Diseases of metabolism


European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 81

This document contains 11 pathways (*see Table of Contents*)
Diseases of metabolism

Stable identifier: R-HSA-5668914

Diseases: disease of metabolism

Metabolic processes in human cells generate energy through the oxidation of molecules consumed in the diet and mediate the synthesis of diverse essential molecules not taken in the diet as well as the inactivation and elimination of toxic ones generated endogenously or present in the extracellular environment. Mutations that disrupt these processes by inactivating a required enzyme or regulatory protein, or more rarely by changing its specificity can lead to severe diseases. Metabolic diseases annotated here involve aspects of carbohydrate, glycosylation, amino acid (phenylketonuria), surfactant and vitamin metabolism, and biological oxidations. One somatic mutation that affects cytosolic isocitrate metabolism, often found in glioblastomas and some lymphoid neoplasms, is also annotated. Also described are mutated forms of adrenocorticotropic hormone (ACTH) that can lead to obesity, resulting in excessive accumulation of body fat.
Diseases of carbohydrate metabolism

Location: Diseases of metabolism

Stable identifier: R-HSA-5663084

Diseases: carbohydrate metabolic disorder

The processes by which dietary carbohydrate is digested to monosaccharides and these are taken up from the gut lumen into cells where they are oxidized to yield energy or consumed in biosynthetic processes are a central part of human metabolism and defects in them can lead to serious disease. Defects annotated here affect saccharide digestion in the gut lumen, fructose metabolism, and the pentose phosphate pathway. In addition, the defect in glucuronate catabolism that leads to essential pentosuria, a benign phenotype that is one of Garrod’s original four inborn errors of metabolism, is annotated.
Phenylketonuria

**Location:** Diseases of metabolism

**Stable identifier:** R-HSA-2160456

**Diseases:** phenylketonuria

Phenylalanine hydroxylase (PAH) normally catalyzes the conversion of phenylalanine to tyrosine. In the absence of functional PAH, phenylalanine accumulates to high levels in the blood and is converted to phenylpyruvate and phenyllactate (Clemens et al. 1990; Langenbeck et al. 1992; Mitchell et al. 2011). The extent of these conversions is modulated by genetic factors distinct from PAH, as siblings with the identical PAH defect can produce different amounts of them (Treacy et al. 1996).

Both L-amino acid oxidase (Boulland et al. 2004) and Kynurenine--oxoglutarate transaminase 3 (Han et al. 2004) can catalyze the conversion of phenylalanine to phenylpyruvate and lactate dehydrogenase can catalyze the conversion of the latter molecule to phenyllactate (Meister 1950), in reactions not annotated here.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-03-05</td>
<td>Authored</td>
<td>D’Eustachio, P.</td>
</tr>
<tr>
<td>2012-03-16</td>
<td>Edited</td>
<td>D’Eustachio, P.</td>
</tr>
<tr>
<td>2012-03-16</td>
<td>Reviewed</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2015-01-28</td>
<td>Revised</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>
Defects in vitamin and cofactor metabolism

Location: Diseases of metabolism

Stable identifier: R-HSA-3296482

Diseases: vitamin metabolic disorder

Vitamins are essential nutrients, required in small amounts from the diet for the normal growth and development of a multicellular organism. Where there is vitamin deficiency, either by poor diet or a defect in metabolic conversion, diseases called Avitaminoses occur. Currently, cobalamin (Cbl, vitamin B12) metabolic defects are described below (Chapter 155 in The Metabolic and Molecular Bases of Inherited Disease, 8th ed, Scriver et al. 2001)

Literature references


Editions

<table>
<thead>
<tr>
<th>Edition Date</th>
<th>Role</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-04-18</td>
<td>Authored, Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2013-08-14</td>
<td>Reviewed</td>
<td>Watkins, D.</td>
</tr>
</tbody>
</table>
Metabolic disorders of biological oxidation enzymes

Location: Diseases of metabolism
Stable identifier: R-HSA-5579029
Diseases: inherited metabolic disorder

The ability to process xenobiotica and many endogenous compounds is called biotransformation and is catalysed by enzymes mainly in the liver of higher organisms but also a number of other organs such as kidneys, gut and lungs. Metabolism occurs in two stages; phase 1 functionalisation and phase 2 conjugation. Defects in enzymes in these two phases can lead to disease (Nebert et al. 2013, Pikuleva & Waterman 2013, Zanger & Schwab 2013, Mudd 2013, Messenger et al. 2013, Aoyama & Nakaki 2013, Shih 2004, Millington 2013, Azimi et al. 2014, Sticova & Jirsa 2013).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-06-06</td>
<td>Authored, Edited</td>
<td></td>
</tr>
<tr>
<td>2014-11-03</td>
<td>Reviewed</td>
<td>Nakaki, T.</td>
</tr>
</tbody>
</table>
Abnormal conversion of 2-oxoglutarate to 2-hydroxyglutarate

Location: Diseases of metabolism

Stable identifier: R-HSA-2978092

Compartments: cytosol

Diseases: glioblastoma multiforme

Somatic mutations affecting arginine residue 132 of IDH1 (isocitrate dehydrogenase 1, a cytosolic enzyme that normally catalyzes the NADP+-dependent conversion of isocitrate to 2-oxoglutarate), are very commonly found in human glioblastomas (Parsons et al. 2008). These mutant proteins efficiently catalyze the NADPH-dependent reduction of 2-oxoglutarate to form 2-hydroxyglutarate. Cells expressing the mutant protein accumulate elevated levels of 2-hydroxyglutarate, probably in the cytosol as IDH1 is a cytosolic enzyme. The fate of the 2-hydroxyglutarate is unclear, but the high frequency with which the mutation is found in surveys of primary tumors is consistent with the possibility that it is advantageous to the tumor cells (Dang et al 2009).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-06-26</td>
<td>Authored, Edited</td>
<td>D’Eustachio, P.</td>
</tr>
<tr>
<td>2010-11-09</td>
<td>Reviewed</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2011-01-31</td>
<td>Reviewed</td>
<td>Rush, MG.</td>
</tr>
</tbody>
</table>
Diseases associated with surfactant metabolism

Location: Diseases of metabolism

Stable identifier: R-HSA-5687613

Diseases: lung disease

The reactions annotated here describe genetic defects in genes regulating surfactant homeostasis which are associated with severe acute and chronic lung diseases in newborns and older infants (Whitsett et al. 2015).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-04-08</td>
<td>Authored, Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2015-08-17</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
</tr>
</tbody>
</table>
Diseases of glycosylation, usually referred to as congenital disorders of glycosylation (CDG), are rare inherited disorders ascribing defects of nucleotide-sugar biosynthesis and transport, glycosyl transfer events and vesicular transport. Most CDGs cause neurological impairment ranging from severe psychomotor retardation to mild intellectual disability. Defects in N-glycosylation are the main cause of CDGs (Marquardt & Denecke 2003, Grunewald et al. 2002, Hennet 2012, Goreta et al. 2012) and can be identified by a characteristic abnormal isoelectric focusing profile of plasma transferrin (Jaeken et al. 1984, Stibler & Jaeken 1990). Disorders of O-glycosylation, glycosaminoglycan and glycolipid metabolism have recently been discovered and, together with N-glycosylation, represent the major pathways affected by glycan biosynthetic disorders (Freeze 2006, Jaeken 2011). In addition, glycosylation diseases associated with the enzymes that mediate the biosynthesis of glycosylation precursors are described in this section. As the number of these disorders has increased, nomenclature has been simplified so that now, the name of the mutant gene is followed by the abbreviation CDG (Jaeken et al. 2009). Effective therapies for most types of CDGs are so far not available (Thiel & Körner 2013).

Literature references


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-06-28</td>
<td>Authored</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2013-07-29</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2014-07-09</td>
<td>Reviewed</td>
<td>Spillmann, D.</td>
</tr>
</tbody>
</table>
Defective ACTH causes obesity and POMCD

Location: Diseases of metabolism

Stable identifier: R-HSA-5579031

Diseases: adrenal gland disease, obesity

The precursor peptide pro-opiomelanocortin (POMC) gives rise to many peptide hormones through cleavage. The cleavage products corticotropin (ACTH) and beta-lipotropin give rise to smaller peptides that have distinct biologic activities: alpha-melanotropin and corticotropin-like intermediate lobe peptide (CLIP) are formed from ACTH; gamma-LPH and beta-endorphin are formed from beta-LPH. ACTH (POMC(138-176)) stimulates the adrenal glands to release cortisol, a glucocorticoid released in response to stress whose primary functions are to stimulate gluconeogenesis, suppress the immune system and aid metabolism of fats, proteins and carbohydrates.

Defects in ACTH can cause obesity (MIM:601665) resulting in excessive accumulation of body fat (Challis et al. 2002, Millington 2013). Defects in ACTH can also cause pro-opiomelanocortinin deficiency (POMCD; MIM:609734) where affected individuals present early-onset obesity, adrenal insufficiency and red hair (Krude et al. 1998, Krude et al. 2003).

Literature references


Diseases of nucleotide metabolism

**Location:** Diseases of metabolism

**Stable identifier:** R-HSA-9735804

**Compartments:** cytosol

**Diseases:** purine-pyrimidine metabolic disorder

Metabolic reactions disrupted by deficiencies of ADA, APRT, HPRT1, and PNP are annotated here.

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021-07-09</td>
<td>Authored</td>
<td>D'Eustachio, P.</td>
</tr>
<tr>
<td>2021-07-09</td>
<td>Edited, Reviewed</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>
Diseases of mitochondrial beta oxidation

Location: Diseases of metabolism

Stable identifier: R-HSA-9759774

Diseases: lipid metabolism disorder

Of the array of known defects of mitochondrial lipid metabolism, one is annotated in Reactome, methylmalonic aciduria due to deficiencies of the MMUT (Methylmalonyl-CoA mutase, mitochondrial) enzyme (Worgan et al. 2006)

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021-08-06</td>
<td>Reviewed</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2021-12-13</td>
<td>Authored, Edited</td>
<td>D'Eustachio, P.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

Diseases of metabolism 2

Diseases of carbohydrate metabolism 3

Phenylketonuria 4

Defects in vitamin and cofactor metabolism 5

Metabolic disorders of biological oxidation enzymes 6

Abnormal conversion of 2-oxoglutarate to 2-hydroxyglutarate 7

Diseases associated with surfactant metabolism 8

Diseases of glycosylation 9

Defective ACTH causes obesity and POMCD 11

Diseases of nucleotide metabolism 13

Diseases of mitochondrial beta oxidation 14

Table of Contents 15