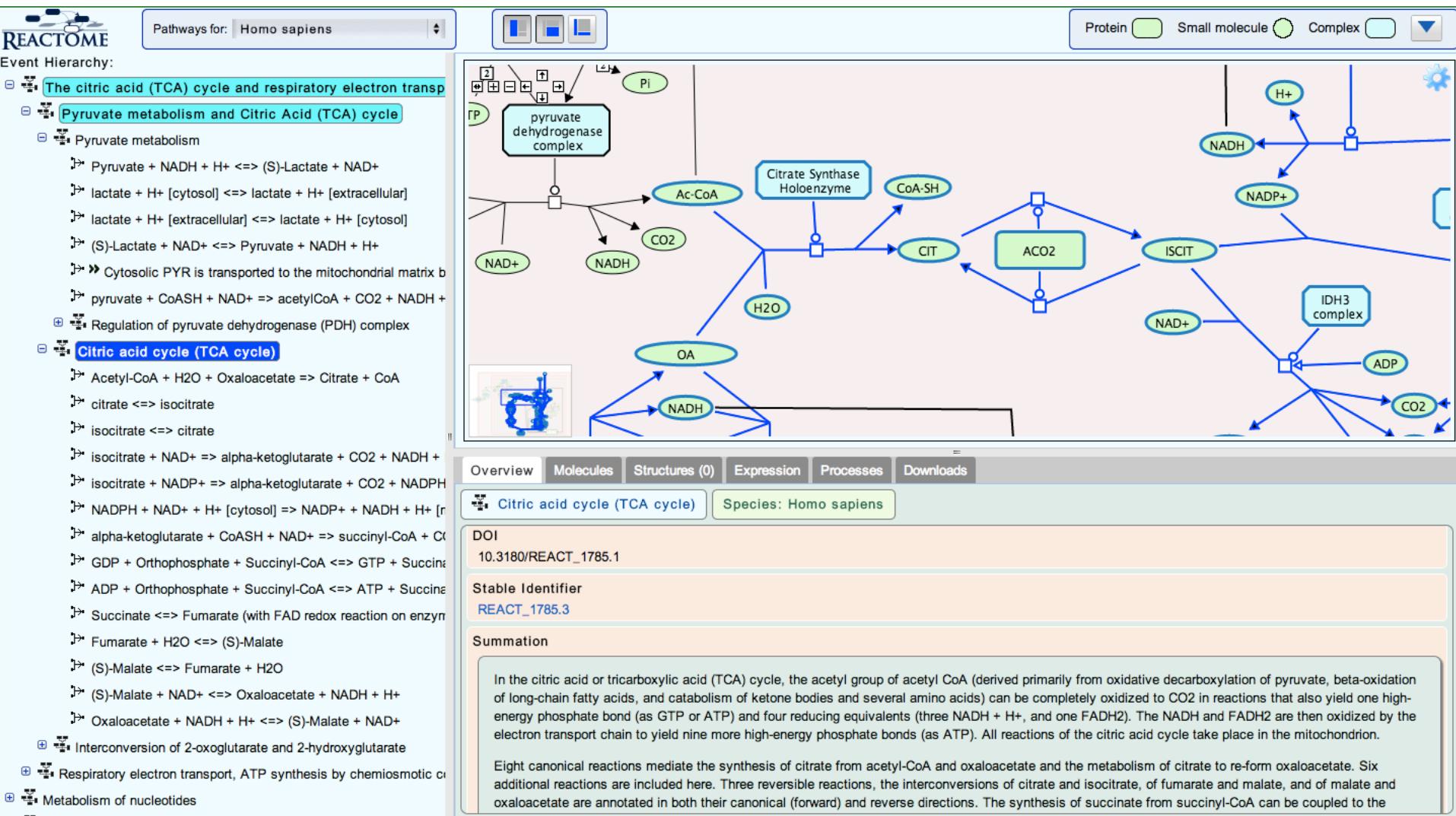


Polygenic disease



SBGN Pathway Browser

- Google-map style pathway diagrams



Balanced reactions from Rhea

Pathways for: Homo sapiens

Event Hierarchy:

- The citric acid (TCA) cycle and respiratory electron transport
- Pyruvate metabolism and Citric Acid (TCA) cycle
 - Pyruvate metabolism
 - Pyruvate + NADH + H+ \leftrightarrow (S)-Lactate + NAD+
 - Lactate + H+ [cytosol] \leftrightarrow lactate + H+ [extracellular]
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 - Regulation of pyruvate dehydrogenase (PDH) complex
- Citric acid cycle (TCA cycle)
 - Acetyl-CoA + H2O + Oxaloacetate \Rightarrow Citrate + CoASH
 - citrate \leftrightarrow isocitrate
 - isocitrate \leftrightarrow citrate
 - isocitrate + NAD+ \Rightarrow alpha-ketoglutarate + CO2 + NADH +
 - isocitrate + NADP+ \Rightarrow alpha-ketoglutarate + CO2 + NADPH +
 - NADPH + NAD+ + H+ [cytosol] \Rightarrow NADP+ + NADH + H+ [
 - alpha-ketoglutarate + CoASH + NAD+ \Rightarrow succinyl-CoA + CO2 + NADH +
 - GDP + Orthophosphate + Succinyl-CoA \leftrightarrow GTP + Succinate
 - ADP + Orthophosphate + Succinyl-CoA \leftrightarrow ATP + Succinate
 - Succinate \leftrightarrow Fumarate (with FAD redox reaction on enzy)
 - Fumarate + H2O \leftrightarrow (S)-Malate
 - (S)-Malate \leftrightarrow Fumarate + H2O
 - (S)-Malate + NAD+ \leftrightarrow Oxaloacetate + NADH + H+
 - Oxaloacetate + NADH + H+ \leftrightarrow (S)-Malate + NAD+
- Interconversion of 2-oxoglutarate and 2-hydroxyglutarate
- Respiratory electron transport, ATP synthesis by chemiosmotic coupling
- Metabolism of nucleotides

RHEA:16846

acetyl-CoA	+	H2O	+	oxaloacetate	\Rightarrow	citrate
CHEBI:57288	+	CHEBI:15377	+	CHEBI:16452	\Rightarrow	CHEBI:16947

Chemical structures for the balanced reaction:

Reaction: acetyl-CoA + H2O + oxaloacetate \Rightarrow citrate

Chemical structures for the second balanced reaction:

Reaction: CHEBI:57288 + CHEBI:15377 + CHEBI:16452 \Rightarrow CHEBI:16947

Protein structures from PDBe

REACTOME

Pathways for: Homo sapiens

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 - Oxaloacetate + NADH + H+ \leftrightarrow (S)-Malate + NAD+
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Protein Small molecule Complex

Overview Molecules Structures (5/5) Expression Processes Downloads

UniProt: P10515 DLAT Chain: A Resolution: 8.80 Coverage: 0.37 PDB Range: [1, 239] UniProt Range: [409, 647]

3b8k PDBe

All other structures for P10515

UniProt: P08559 PDHA1 Chain: C Resolution: 1.90 Coverage: 0.93 PDB Range: [5, 365]

2ozl PDBe

All other structures for P08559

Chemical structures from ChEBI

REACTOME

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Protein Small molecule Complex

Overview Molecules Structures (1/1) Expression Processes Downloads

ChEBI Name: citric acid

ChEBI ID: CHEBI:30769

Definition: A tricarboxylic acid that is propane-1,2,3-tricarboxylic acid bearing a hydroxy substituent at position 2.

Stars: ★★★

Secondary ChEBI IDs: CHEBI:3727, CHEBI:340769, CHEBI:41523, CHEBI:23322

OC(=O)C(O)C(O)C(=O)O

Expression data from the Expression Atlas

Pathways for: **Homo sapiens**

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The diagram illustrates the Citric Acid Cycle (TCA) and Respiratory Electron Transport. Key components include the Citrate Synthase Holoenzyme, Acetyl-CoA, Citrate (CIT), ACO2, ISCIT, IDH3 complex, and various electron carriers like NAD+, NADH, and NADP+. Pyruvate is converted to Ac-CoA by the Pyruvate Dehydrogenase Complex, releasing CO2 and NADH. Ac-CoA enters the TCA cycle via Citrate Synthase. The cycle produces CO2 and NADH. Respiratory electron transport involves the reduction of NAD+ to NADH, which then reduces O2 to H2O. NADH is oxidized back to NAD+ by the IDH3 complex, releasing CO2 and ADP.

Overview Molecules Structures (0/1) Expression Processes Downloads

E-MTAB-513

RNA-Seq of human individual tissues and mixture of 16 tissues (Illumina Body Map)

Organism(s): *Homo sapiens*
Reference(s): 22496456 22955988 23258890

Showing 1 of 1 genes found:

Gene	adipose	adrenal	brain	breast	colon	heart	kidney	leukocyte	liver	lung	lymph node	ovary	prostate	skeletal muscle	testis	thyroid
CS	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High

PSICQUIC - Interaction Data from STRING

Pathways for: Homo sapiens

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Protein Small molecule Complex

Overview Molecules Structures Expression Processes Downloads

Species: Homo sapiens

Involved in pathways

- Citric acid cycle (TCA cycle) [Homo sapiens]

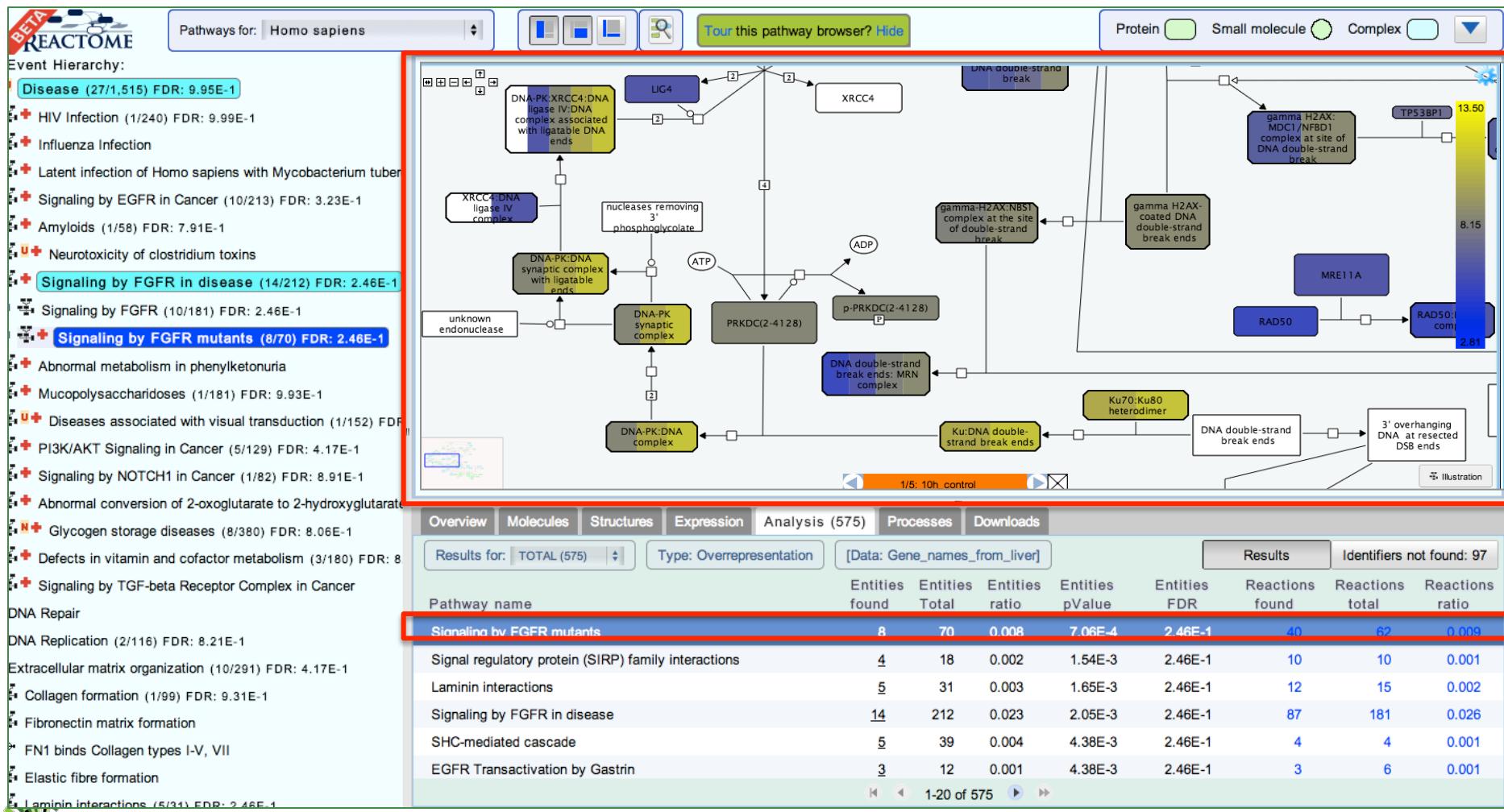
Other forms of this molecule

- ACO2(1-780) [cytosol]
- ACO2(1-780) [mitochondrial intermembrane space]

Pathway Diagrams support Reactome Tools

- Pathway Mapping and Enrichment Analysis
- Expression Overlay onto Pathways
- Compare Pathways between Species

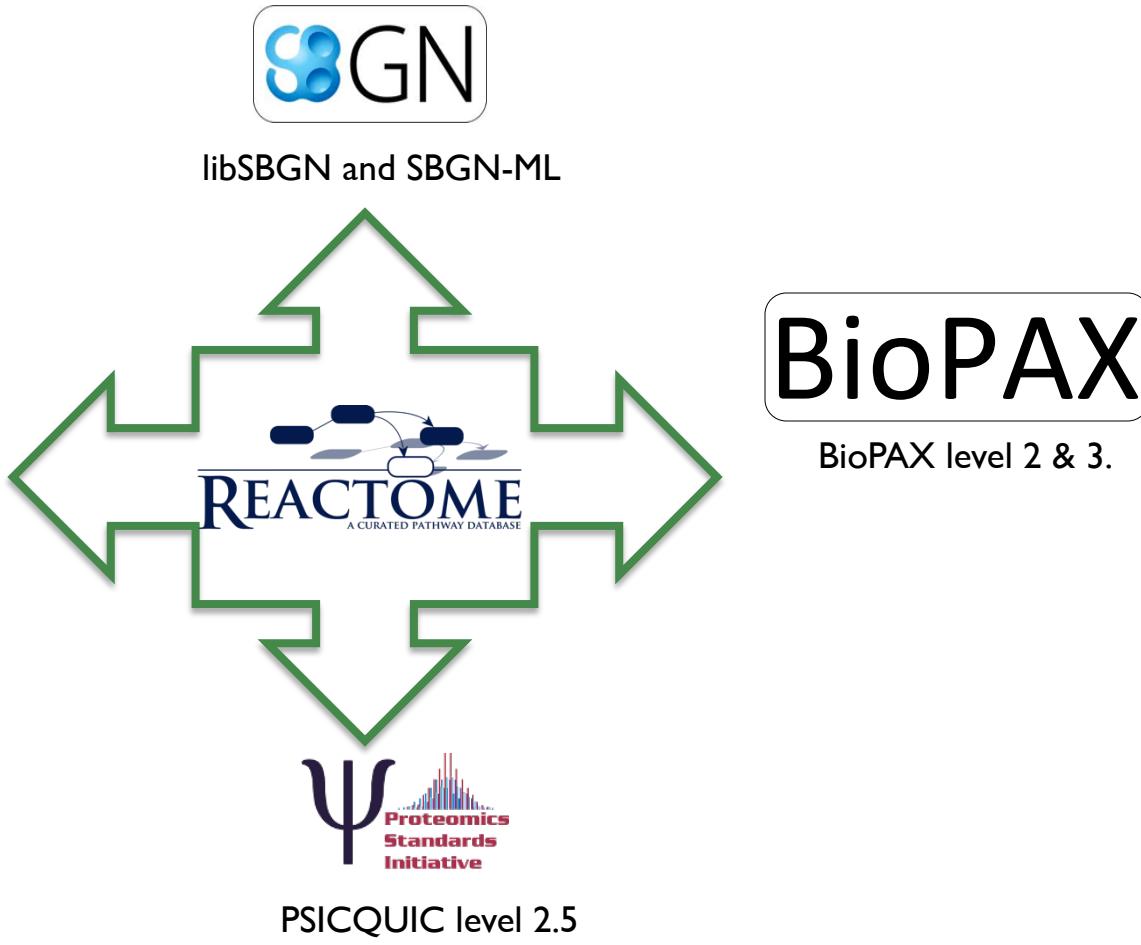
In 2 months reached 6,622 analysis
(15/09/14)



Reactome supports Open Data Standards



SBML level 2.4



Single vs Bulk Pathway Downloads

The download options below are for the selected pathway, not individual events or entities selected in it.

Specialized data formats:

- Gene association file (GO annotation in Reactome)
- Human reactions in SBML (level 2, version 3) format.
- Events in the BioPAX level 2 format.
- Events in the BioPAX level 3 format.
- Reactome Pathways Gene Set.
- Protégé 2.0 ontology for Reactome data model: pins file, pont file, pprj file.
- Human pathway diagrams: PDF, or PNG

OICR
Ontario Institute
for Cancer Research

REACTOME
A CURATED PATHWAY DATABASE

Reactome Web Services

```
<?xml version='1.0' encoding='UTF-8' standalone='no'?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
<model id="pathway_977225" name="Amyloids" metaid="metaid_0">
<notes><p xmlns="http://www.w3.org/1999/xhtml">Amyloid is a term used to describe typically extracellular deposits of aggregated proteins, sometimes known as plaques. Abnormal accumulation of amyloid is amyloidosis, a term associated with diseased organs and tissues, particularly neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntingdon's. Amyloid deposits consist predominantly of amyloid fibrils, rigid, nonbranching structures that form ordered assemblies, characteristically with a cross betasheet structure where the sheets run parallel to the direction of the fibril (Sawaya et al. 2007). Often the fibril has a lefthanded twist (Nelson Eisenberg 2006). At least 27 human proteins form amyloid fibrils (Sipe et al. 2010). Many of these proteins have nonpathological functions; the trigger that leads to abnormal aggregations differs between proteins and is not well understood but in many cases the peptides are abnormal fragments or mutant forms arising from polymorphisms, suggesting that the initial event may be aggregation of misfolded or unfolded peptides. Early studies of AmyloidBeta assembly led to a widely accepted model that assembly was a nucleationdependent polymerization reaction (Teplow 1998) but it is now understood to be more complex, with multiple 'offpathway' events leading to a variety of oligomeric structures in addition to fibrils (Roychaudhuri et al. 2008). An increasing body of evidence suggests that these oligomeric forms are primarily responsible for the neurotoxic effects of Amyloidbeta (Roychaudhuri et al. 2008), alphasynuclein (Winner et al. 2011) and tau (Dance Strobel 2009, MerazRios et al. 2010). Amyloid oligomers are believed to have a common structural motif that is independent of the protein involved and not present in fibrils (Kayed et al. 2003). Conformation dependent, aggregation specific antibodies suggest that there are 3 general classes of amyloid oligomer structures (Glabe 2009) including annular structures which may be responsible for the widely reported membrane permeabilization effect of amyloid oligomers. Toxicity of amyloid oligomers precedes the appearance of plaques in mouse models (Ferretti et al. 2011). </p><p xmlns="http://www.w3.org/1999/xhtml">Fibrils are often associated with other molecules, notably heparan sulfate proteoglycans and Serum Amyloid Pcomponent, which are universally associated and seem to stabilize fibrils, possibly by protecting them from degradation.</p></notes>
<annotation>
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x="273.0" y="267.0"/><glyph class="unit of information" id="entityVertex_7193679_mt"><label text="mt:prot"/><bbox h="24.0"
w="56.0" x="289.0" y="255.0"/></glyph><glyph class="simple chemical" id="entityVertex_7193680"><label text="Ca2+/">
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class="complex" id="entityVertex_7193685"><label text="Amyloid_fibrils"/><bbox h="36.0" w="168.0" x="273.0" y="267.0"/></glyph><glyph
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```

Reactome Web services

Our new RESTful API provides outside users with direct access to pathway data in Reactome. The Reactome pathway analysis tools are also available for integration into third party websites.

- RESTful API is available to access the Reactome data (Note: The RESTful API has been moved to reactomews.oicr.on.ca for better performance.). For details about this API, please see this document: [Reactome RESTful API](#).
- SOAP based Web Services API is available to access the Reactome data. For details about this API, please follow the following links:

- [Simple Description for the Reactome Web Services API](#).
- [Training Materials for the Reactome Web Services API](#)
 - [Reactome SOAP WS User's Guide in PDF \(1M\)](#).
 - [Reactome SOAP WS Tutorial in Power Point Slides \(2M\)](#).
 - [Reactome SOAP WS Tutorial in Flash Movie \(640 x 480\) \(11M\)](#).
 - [Reactome SOAP WS Tutorial in Flash Movie \(800 x 600\) \(12M\)](#).
 - [XML Schema for the data model](#).
 - [WSDL file for the Reactome Web Services API](#).

<http://reactomews.oicr.on.ca:8080/ReactomeRESTfulAPI/>
[RESTfulWS/sbmlExporter/977225](http://reactomews.oicr.on.ca:8080/ReactomeRESTfulWS/sbmlExporter/977225)

Current and Future Work

- ORCID iD as a key mechanism for credit attribution for Reactome contributors.
- Supplement normal pathways with variant reactions representing disease states.
- Improve annotation consistency and enrich the data model.
- Work with the biocuration community for improved ontology support.
- Continued support for SBGN, SBML, BioPAX and PSI data exchange.
 - SBGN Single pathway and bulk pathways downloads.
 - Custom exports for SBML, BioPAX, SBGN via RESTful API.
- Improving the web site and resources to meet the needs of a growing and diverse user community.

Acknowledgements



- Michael Caudy
- David Croft
- Eric Dawson
- Adrian Duong
- Phani Garapati
- Marc Gillespie
- Bijay Jassal
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- Irina Kalatskaya
- Maulik Kamdar
- Bruce May
- Sheldon MacKay
- Lisa Matthews
- Antonio Fabregat Mundo
- Marija Orlic-Milacic
- Karen Rothfels
- Veronica Shamovsky
- Heeyeon Song
- Joel Weiser
- Mark Williams
- Guanming Wu
- Christina Yung
- **Henning Hermjakob**
- **Peter D'Eustachio**
- **Lincoln Stein**



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