Surfactant metabolism

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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.

31/10/2022
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 29 reactions (see Table of Contents)

https://reactome.org
Surfactant metabolism

Stable identifier: R-HSA-5683826

The alveolar region of the lung creates an extensive epithelial surface that mediates the transfer of oxygen and carbon dioxide required for respiration after birth. Type I epithelial cells form the alveolar surface and mediate gaseous exchange. Type II epithelial cells secrete pulmonary surfactant, a lipoprotein complex that forms a thin interfacial film, lowering surface tension at the air-liquid interface in alveoli and maintaining the structural integrity of alveoli, preventing their collapse at low volumes (Agassandian & Mallampalli 2013). Surfactant production is increased prior to birth, in preparation for air breathing at birth (Hallman 2013). Pre-term infants, where type II epithelial cells are not fully differentiated yet, can produce insufficient surfactant and result in respiratory distress syndrome. Surfactant is composed primarily of phospholipids enriched in phosphatidylcholine (PC) and phosphatidylglycerol (PG) (Agassandian & Mallampalli 2013) and the pulmonary collectins, termed surfactant proteins A, B, C and D (SFTPA-D). They influence surfactant homeostasis, contributing to the physical structures of lipids in the alveoli and to the regulation of surfactant function and metabolism. They are directly secreted from alveolar type II cells into the airway to function as part of the surfactant. SFTPA and D are large, hydrophilic proteins while SFTPB and C are small, very hydrophobic proteins (Johansson et al. 1994). In addition to their surfactant functions, SFTPA and D play important roles in innate host defense by binding and clearing invading microbes from the lung (Kingma & Whitsett 2006). Nuclear regulation, transport, metabolism, reutilisation and degradation of surfactant are described here (Ikegami 2006, Boggaram 2009, Whitsett et al. 2010). Mutations in genes involved in these processes can result in respiratory distress syndrome, lung proteinosis, interstitial lung diseases and chronic lung diseases (Perez-Gil & Weaver 2010, Whitsett et al. 2010, Akella & Deshpande 2013, Jo 2014).

Literature references


**Editions**

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CCDC59 binds TTF1

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-5683831

**Type:** binding

**Compartments:** nucleoplasm

Surfactant proteins B and C (SFTPB and C) are small hydrophobic surfactant proteins that maintain surface tension in alveoli. Both SFTPB and C are regulated by a key factor, transcription termination factor 1 (TTF1), in lung cells (Evers & Grummt 1995). Thyroid transcription factor 1-associated protein 26 (CCDC59 aka TAP26, BR22) (Yang et al. 2003) binds to TTF1 and enhances TTF1-transactivated SFTPB and C promoter activity (Yang et al. 2006).

**Followed by:** CCDC59:TTF1 binds SFTPB gene, CCDC59:TTF1 binds SFTPC gene

**Literature references**


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https://reactome.org
Surfactant proteins B (SFTP B) is a small hydrophobic surfactant protein that maintains surface tension in alveoli. In the nucleus, SFTP B is regulated by a key factor, transcription termination factor 1 (TTF1), bound to thyroid transcription factor 1-associated protein 26 (CCDC59 aka TAP26, BR22), to enhance TTF1-transactivated SFTP B promoter activity (Whitsett & Glasser 1998, Yang et al. 2006).

**Preceded by:** CCDC59 binds TTF1

**Followed by:** SFTP B gene produces pro-SFTP B protein

**Literature references**


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**Preceded by:** CCDC59: TTF1 binds SFTP B gene

**Followed by:** pro-SFTP B translocates from ER membrane to multivesicle body

**Literature references**


**Editions**

- **2015-03-17** Authored, Edited
  - Jassal, B.
- **2015-08-17** Reviewed
  - D’Eustachio, P.
Surfactant protein C (SFTPC) is a small hydrophobic surfactant protein that maintains surface tension in alveoli. In the nucleus, SFTPC is regulated by a key factor, transcription termination factor 1 (TTF1), bound to thyroid transcription factor 1-associated protein 26 (CCDC59 aka TAP26, BR22), to enhance TTF1-transactivated SFTPC promoter activity (Kelly et al. 1996, Whitsett & Glasser 1998, Yang et al. 2006).

**Preceded by:** CCDC59 binds TTF1

**Followed by:** SFTPC gene produces pro-SFTPC protein

**Literature references**


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https://reactome.org

Preceded by: CCDC59:TTF1 binds SFTPC gene

Followed by: pro-SFTPC translocates from ER membrane to multivesicle body

Literature references


GATA6 binds SFTPA genes

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-5685296

**Type:** binding

**Compartments:** nucleoplasm

Transcription factor GATA-6 (GATA6) binds to a cis-acting element in the surfactant protein A1-3 (SFTPAs) gene promoters, activating the transcription of the genes (Bruno et al. 2000).

**Followed by:** SFTPA genes produce SFTPA proteins

**Literature references**


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**SFTPA genes produce SFTPA proteins**

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-5683879

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane, nucleoplasm

Human SFTPA1, 2 and 3 produces the equivalent pulmonary surfactant-associated proteins A1, A2 and A3. Their function is to bind surfactant phospholipids and contribute to lowering the surface tension at the air-liquid interface in the alveoli (White et al. 1985, Flores et al. 1986, Schicht et al. 2014). Surfactant proteins A and D function as innate immunity molecules and inflammatory mediators in the lung (Silveyra & Floros 2013). Transcription factor GATA-6 (GATA6) can bind to a cis-acting element in the surfactant protein A (SFTPA) gene promoter, activating the transcriptional activity of the gene (Bruno et al. 2000). The final processed products for SFTPA1 and 2 are six sets of trimers (Haagsman et al. 1989).

**Preceded by:** GATA6 binds SFTPA genes

**Followed by:** SFTPAs translocate from ER membrane to extracellular region

**Literature references**


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LMCD1 binds GATA6, sequestering it

Location: Surfactant metabolism

Stable identifier: R-HSA-5683888

Type: binding

Compartments: nucleoplasm

The GATA transcription factors regulate gene expression in a variety of cell types including cardiovascular, pulmonary and hematopoietic tissues. LIM and cysteine-rich domains protein 1 (LMCD1) is a transcriptional cofactor that binds GATA6 and thus restricts its function by inhibiting its DNA-binding, resulting in repression of GATA6 transcriptional activation of downstream target genes (Rath et al. 2005).

Literature references


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https://reactome.org
The human gene SFTPD produces pulmonary surfactant-associated protein D. The final processed product is a 12mer consisting of four sets of SFTPD trimer (Rust et al. 1991, Lu et al. 1992, Hakansson et al. 1999). It is secreted into the pulmonary alveoli. In addition to its surfactant-related functions, SFTPD, like SFTPA, contributes to the lung's defense against inhaled pathogens and allergens by binding and clearing these entities from the lung (Lu et al. 1992, Crouch et al. 1993) (not annotated here).

Followed by: SFTPD binds with itself to form SFTPD 12mer

Literature references


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SFTPD binds with itself to form SFTPD 12mer

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-8961021

**Type:** binding

**Compartments:** endoplasmic reticulum membrane

The human gene SFTPD produces pulmonary surfactant-associated protein D. The final processed product is a 12mer consisting of four sets of SFTPD trimer (Rust et al. 1991, Lu et al. 1992, Håkansson et al. 1999). It is secreted into the pulmonary alveoli. In addition to its surfactant-related functions, SFTPD, like SFTPA, contributes to the lung's defense against inhaled pathogens and allergens by binding and clearing these entities from the lung.

**Preceded by:** SFTPD gene produces SFTPD protein

**Followed by:** SFTPD 12mer translocates from ER membrane to extracellular region

**Literature references**


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The pulmonary collectins, surfactant proteins A1, A2, A3 and D (SFTPAs, D), play important roles in innate host defense by binding and clearing invading microbes from the lung. They also influence surfactant homeostasis, contributing to the physical structures of lipids in the alveoli and to the regulation of surfactant function and metabolism. They are directly secreted from alveolar type II cells into the airway to function as part of the surfactant. The mechanism of secretion is unknown. Mutations in SFTPA2 disrupt protein structure and the defective protein is retained in the ER membrane (thus not secreted). Lack of SFTPA2 in surfactant contributes towards idiopathic pulmonary fibrosis (IPF; MIM:178500) (Wang et al. 2009). The mechanism of pathophysiology is unknown.

Preceded by: SFTPA genes produce SFTP proteins

Followed by: DMBT1 binds SFTPD 12mer, SFTPAs, PALM-C100-CKAP4 binds SFTPAs, CSF2RA:CSF2RB binds SFTPs

Literature references


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The pulmonary collectins, surfactant proteins A1, A2, A3 and D (SFTPAs, SFTP D12mer), play important roles in innate host defense by binding and clearing invading microbes from the lung. They also influence surfactant homeostasis, contributing to the physical structures of lipids in the alveoli and to the regulation of surfactant function and metabolism. They are directly secreted from alveolar type II cells into the airway to function as part of the surfactant. The mechanism of secretion is unknown (Andreeva et al. 2007).

**Preceded by:** SFTPD binds with itself to form SFTPD 12mer

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DMBT1 binds SFTPD 12mer, SFTPAs

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-5687284

**Type:** binding

**Compartments:** extracellular region

Deleted in malignant brain tumors 1 protein (DMBT1 aka Gp-340, Hensin, salivary agglutinin) is a binding protein that could play a role in mucosal innate immunity. It is secreted into the broncho-alveolar surface lining fluid and in saliva. DMBT1 can bind surfactant proteins SFTPA and D in macrophage tissues, the resulting complex being able to interact with and agglutinate several Gram-negative and Gram-positive bacteria (Holmskov et al. 1999, Ligtenberg et al. 2001; reviews - Lightenberg et al. 2007, Madsen et al. 2010). DMBT1 has been proposed as a tumor suppressor gene candidate in human brain tumors. Two mutations, one of which resulted in an amino acid change (Q420H), occurred in glioblastomas (Mueller et al. 2002).

**Preceded by:** SFTPAs translocate from ER membrane to extracellular region

**Literature references**


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Surfactant proteins (SFTPs) are trafficked from the ER membrane to lamellar bodies (LBS) via the multivesicle body (MVB). The pro-SFTPs B and C are cleaved here to produce functional SFTPs (Voorhout et al. 1992, Weaver et al. 1992).

**Preceded by:** SFTPB gene produces pro-SFTPB protein

**Literature references**


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pro-SFTPC translocates from ER membrane to multivesicle body

Location: Surfactant metabolism

Stable identifier: R-HSA-5684868

Type: uncertain

Compartments: endoplasmic reticulum membrane, multivesicular body lumen

Surfactant proteins (SFTPs) are trafficked from the ER membrane to lamellar bodies (LBS) via the multivesicle body (MVB). The pro-SFTPs B and C are cleaved here to produce functional SFTPs (Conkright et al. 2001).

Preceded by: SFTPC gene produces pro-SFTPC protein

Followed by: NAPSA, CTSH, PGA3-5 cleave pro-SFTPC, NAPSA, CTSH, PGA3-5 cleave pro-SFTP B

Literature references


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**NAPSA, CTSH, PGA3-5 cleave pro-SFTP**

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-5684864

**Type:** transition

**Compartments:** multivesicular body lumen

In the multivesicular body, surfactant precursor protein pro-SFTP is most likely proteolytically cleaved by napsin-A (NAPSA), cathepsin-H (CTSH) and pepsinogens 3-5 (PGA3-5) (Chuman et al. 1999, Fuchs & Gassen 1989, Athauda et al. 1989, Johansson et al. 1992). The resultant mature peptide SFTP (chain 201-279) forms a dimeric, disulfide-linked protein (Johansson et al. 1992) and is trafficked to lamellar bodies.

**Preceded by:** pro-SFTPC translocates from ER membrane to multivesicle body

**Followed by:** SFTP binds itself

**Literature references**


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[https://reactome.org](https://reactome.org)
SFTPB binds itself

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-6791016

**Type:** binding

**Compartments:** multivesicular body lumen

After pro-SFTPB is cleaved, the resultant mature peptide SFTPB (chain 201-279) forms a dimeric, disulfide linked protein (Johansson et al. 1992) and is trafficked to lamellar bodies.

**Preceded by:** NAPSA, CTSH, PGA3-5 cleave pro-SFTPB

**Followed by:** SFTPB dimer, C translocate from multivesicle body to lamellar body

**Literature references**

NAPSA, CTSH, PGA3-5 cleave pro-SFTPC

Location: Surfactant metabolism

Stable identifier: R-HSA-5685902

Type: transition

Compartments: multivesicular body lumen

In the multivesicular body, surfactant precursor protein pro-SFTPC is most likely proteolytically cleaved by napsin-A (NAPSA), cathepsin-H (CTSH) and pepsinogens 3-5 (PGA3-5) (Chuman et al. 1999, Fuchs & Gassen 1989, Athauda et al. 1989, Johansson et al. 1988). The resultant mature peptide SFTPC (chain 24-58) is trafficked to lamellar bodies.

Preceded by: pro-SFTPC translocates from ER membrane to multivesicle body

Literature references


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SFTPB dimer, C translocate from multivesicle body to lamellar body

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-5684865

**Type:** omitted

**Compartments:** multivesicular body lumen, lamellar body

The mature surfactant proteins B dimer and C (SFTPB dimer and C) are translocated to lamellar bodies (LBs), ready for secretion (Whitsett et al. 2010). The mechanism of transport is unknown.

**Preceded by:** SFTPB binds itself

**Literature references**


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ATP-binding cassette sub-family A member 3 (ABCA3) plays an important role in the formation of pulmonary surfactant, probably by transporting phospholipids such as phosphatidylcholine (PC) and phosphatidylglycerol (PG) from the ER membrane to lamellar bodies (LBs). PC and PG are the major phospholipid constituents of pulmonary surfactant. LBs are the surfactant storage organelles of type II epithelial cells from where phospholipids can be secreted together with surfactant proteins (SFTPs) into the alveolar airspace (Klugbauer & Hofmann 1996, Yamano et al. 2001). Defects in ABCA3 are the cause of pulmonary surfactant metabolism dysfunction type 3 (SMDP3; MIM:610921) (Shulenin et al. 2004).

**Literature references**


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Adenosine deaminase (CECR1, ADA2) degrades extracellular adenosine (Ade-Rib), a signaling molecule that controls a variety of cellular responses (Zavialov & Engstrom 2005). Extracellular adenosine can bind and activate four adenosine receptors (ADRs), triggering multiple intracellular processes leading to either cell activation or in suppression of cell function and cell death. ADA2 (and ADA1) decrease the local concentration of adenosine by catalysing the deamination of adenosine to inosine (Ino). ADA2 is dimeric, binding one Zn2+ ion per subunit (Zavialov et al. 2010).

**Literature references**


Adenosine receptors A2a and A2b (ADORA2A and ADORA2B) bind extracellular adenosine (Ado-Rib) and are believed to play a role in regulating myocardial oxygen consumption and coronary blood flow (Peterfreund 1996). The A2A receptor is responsible for regulating myocardial blood flow by vasodilation of the coronary arteries, which increases blood flow to the myocardium, but may lead to hypotension. Just as in A1 receptors, this normally serves as a protective mechanism. A2B receptor work (Pierce KD et al, 1992) has lagged behind research in the other adenosine receptors.

Both ADORA receptors mediate their actions by coupling with the G protein alpha s subunit which activates adenylly cyclase and increases intracellular cAMP concentrations. In surfactant physiology, the receptor:adenosine complex positively regulates surfactant export from lamellar bodies. (Cooper JA et al, 1995; Linden J et al, 1999). Adenosine deaminase (CECR1, ADA2) degrades extracellular adenosine (Ado-Rib), reducing or neutralising the positive regulatory effect of adenosine in surfactant export.

**Literature references**


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Surfactant-containing lamellar bodies (LBs) are secreted from alveolar type II cells. Regulation of this secretion process is mediated by three G protein-coupled receptor (GPCR)-mediated pathways; P2RY2 purinoreceptor pathway (Rice & Singleton 1986), beta2 adrenergic receptor (beta2AR) pathway (Dobbs & Mason 1979) and adenosine A2B pathway (Gilfillan & Rooney 1987). Activation of these GPCR pathways cause increases in second messengers, such as adenosine 3‘,5‘-cyclic monophosphate (cAMP) or cytosolic Ca2+, and stimulation of downstream kinases such as protein kinase C that leads to surfactant secretion (Voyno-Yasenetskaya et al. 1991). The orphan receptor GPR116 can negatively mediate this secretory process as well as having a stimulatory effect on surfactant reuptake. Gpr116-deficient mice were found to have excessive secretion and accumulation of surfactant in their airspaces after birth (Yang et al. 2013, Bridges et al. 2013, Fukuzawa et al. 2013, Liebscher et al. 2014).

Followed by: CSF2RA:CSF2RB binds SFTPs

Literature references


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<td>Jassal, B.</td>
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<td>2015-08-17</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
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ZDHHC2 transfers PALM from PALM-CoA to CKAP4

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-5686304

**Type:** transition

**Compartments:** plasma membrane, cytosol

The palmitoyltransferase ZDHHC2 transfers a palmitoyl group (PALM) from the high energy donor palmitoyl-CoA (PALM-CoA) to cytoskeleton-associated protein 4 (CKAP4 aka p63). CKAP4 is thought to be a surfactant A binding protein on the surface of alveolar type II epithelial cells where it plays a role in bridging the plasma membrane to the cytoskeleton and in the reuptake of surfactant A. CKAP4 palmitoylation on the cysteine 100 residue by DHHC2 is required for its trafficking from the ER to the plasma membrane (Schweizer et al. 1993, Planey et al. 2009).

Followed by: PALM-C100-CKAP4 binds SFTPAs

**Literature references**


**Editions**

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<td>2015-04-01</td>
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<td>D'Eustachio, P.</td>
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Alveolar surfactant is cleared by distinct pathways. Surfactant proteins (SFTPs) are reutilised by type II cells that internalise alveolar phospholipids destined for re-incorporation into LB for secretion. Alternatively, intra-alveolar or extracellular surfactant is degraded. A substantial portion of surfactant is reutilised (25-95%) in type II cells, promoted by SFTPA (the most abundant surfactant protein) via interaction with a high-affinity receptor present on the cell surface. A candidate for the SFTPA receptor detected on type II epithelial cells is cytoskeleton-associated protein 4 (CKAP4 aka p63), a reversibly palmitoylated transmembrane protein (PALM-C100-CKAP4), initially identified in the ER and Golgi apparatus (Bates 2010).

**Preceded by:** SFTPAs translocate from ER membrane to extracellular region, ZDHHC2 transfers PALM from PALM-CoA to CKAP4

**Followed by:** PALM-C100-CKAP4 transports SFTPAs from extracellular region to lamellar body

**Literature references**


**Editions**

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[https://reactome.org](https://reactome.org)
Alveolar surfactant is cleared by distinct pathways. Surfactant proteins (SFTPs) are reutilised by type II cells that internalise alveolar phospholipids destined for re-incorporation into LB for secretion or intra-alveolar or extracellular surfactant is degraded. A substantial portion of surfactant is reutilised (25-95%) in type II cells, promoted by SFTPA (the most abundant surfactant protein) via interaction with a high-affinity receptor present on the cell surface. A candidate for the SFTPA receptor detected on type II epithelial cells is cytoskeleton-associated protein 4 (CKAP4 aka p63), a reversibly palmitoylated transmembrane protein (PALM-C100-CKAP4), initially identified in the ER and Golgi apparatus (Bates 2010). SFTPA and CKAP4 seem to enter the cell as a unit since both are found in early endosomes. At what point SFTPA and CKAP4 separate or whether CKAP4 chaperones SFTPA to the lamellar body is currently unknown. The receptors for the other surfactant proteins (SFTPB, C, D) that are also recycled are not yet identified.

Preceded by: PALM-C100-CKAP4 binds SFTPAs

Literature references


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Surfactant catabolism by alveolar macrophages plays a small but critical part in surfactant recycling and metabolism. Upon ligand binding, granulocyte-macrophage colony-stimulating factor receptor (GM-CSF), a heterodimer of alpha (CSF2RA) and beta (CSF2RB) subunits (Hansen et al. 2008), initiates a signalling process that not only induces proliferation, differentiation and functional activation of hematopoietic cells but can also determine surfactant uptake into alveolar macrophages and its degradation via clathrin-coated vesicles. The exact mechanism of surfactant degradation in macrophages is poorly understood (Jain et al. 2005, Ikegami 2006). GM-CSF-deficiency can result in pulmonary alveolar proteinosis (PAP), a lung disease characterised by surfactant accumulation and lipid-engorged alveolar macrophages (Carey & Trapnell 2010).

Preceded by: SFTPB,C, PC, PG translocate from lamellar body to extracellular region., SFTPAs translocate from ER membrane to extracellular region

Followed by: SFTPs translocate from extracellular region to clathrin-coated vesicle

Literature references


https://reactome.org
### Editions

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SFTPs translocate from extracellular region to clathrin-coated vesicle

Location: Surfactant metabolism

Stable identifier: R-HSA-5686359

Type: dissociation

Compartments: plasma membrane, extracellular region, clathrin-coated endocytic vesicle

Surfactant catabolism by alveolar macrophages plays a small but critical part in surfactant recycling and metabolism. Upon ligand binding, granulocyte-macrophage colony-stimulating factor receptor (GM-CSF), a heterodimer of alpha (CSF2RA) and beta (CSF2RB) subunits (Hansen et al. 2008), initiates a signalling process that not only induces proliferation, differentiation and functional activation of haematopoietic cells but can also determine surfactant uptake into alveolar macrophages and its degradation via clathrin-coated vesicles. The exact mechanism of surfactant degradation in macrophages is poorly understood (Jain et al. 2005, Ikegami 2006). GM-CSF-deficiency can result in pulmonary alveolar proteinosis (PAP), a lung disease characterised by surfactant accumulation and lipid-engorged alveolar macrophages (Carey & Trapnell 2010).

Preceded by: CSF2RA:CSF2RB binds SFTPs

Literature references


Editions

2015-04-01 Authored, Edited Jassal, B.

2015-08-17 Reviewed D'Eustachio, P.
SLC34A1,2 cotransports Pi, 3Na+ from extracellular region to cytosol

**Location:** Surfactant metabolism

**Stable identifier:** R-HSA-427656

**Type:** transition

**Compartments:** plasma membrane

SLC34A1 encodes Na+/Pi cotransporter (NaPi-IIa) which is expressed in the kidney in the renal proximal tubule (Magagnin et al. 1993). SLC34A2 encodes NaPi-IIb which is abundantly expressed in lung and to a lesser degree in tissues of epithelial origin including small intestine, pancreas, prostate, and kidney (Field et al. 1999). In the lung, SLC34A2 is expressed only in alveolar type II cells, which are responsible for surfactant production, so it is proposed that it uptakes liberated phosphate from the alveolar fluid for surfactant production. Both NaPi-IIa and NaPi-IIb cotransport inorganic phosphate (Pi) with three Na+ ions (electrogenic transport) (Forster et al. 1999, 2002).

Defects in SLC34A1 are the cause of hypophosphatemic nephrolithiasis/osteoporosis type 1 (NPHLOP1) (Prie et al. 2002). Defects in SLC34A2 are a cause of pulmonary alveolar microlithiasis, a rare disease characterised by the deposition of calcium phosphate microliths throughout the lung (Corut et al. 2006).

**Literature references**


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<td>Reviewed</td>
<td>He, L.</td>
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CCDC59:TTF1 binds SFTPC gene

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SFTPD 12mer translocates from ER membrane to extracellular region

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NAPSA, CTSH, PGA3-5 cleave pro-SFTPC

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