



Maturation of nucleoprotein

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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.

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Literature references

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- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. A
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, *14*, e1005968. *オ*

This document contains 1 pathway and 14 reactions (see Table of Contents)

Maturation of nucleoprotein 7

Stable identifier: R-HSA-9694631

Diseases: COVID-19

Inferred from: Maturation of nucleoprotein (Homo sapiens)



This COVID-19 pathway has been created by a combination of computational inference from SARS-CoV-1 data (https://reactome.org/documentation/inferred-events) and manual curation, as described in the summation for the overall SARS-CoV-2 infection pathway.

Nucleoprotein, the most abundant viral protein expressed during infection, is found in the host cell cytosol, the nucleus and plasma membrane. After phosphorylation and sumoylation it di-/tetramerizes and is moved to the Golgi, the virion budding site (Li et al, 2005; Surjit et al, 2005).

Literature references

- Liu, DX., Xiao, H., Li, FQ., Tam, JP. (2005). Sumoylation of the nucleocapsid protein of severe acute respiratory syndrome coronavirus. *FEBS Lett.*, 579, 2387-96. 7
- Mishra, RN., Kumar, R., Reddy, MK., Chow, VT., Surjit, M., Lal, SK. (2005). The severe acute respiratory syndrome coronavirus nucleocapsid protein is phosphorylated and localizes in the cytoplasm by 14-3-3-mediated translocation. J. Virol., 79, 11476-86.

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SRPK1/2 phosphorylates nucleoprotein *オ*

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9729330

Type: transition

Compartments: cytosol

Diseases: COVID-19



Full phosphorylation of SARS-CoV-2 nucleoprotein (N) depends on priming phosphorylations on at least two sites by SRPK1/2 protein kinases (Heaton et al, 2020; Carlson et al, 2020). Both kinases are monomers that need a magnesium cofactor to work, and are activated through phosphorylation by CK2 kinase (Daub et al, 2002).

Followed by: GSK3 phosphorylates nucleoprotein

Literature references

- Howard, CJ., Hartooni, N., Ghent, CM., Carlson, CR., Morgan, DO., Frankel, AD. et al. (2020). Phosphoregulation of Phase Separation by the SARS-CoV-2 N Protein Suggests a Biophysical Basis for its Dual Functions. *Mol Cell, 80*, 1092-1103.e4.
- Chaparian, RR., Bulaon, DK., Anand, SK., Johnson, JL., Shobana-Ganesh, K., Trimarco, JD. et al. (2020). The FDA-approved drug Alectinib compromises SARS-CoV-2 nucleocapsid phosphorylation and inhibits viral infection in vitro. *bioRxiv*. 7

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GSK3 phosphorylates nucleoprotein 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9729260

Type: transition

Compartments: cytosol

Diseases: COVID-19



Phosphorylation of SARS-Cov-2 nucleocapsid is catalyzed by glycogen synthase kinase 3 (GSK3) and several other host cell kinases. Phosphorylated N forms a liquid-like compartment, possibly suited for viral genome processing (Carlson et al, 2020). GSK3 phosphorylations depend on priming phosphorylations on at least two sites by SRPK1/2 protein kinases (Heaton et al, 2020).

Three proteomics papers show varying sites for phosphorylations on N that can be explained by specific phosphorylation catalyzed by GSK3 when primed by phosphorylations on S188 and S206. The sites S176, S180, S184, S194, T198 and S202 are supported by at least two of the three papers (Bouhaddou et al, 2020; Davidson et al, 2020; Klann et al, 2020). Another analysis found S176 phosphorylated in about half of the cases (Supekar et al, 2021)..

Preceded by: SRPK1/2 phosphorylates nucleoprotein

Followed by: CSNK1A1 phosphorylates nucleoprotein

Literature references

- Howard, CJ., Hartooni, N., Ghent, CM., Carlson, CR., Morgan, DO., Asfaha, JB. (2020). Phosphorylation modulates liquid-liquid phase separation of the SARS-CoV-2 N protein. *bioRxiv*.
- Williamson, MK., Ellis, J., Heesom, KJ., Lewis, PA., Matthews, DA., Zambon, M. et al. (2020). Characterisation of the transcriptome and proteome of SARS-CoV-2 reveals a cell passage induced in-frame deletion of the furin-like cleavage site from the spike glycoprotein. *Genome Med*, *12*, 68. *¬*
- Ciesek, S., Cinatl, J., Tascher, G., Münch, C., Bojkova, D., Klann, K. (2020). Growth Factor Receptor Signaling Inhibition Prevents SARS-CoV-2 Replication. *Mol Cell*, *80*, 164-174.e4.
- Beltrao, P., Fischer, ER., Koh, C., Vignuzzi, M., Johnson, JR., Richards, AL. et al. (2020). The Global Phosphorylation Landscape of SARS-CoV-2 Infection. *Cell, 182*, 685-712.e19.

Chaparian, RR., Bulaon, DK., Anand, SK., Johnson, JL., Shobana-Ganesh, K., Trimarco, JD. et al. (2020). The FDA-approved drug Alectinib compromises SARS-CoV-2 nucleocapsid phosphorylation and inhibits viral infection in vitro. *bioRxiv.* 7

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GSK3B binds GSKi 🛪

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9687724

Type: binding

Compartments: cytosol



Many GSK-3 β inhibitors (GSKi) have been identified. They are known to induce apoptosis in leukemia and pancreatic cancer cells, and can destabilize p53, which may promote cellular death in response to DNA damaging agents (Wang et al, 2008; Beurel et al, 2009). Administration of GSKi inhibited cochlear destruction in cisplatin-injected mice (Park et al, 2009).

Lithium is a selective ATP competitive inhibitor of GSK-3 (Ryves and Harwood, 2001). Lithium carbonate is used with bipolar disorder patients (Moore et al, 2009). In a retrospective study of 162,118 COVID-19 patients from several U.S. health systems 7% of patients taking lithium developed COVID-19 compared with 15% among the general population (Liu et al, 2021). LY2090314 has been in clinical trials for metastatic pancreatic cancer and acute leukemia ([NCT01632306], [NCT01287520], [NCT01214603]). Clinical trials of GSKi for Alzheimer's disease were unsuccessful.

The use of GSKi remains controversial because of their possibly oncogenic properties. Evaluation of GSKi in clinical trials has been hampered by the fear that inhibition of GSK-3 may stimulate or aid in malignant transformation as GSK-3 can phosphorylate pro-oncogenic factors such as beta-catenin, c-Jun and c-Myc which targets them for degradation (Patel & Woodgett, 2008). However, no studies have been reported suggesting that treatment of mice with GSKi resulted in an increase in cancer incidence. In fact, many patients with bipolar disorder have been treated with lithium for prolonged periods of time, with no evidence that these patients have increased incidences of cancer (McCubrey et al, 2014).

The GSKi kenpaullone and lithium chloride were found to reduce viral Nucleoprotein phosphorylation in the severe acute respiratory syndrome CoV-infected VeroE6 cells and decrease the viral titer and cytopathic symptoms. Effects of GSK-3 inhibition were reproduced in another coronavirus, the neurotropic JHM strain of mouse hepatitis virus (Wu et al, 2009).

Literature references

- Wu, CH., Tsay, YG., Chen, PJ., Kao, CL., Kuo, TJ., Chen, DS. et al. (2009). Glycogen synthase kinase-3 regulates the phosphorylation of severe acute respiratory syndrome coronavirus nucleocapsid protein and viral replication. J. Biol. Chem., 284, 5229-39. *¬*
- Rader, DJ., Klein, PS., Schultz, DC., Arumugaswami, V., Ritchie, MD., Kumar, A. et al. (2021). Targeting the coronavirus nucleocapsid protein through GSK-3 inhibition. *Proc Natl Acad Sci U S A*, 118. 7

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CSNK1A1 phosphorylates nucleoprotein 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9729318

Type: transition

Compartments: cytosol

Diseases: COVID-19



SARS-Cov-2 nucleoprotein is phosphorylated by several host cell kinases. It is probable that phosphorylations by SRPK and GSK3 are priming further phosphorylations by other kinases. Modelled CSNK1A1 phosphorylation sites at S201 and T205 (Heaton et al, 2020) were confirmed experimentally by three proteomics papers (Bouhaddou et al, 2020; Davidson et al, 2020; Klann et al, 2020).

Preceded by: GSK3 phosphorylates nucleoprotein

Followed by: Nucleoprotein is methylated by PRMT1, Unknown kinase phosphorylates nucleoprotein

Literature references

- Williamson, MK., Ellis, J., Heesom, KJ., Lewis, PA., Matthews, DA., Zambon, M. et al. (2020). Characterisation of the transcriptome and proteome of SARS-CoV-2 reveals a cell passage induced in-frame deletion of the furin-like cleavage site from the spike glycoprotein. *Genome Med*, *12*, 68. *¬*
- Ciesek, S., Cinatl, J., Tascher, G., Münch, C., Bojkova, D., Klann, K. (2020). Growth Factor Receptor Signaling Inhibition Prevents SARS-CoV-2 Replication. *Mol Cell*, *80*, 164-174.e4.
- Beltrao, P., Fischer, ER., Koh, C., Vignuzzi, M., Johnson, JR., Richards, AL. et al. (2020). The Global Phosphorylation Landscape of SARS-CoV-2 Infection. *Cell, 182*, 685-712.e19. *¬*
- Chaparian, RR., Bulaon, DK., Anand, SK., Johnson, JL., Shobana-Ganesh, K., Trimarco, JD. et al. (2020). The FDA-approved drug Alectinib compromises SARS-CoV-2 nucleocapsid phosphorylation and inhibits viral infection in vitro. *bioRxiv.* 7

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Unknown kinase phosphorylates nucleoprotein 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9729300

Type: transition

Compartments: cytosol

Diseases: COVID-19



Most of SARS-Cov-2 nucleocapsid phosphorylations in its S/R-rrich region are shown or proposed to be catalyzed by the host cell kinases SRPK1/2, GSK3, and CSNK1A1. However, the phosphorylation sites at S23, S79, and S183 were confirmed experimentally by three proteomics papers but the responsible kinase is unknown (Bouhaddou et al, 2020; Davidson et al, 2020; Klann et al, 2020).

Preceded by: CSNK1A1 phosphorylates nucleoprotein

Followed by: Nucleoprotein is methylated by PRMT1

Literature references

- Williamson, MK., Ellis, J., Heesom, KJ., Lewis, PA., Matthews, DA., Zambon, M. et al. (2020). Characterisation of the transcriptome and proteome of SARS-CoV-2 reveals a cell passage induced in-frame deletion of the furin-like cleavage site from the spike glycoprotein. *Genome Med*, *12*, 68. *¬*
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- Beltrao, P., Fischer, ER., Koh, C., Vignuzzi, M., Johnson, JR., Richards, AL. et al. (2020). The Global Phosphorylation Landscape of SARS-CoV-2 Infection. *Cell*, *182*, 685-712.e19. *¬*
- Chaparian, RR., Bulaon, DK., Anand, SK., Johnson, JL., Shobana-Ganesh, K., Trimarco, JD. et al. (2020). The FDA-approved drug Alectinib compromises SARS-CoV-2 nucleocapsid phosphorylation and inhibits viral infection in vitro. *bioRxiv.* 7

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Nucleoprotein is methylated by PRMT1 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9729283

Type: transition

Compartments: cytosol

Diseases: COVID-19



Protein arginine methyltransferase 1 (PRMT1) methylates SARS-CoV-2 nucleoprotein on two arginines (R95 and R177). This modification is required for its RNA binding capacity, since treatment with a type I PRMT inhibitor (MS023) or substitution of R95K or R177K inhibited interaction with the 5'-UTR of the SARS-CoV-2 genomic RNA. Pre-treatment of VeroE6 cells with MS023 significantly reduced SARS-CoV-2 replication (Cai et al, 2021).

Preceded by: CSNK1A1 phosphorylates nucleoprotein, Unknown kinase phosphorylates nucleoprotein

Followed by: Nucleoprotein is ADP-ribosylated

Literature references

Richard, S., Liang, C., Wang, Z., Yu, Z., Cai, T. (2021). Arginine methylation of SARS-Cov-2 nucleocapsid protein regulates RNA binding, its ability to suppress stress granule formation, and viral replication. *J Biol Chem*, 297, 100821

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PRMT1 binds type I PRMT inhibitors 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9766608

Type: binding

Compartments: cytosol



Type I protein arginine methyltransferases (PRMTs) catalyze mono- and asymmetric dimethylation of arginine residues. In humans there are five enzymes of this type: PRMT1, PRMT3, PRMT4, PRMT6, and PRMT8. MS023 is a selective inhibitor of type I PRMTs. It inhibits PRMT1 with an IC50 of 30 +- 9 nM (Eram et al, 2015).

Literature references

Vedadi, M., Li, F., Barsyte-Lovejoy, D., Szewczyk, M., Brown, PJ., Liu, J. et al. (2016). A Potent, Selective, and Cell-Active Inhibitor of Human Type I Protein Arginine Methyltransferases. ACS Chem Biol, 11, 772-781.

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Nucleoprotein is ADP-ribosylated 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9729279

Type: transition

Compartments: cytosol

Diseases: COVID-19

Inferred from: Nucleoprotein is ADP-ribosylated (Homo sapiens)



This COVID-19 event has been created by a combination of computational inference (see https://reactome.org/documentation/inferred-events) from SARS-CoV-1 data and manual curation, as described in the summation for the overall SARS-CoV-2 infection pathway.

Nucleoprotein (N) is ADP-ribosylated. The modification is maintained both in the cell and in virions (Grunewald et al, 2018). Members of the protein mono-ADP-ribosyltransferase (PARP) enzyme family are thought to catalyze this reaction (Fehr et al. 2020)

Preceded by: Nucleoprotein is methylated by PRMT1

Followed by: Nucleoprotein is SUMOylated

Literature references

- Aikawa, M., Fehr, AR., Higashi, H., Kerr, CM., Mukai, S., Singh, SA. (2020). The impact of PARPs and ADP-ribosylation on inflammation and host-pathogen interactions. *Genes Dev.*, 34, 341-359.
- Perlman, S., Grunewald, ME., Fehr, AR., Athmer, J. (2018). The coronavirus nucleocapsid protein is ADP-ribosylated. Virology, 517, 62-68. ↗

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Nucleoprotein is SUMOylated 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9729307

Type: transition

Compartments: cytosol

Diseases: COVID-19

Inferred from: Nucleoprotein is SUMOylated (Homo sapiens)



This COVID-19 event has been created by a combination of computational inference (see https://reactome.org/documentation/inferred-events) from SARS-CoV-1 data and manual curation, as described in the summation for the overall SARS-CoV-2 infection pathway.

N protein is sumoylated at a lysine residue. Abolition of sumoylation of nucleoprotein significantly decreases homooligomerisation of the protein (Li et al, 2005)

Preceded by: Nucleoprotein is ADP-ribosylated

Followed by: Dimerisation of nucleoprotein

Literature references

Liu, DX., Xiao, H., Li, FQ., Tam, JP. (2005). Sumoylation of the nucleocapsid protein of severe acute respiratory syndrome coronavirus. *FEBS Lett.*, 579, 2387-96.

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Dimerisation of nucleoprotein 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9694363

Type: binding

Compartments: cytosol

Diseases: COVID-19



Nucleoprotein of SARS-Cov-2 forms stable dimers in solution that partly oligomerize further. The predominant form interacting with RNA is the dimer, with tetramer and higher oligomers appearing temporarily (Wu et al, 2021; Zhao et al, 2021; Slavin et al, 2021; Ye et al, 2020).

Preceded by: Nucleoprotein is SUMOylated

Followed by: Nucleoprotein translocates to the plasma membrane, Nucleoprotein translocates to the nucleolus, Nucleoprotein translocates to the ERGIC outer membrane

Literature references

- Howard, CJ., Hartooni, N., Ghent, CM., Carlson, CR., Morgan, DO., Asfaha, JB. (2020). Phosphorylation modulates liquid-liquid phase separation of the SARS-CoV-2 N protein. *bioRxiv*.
- Barbar, E., Forsythe, HM., Reardon, P., Yu, Z., Rolland, AD., Prell, JS. et al. (2021). Multivalent binding of the partially disordered SARS-CoV-2 nucleocapsid phosphoprotein dimer to RNA. *Biophys J.* 7
- Silletti, S., Ye, Q., Corbett, KD., West, AMV. (2020). Architecture and self-assembly of the SARS-CoV-2 nucleocapsid protein. *Protein Sci.*. 7
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- Stolovich-Rain, M., Kalisman, N., Baraz, L., Rouvinski, A., Braitbard, M., Friedman, A. et al. (2021). Targeted in situ cross-linking mass spectrometry and integrative modeling reveal the architectures of three proteins from SARS-CoV-2. *Proc Natl Acad Sci U S A*, 118.

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Nucleoprotein translocates to the plasma membrane 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9694575

Type: uncertain

Compartments: plasma membrane, cytosol

Diseases: COVID-19

Inferred from: Nucleoprotein translocates to the plasma membrane (Homo sapiens)



This COVID-19 event has been created by a combination of computational inference (see https://reactome.org/documentation/inferred-events) from SARS-CoV-1 data and manual curation, as described in the summation for the overall SARS-CoV-2 infection pathway.

Some phosphorylated N is found to associate with the cell membrane (Surjit et al, 2005).

Preceded by: Dimerisation of nucleoprotein

Literature references

Mishra, RN., Kumar, R., Reddy, MK., Chow, VT., Surjit, M., Lal, SK. (2005). The severe acute respiratory syndrome coronavirus nucleocapsid protein is phosphorylated and localizes in the cytoplasm by 14-3-3-mediated translocation. J. Virol., 79, 11476-86.

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Nucleoprotein translocates to the ERGIC outer membrane 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9694568

Type: uncertain

Compartments: cytosol, endoplasmic reticulum-Golgi intermediate compartment membrane

Diseases: COVID-19

Inferred from: Nucleoprotein translocates to the ERGIC outer membrane (Homo sapiens)



This COVID-19 event has been created by a combination of computational inference (see https://reactome.org/documentation/inferred-events) from SARS-CoV-1 data and manual curation, as described in the summation for the overall SARS-CoV-2 infection pathway.

As early as 3 hours post-infection, cytoplasmic accumulations of N are formed in infected cells, they colocalize with viral RNA. From 5 hours post-infection on, N can be detected in the Golgi, the budding site (Stertz et al, 2007)

Preceded by: Dimerisation of nucleoprotein

Literature references

Reichelt, M., Weber, F., Martínez-Sobrido, L., García-Sastre, A., Kochs, G., Kuri, T. et al. (2007). The intracellular sites of early replication and budding of SARS-coronavirus. *Virology*, *361*, 304-15.

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Nucleoprotein translocates to the nucleolus 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9694345

Type: uncertain

Compartments: nucleolus, cytosol

Diseases: COVID-19

Inferred from: Nucleoprotein translocates to the nucleolus (Homo sapiens)



This COVID-19 event has been created by a combination of computational inference (see https://reactome.org/documentation/inferred-events) from SARS-CoV-1 data and manual curation, as described in the summation for the overall SARS-CoV-2 infection pathway.

A certain part of the nucleoprotein can be found in the nucleolus. This localisation seems to depend on the protein's sumoylation (Li et al, 2005)

Preceded by: Dimerisation of nucleoprotein

Literature references

Liu, DX., Xiao, H., Li, FQ., Tam, JP. (2005). Sumoylation of the nucleocapsid protein of severe acute respiratory syndrome coronavirus. *FEBS Lett.*, 579, 2387-96.

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Unphosphorylated nucleoprotein translocates to the plasma membrane 7

Location: Maturation of nucleoprotein

Stable identifier: R-HSA-9694373

Type: uncertain

Compartments: plasma membrane, cytosol

Diseases: COVID-19

Inferred from: Unphosphorylated nucleoprotein translocates to the plasma membrane (Homo sapiens)



This COVID-19 event has been created by a combination of computational inference (see https://reactome.org/documentation/inferred-events) from SARS-CoV-1 data and manual curation, as described in the summation for the overall SARS-CoV-2 infection pathway.

Significant amounts of the unphosphorylated N protein are associated with the cell membrane (Surjit et al, 2005)

Literature references

Mishra, RN., Kumar, R., Reddy, MK., Chow, VT., Surjit, M., Lal, SK. (2005). The severe acute respiratory syndrome coronavirus nucleocapsid protein is phosphorylated and localizes in the cytoplasm by 14-3-3-mediated translocation. J. Virol., 79, 11476-86.

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