Ribavirin ADME

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

13/11/2022
**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: 82

This document contains 1 pathway and 12 reactions (see Table of Contents)
Ribavirin (RBV) is a synthetic nucleoside analog structurally related to guanine. It is given orally as part of the treatment of HCV infection, and by inhalation for the treatment of RSV infection. According to the WHO, ribavirin can also be used for the treatment of viral hemorrhagic fevers (WHO 2015).

RBV is administered orally in doses of 400 to 600 mg. It is highly soluble in water and a typical dose is dissolved completely over a wide range of acidities. RBV is rapidly absorbed into the circulation. After the oral administration of 600 mg radiolabeled ribavirin, approximately 61% of the drug was detected in the urine and 12% was detected in the feces. 17% of an administered dose was in unchanged form. RBV accumulates in human erythrocytes and remains in the body for weeks, with a half-life of >100 hours (Goodarzi et al, 2016). A consequence of the accumulation in erythrocytes is the well-known side effect of hemolytic anemia, which is reversible by cessation of administration (FDA label Rebetol, 2013).

Ribavirin is a prodrug. It is metabolized through two different paths: phosphorylation, yielding the active triphosphate (RBV-TP), and degradation via de-ribosylation and hydrolysis of the amide group. The GI tract, and not the liver, appears to be the major site of first-pass elimination (Dixit and Perelson, 2006).

**Literature references**

Food and Drug Administration, FDA. (n.d.). HIGHLIGHTS OF PRESCRIBING INFORMATION. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020903s052,021546s008lbl.pdf


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SLC28C2,3 cotransports RBV, Na+ from extracellular region to cytosol

**Location:** Ribavirin ADME

**Stable identifier:** R-HSA-9754934

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

The concentrative sodium/nucleoside cotransporters 2 and 3 (CNT2, SLC28A2 and CNT3, SLC28C3) import ribavirin (RBV) together with sodium ions (Na+) into cells. As the transporters are expressed on the plasma membranes of many cell types, RBV may be absorbed extensively (Errasti-Murugarren et al, 2007; Podgorska et al, 2005). Kinetic studies in Xenopus laevis oocytes point to a possible interaction of SLC29A1 with the SLC28A3 transport process (Yamamoto et al, 2010). Presence of interferon-alpha (IFNA) enhances uptake by apparent promotion of SLC28A2 translocation to the plasma membrane (probably by upregulation of SLC28A2 expression), which explains synergistic effects in treatment with both drugs (Pinilla-Macua et al, 2014).

**Preceded by:** SLC29A1 transports RBV from cytosol to extracellular region

**Followed by:** SLC29A3 transports RBV, RBV-TP from cytosol to mitochondrial matrix, ADA deamidates RBV, ADK phosphorylates RBV, PNP trimer transforms RBV to T-CONH2, NT5C2 tetramer phosphorylates RBV, SLC29A1 transports RBV from cytosol to extracellular region

**Literature references**

SLC29A1 transports RBV from extracellular region to cytosol

**Location:** Ribavirin ADME

**Stable identifier:** R-HSA-9755015

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

The equilibrative nucleoside transporter 1 (ENT1, SLC29A1) is directly involved in the transport of ribavirin (RBV) into cells, although a molecular mechanism has not been defined. It is possible that the observed dependency of RBV uptake on the presence of SLC29A1 is mediated by its binding to SLC28C2,3 (Yamamoto et al, 2010; Fukuchi et al, 2010). The role of equilibrative nucleoside transporter 2 (ENT2, SLC29A2) seems to be minor, at least in placental cells (Owen et al, 2005; Govindajaran et al, 2008; Nishimura et al, 2019). As both concentrative and equilibrative transporters are ubiquitously expressed, RBV may be absorbed extensively (Jarvis et al, 1998; Errasti-Murugarren and Pastor-Anglada, 2010).

**Followed by:** SLC29A3 transports RBV, RBV-TP from cytosol to mitochondrial matrix, PNP trimer transforms RBV to T-CONH2

**Literature references**


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Adenosine kinase (ADK) takes part in phosphorylation of ribavirin (RBV) in erythrocytes (Page and Connor, 1990). While 5′-nucleotidase (NT5C2) has a catalytic efficiency much better than that of adenosine kinase (ADK), the actual contribution of ADK to RBV phosphorylation depends on the physiological concentrations of enzymes and other effectors, which are unknown (Wu et al, 2005). Phosphorylation to ribavirin monophosphate (RBV-MP) appears to be the rate-limiting step in the intracellular ribavirin metabolism resulting in the triphosphate (Page and Connor, 1990).

Preceded by: SLC28C2,3 cotransports RBV, Na+ from extracellular region to cytosol

Followed by: NT5C2 tetramer dephosphorylates RBV-MP, Unknown kinase phosphorylates RBV-MP

Literature references


Ribavirin (RBV) phosphorylation to ribavirin monophosphate (RBV-MP) can be catalyzed by the 5’-nucleotidase NT5C2, with a catalytic efficiency much better than that by adenosine kinase (ADK) (Wu et al, 2005). This appears to be the rate-limiting step in the intracellular ribavirin metabolism resulting in the triphosphate (Page and Connor, 1990; Wallden and Nordlund, 2011).

**Preceded by:** SLC28C2,3 cotransports RBV, Na+ from extracellular region to cytosol

**Followed by:** Unknown kinase phosphorylates RBV-MP, NT5C2 tetramer dephosphorylates RBV-MP

**Literature references**


Unknown kinase phosphorylates RBV-MP

Location: Ribavirin ADME

Stable identifier: R-HSA-9754978

Type: uncertain

Compartments: cytosol

Ribavirin diphosphate (RBV-DP) is the intermediate of ribavirin (RBV) activation by phosphorylation, and it is found in cells treated with RBV (Miller et al, 1977; Glue 1999). The enzyme responsible for phosphorylation of the monophosphate is not known. A possible candidate would be cytosolic guanylate kinase 1 (GUK1) which is known to activate carbovir, 6-mercaptopurine and other drugs (see e.g. Miller et al, 1977; Miller et al, 1992 about these activities).

Preceded by: ADK phosphorylates RBV, NT5C2 tetramer phosphorylates RBV

Followed by: NME1,2 hexamers phosphorylate RBV-DP

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Both nucleoside diphosphate kinases A and B (NME1, NME2) hexamers phosphorylate ribavirin diphosphate (RBV-DP) to the triphosphate (RBV-TP) (Bourdais et al, 1996; Gallois-Montbrun et al, 2003).

**Preceded by:** Unknown kinase phosphorylates RBV-MP

**Followed by:** SLC29A3 transports RBV, RBV-TP from cytosol to mitochondrial matrix, ITPA dimer dephosphorylates RBV-TP to RBV-MP

**Literature references**


SLC29A1 transports RBV from cytosol to extracellular region

**Location:** Ribavirin ADME

**Stable identifier:** R-HSA-9755035

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

Equilibrative nucleoside transporters are located on both sides of epithelial cells and are essential to the export of ribavirin (RBV) out of cells. They cannot transport the phosphorylated RBV analogs RBV-MP, RBV-DP, and RBV-TP (Podgorska et al, 2005; Errasti-Murugarren and Pastor-Anglada, 2010). Efflux pumps are not involved in RBV export (Karbanova et al, 2019).

**Preceded by:** SLC28C2,3 cotransports RBV, Na+ from extracellular region to cytosol

**Followed by:** SLC28C2,3 cotransports RBV, Na+ from extracellular region to cytosol

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**ITPA dimer dephosphorylates RBV-TP to RBV-MP**

**Location:** Ribavirin ADME

**Stable identifier:** R-HSA-9755030

**Type:** transition

**Compartments:** cytosol

Ribavirin triphosphate (RBV-TP) was dephosphorylated in vitro by recombinant ITP triphosphatase (ITPase, ITPA) to a similar extent as its naturally occurring substrate ITP. Reduced ITPase activity in one third of humans causes increased intracellular levels of RBV-TP, leading to increased treatment efficacy (Nyström et al, 2018; Tanaka et al, 2018). Polymorphisms in the gene encoding ITPase (ITPA) have been associated with protection against ribavirin-induced anemia (Fellay et al, 2010).

**Preceded by:** NME1,2 hexamers phosphorylate RBV-DP

**Followed by:** NT5C2 tetramer dephosphorylates RBV-MP

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NT5C2 tetramer dephosphorylates RBV-MP

**Location:** Ribavirin ADME

**Stable identifier:** R-HSA-9755078

**Type:** uncertain

**Compartments:** cytosol

Nucleate cell types can hydrolyze ribavirin monophosphate (RBV-MP) to ribavirin (RBV). The enzymes possibly responsible for the reaction are cytosolic purine 5'-nucleotidase (NT5C2) and alkaline phosphatases (Page and Connor, 1990).

**Preceded by:** ADK phosphorylates RBV, ITPA dimer dephosphorylates RBV-TP to RBV-MP, NT5C2 tetramer phosphorylates RBV

**Followed by:** SLC29A3 transports RBV,RBV-TP from cytosol to mitochondrial matrix, ADA deamidates RBV, PNP trimer transforms RBV to T-CONH2

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PNP trimer transforms RBV to T-CONH2

Location: Ribavirin ADME

Stable identifier: R-HSA-9755044

Type: transition

Compartments: cytosol

Significant amounts of ribavirin (RBV) are phosphorolyzed to 1,2,4-triazole-3-carboxamide (T-CONH2), already in the first pass through intestinal cells. The responsible enzyme purine nucleoside phosphorolysis (PNP) is expressed in higher amounts in the small intestine than in the liver, which also correlates with higher cytosolic phosphorolysis activity in intestinal cells. The amount of conversion to T-CONH2 in the liver is additionally reduced by phosphorylation of RBV to RBV-MP. T-CONH2 from this reaction is the major metabolite detectable in urine (Paroni et al, 1989; Furihata et al, 2014).

Preceded by: SLC29A1 transports RBV from extracellular region to cytosol, NT5C2 tetramer dephosphorylates RBV-MP, SLC28C2,3 cotransports RBV, Na+ from extracellular region to cytosol

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Ribavirin (RBV) undergoes hydrolytic deamination to its carboxylic acid derivative (RBV-COOH, ICN3297), which does not possess any antiviral activity. The reaction is catalyzed by adenosine deaminase (ADA). As the amount of detectable RBV-COOH is low, deamination is not important in RBV catalysis (Miller et al, 1977; Wu et al, 2003).

**Preceded by:** SLC28C2,3 cotransports RBV, Na+ from extracellular region to cytosol, NT5C2 tetramer dephosphorylates RBV-MP

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SLC29A3 transports RBV, RBV-TP from cytosol to mitochondrial matrix

**Location:** Ribavirin ADME

**Stable identifier:** R-HSA-9754929

**Type:** transition

**Compartments:** mitochondrial matrix, cytosol, mitochondrial outer membrane

Equilibrative nucleoside transporter 3 (ENT3, SLC29A3) is an intracellular transporter involved in mitochondrial import of ribavirin (RBV) and RBV-TP (Hu et al, 2006; Govindarajan et al, 2009). Mitochondrial import of RBV appears to be a factor contributing to mitochondrial toxicity in patients treated with both RBV and highly active antiretrovirals (HAART) (Reiberger et al, 2010).

**Preceded by:** SLC29A1 transports RBV from extracellular region to cytosol, NT5C2 tetramer dephosphorylates RBV-MP, SLC28C2,3 cotransports RBV, Na+ from extracellular region to cytosol, NME1,2 hexamers phosphorylate RBV-DP

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