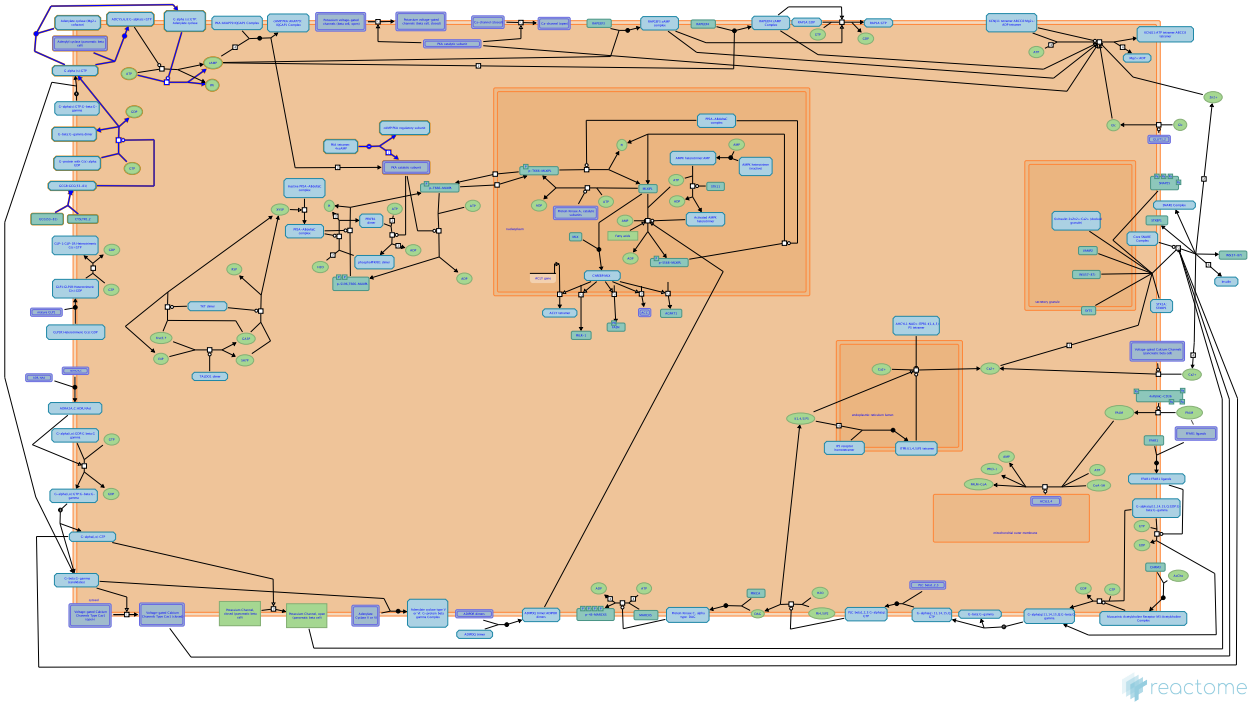
Glucagon signaling in metabolic regulation



Akkerman, JW., D'Eustachio, P., Gillespie, ME., Gopinathrao, G., Jassal, B., Jupe, S., May, B., Varusai, TM.

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

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16/09/2021

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

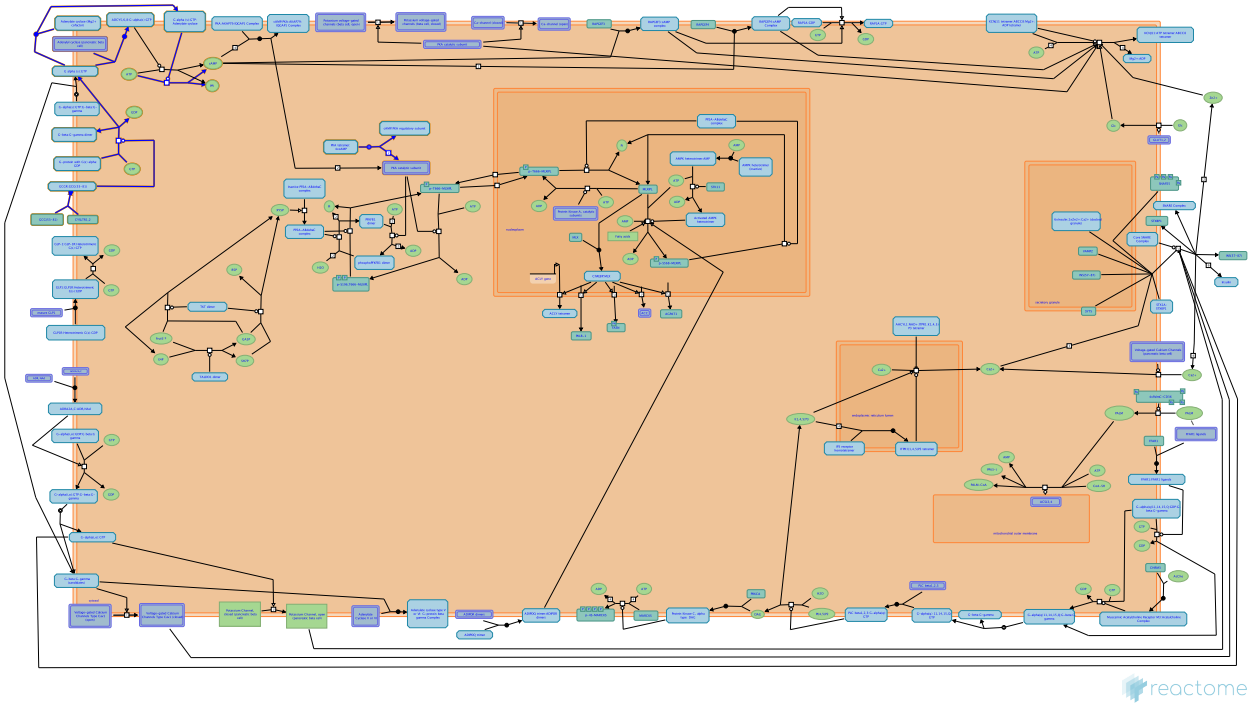
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Glucagon signaling in metabolic regulation ↗

Stable identifier: R-HSA-163359



Glucagon and insulin are peptide hormones released from the pancreas into the blood, that normally act in complementary fashion to stabilize blood glucose concentration. When blood glucose levels rise, insulin release stimulates glucose uptake from the blood, glucose breakdown (glycolysis), and glucose storage as glycogen. When blood glucose levels fall, glucagon release stimulates glycogen breakdown and de novo glucose synthesis (gluconeogenesis), while inhibiting glycolysis and glycogen synthesis.

At a molecular level, the binding of glucagon to the extracellular face of its receptor causes conformational changes in the receptor that allow the dissociation and activation of subunits Gs and Gq. The activation of Gq leads to the activation of phospholipase C, production of inositol 1,4,5-triphosphate, and subsequent release of intracellular calcium. The activation of Gs leads to activation of adenylate cyclase, an increase in intracellular cAMP levels, and activation of protein kinase A (PKA). Active PKA phosphorylates key enzymes of glycogenolysis, glycogenesis, gluconeogenesis, and glycolysis, modifying their activities. These signal transduction events, and some of their downstream consequences, are illustrated below (adapted from Jiang and Zhang, 2003).

Literature references

Jiang, G., Zhang, BB. (2003). Glucagon and regulation of glucose metabolism. *Am J Physiol Endocrinol Metab, 284,* E671-8. ↗

Editions

2005-04-28	Authored	Gopinathrao, G.

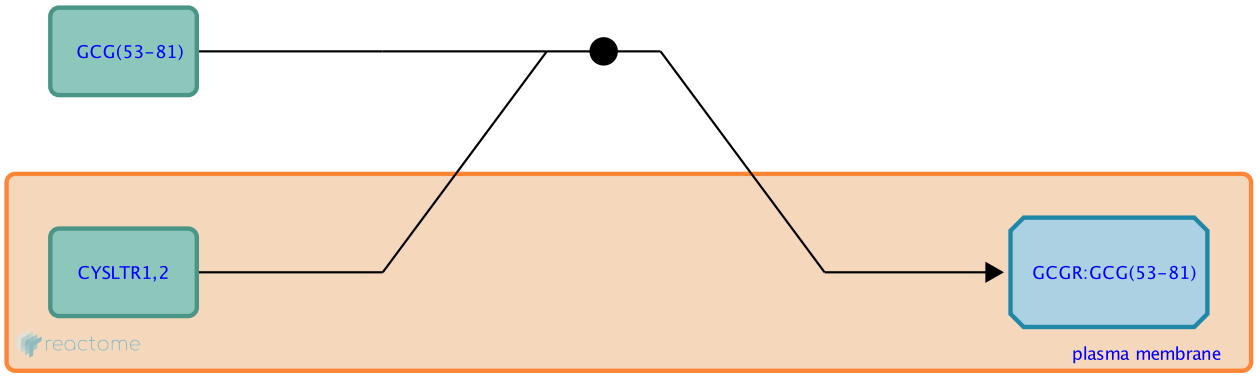
Glucagon binds to Glucagon receptor ↗

Location: Glucagon signaling in metabolic regulation

Stable identifier: R-HSA-163625

Type: binding

Compartments: extracellular region, plasma membrane



Glucagon (Thomsen J et al, 1972) is an important peptide hormone produced by the pancreas. It is released when the glucose level in the blood is low (hypoglycemia), causing the liver to convert stored glycogen into glucose and release it into the bloodstream. The action of glucagon is thus opposite to that of insulin. Glucagon, together with glucagon-like peptide 1 (GLP-1) and glucagon-like peptide 2 (GLP-2), are peptide hormones encoded by a single common prohormone precursor, proglucagon.The glucagon receptor (Lok S et al, 1994) plays a central role in regulating the level of blood glucose by controlling the rate of hepatic glucose production and insulin secretion. The activity of this receptor is mediated by coupling to Gs and q, which stimulate adenylyl cyclase and a phosphatidylinositol-calcium second messenger system respectively.

Followed by: Glucagon:GCGR mediates GTP-GDP exchange

Literature references

Rall, T., Harris, BA. (1987). Identification of the lesion in the stimulatory GTP-binding protein of the uncoupled S49 lymphoma. *FEBS Lett, 224*, 365-71. ↗

Dallas-Yang, Q., Shen, X., Strowski, M., Brady, E., Saperstein, R., Gibson, RE. et al. (2004). Hepatic glucagon receptor binding and glucose-lowering in vivo by peptidyl and non-peptidyl glucagon receptor antagonists. *Eur J Pharmacol, 501*, 225-34. ↗

Thomsen, J., Kristiansen, K., Brunfeldt, K., Sundby, F. (1972). The amino acid sequence of human glucagon. *FEBS Lett, 21*, 315-319. ↗

Lok, S., Kuijper, JL., Jelinek, LJ., Kramer, JM., Whitmore, TE., Sprecher, CA. et al. (1994). The human glucagon receptor encoding gene: structure, cDNA sequence and chromosomal localization. *Gene, 140*, 203-9. ↗

Editions

2005-05-04	Authored	Gopinathrao, G.
2009-05-11	Edited	Jassal, B.
2009-05-29	Reviewed	D'Eustachio, P.

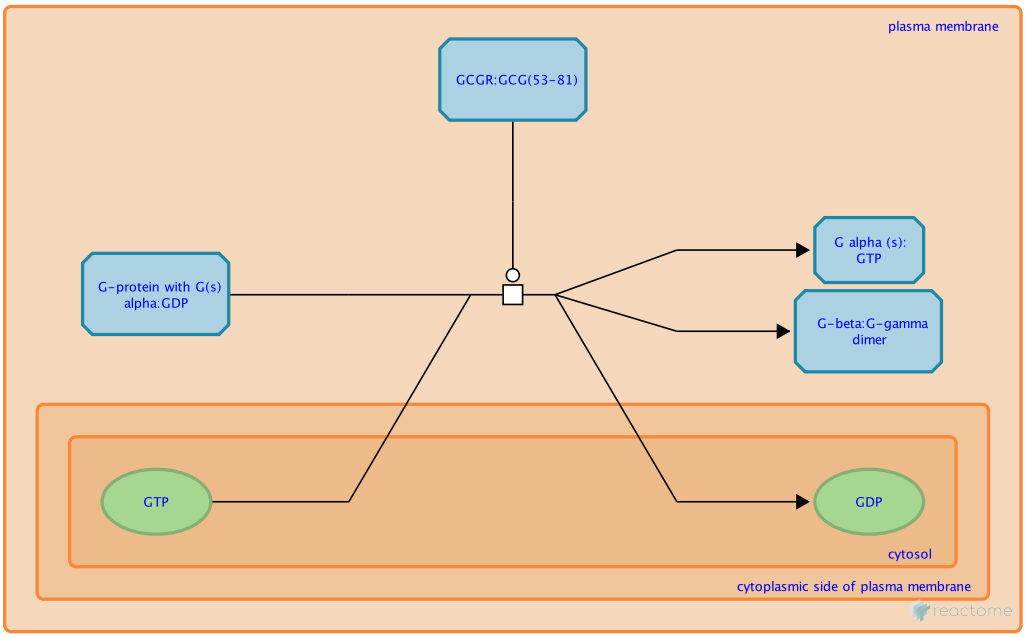
Glucagon:GCGR mediates GTP-GDP exchange ↗

Location: Glucagon signaling in metabolic regulation

Stable identifier: R-HSA-825631

Type: transition

Compartments: plasma membrane, cytosol



The G(s)alpha G-beta G-gamma complex bound to glucagon, in the plasma membrane, releases a molecule of bound GDP, binds a molecule of GTP, and dissociates to yield a G(s)alpha:GTP complex and a G-beta:G-gamma dimer (Siu et al. 2013).

Preceded by: Glucagon binds to Glucagon receptor

Followed by: G alpha (s) activates adenylate cyclase

Literature references

Siu, FY., He, M., de Graaf, C., Han, GW., Yang, D., Zhang, Z. et al. (2013). Structure of the human glucagon class B G-protein-coupled receptor. *Nature, 499*, 444-9. ↗

Editions

2005-08-12	Authored	Gopinathrao, G.
2010-05-26	Edited, Reviewed	D'Eustachio, P.

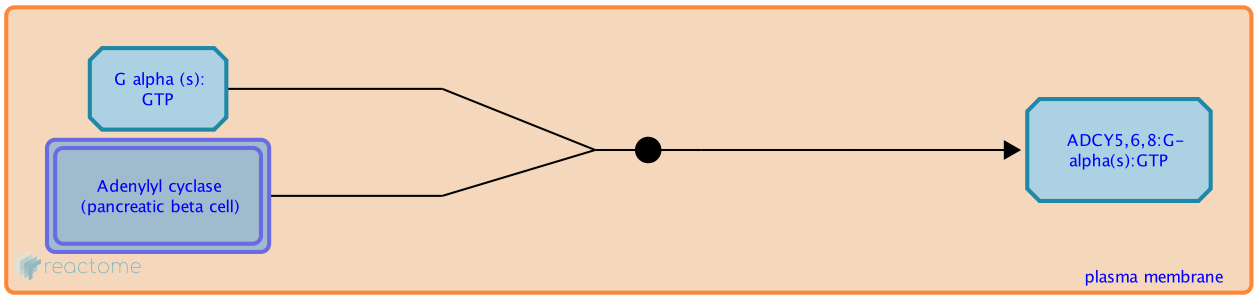
G(s):GTP activates Adenylyl cyclase ↗

Location: Glucagon signaling in metabolic regulation

Stable identifier: R-HSA-381704

Type: binding

Compartments: plasma membrane



By analogy with adenylyl cyclases I and II, adenylyl cyclase VIII is activated by G(s) alpha:GTP by protein-protein interaction between G(s) alpha and the C2 region of adenylyl cyclase VIII, forming a complex. Adenylyl cyclase VIII is present in beta cells of rat and is activated by both G(s) alpha:GTP and calcium:calmodulin, thus integrating signals from both GLP-1 via G(s) alpha and glucose via calcium. Human beta cells contain adenylyl cyclases V and VI, which are also activated by G(s) alpha:GTP, and may contain additional adenylyl cyclases.

Literature references

Leech, CA., Castonguay, MA., Habener, JF. (1999). Expression of adenylyl cyclase subtypes in pancreatic beta-cells. *Biochem Biophys Res Commun, 254*, 703-6. ↗

Tesmer, JJ., Sunahara, RK., Gilman, AG., Sprang, SR. (1997). Crystal structure of the catalytic domains of adenylyl cyclase in a complex with Gsalpha.GTPgammaS. *Science, 278*, 1907-16. ↗

Delmeire, D., Flamez, D., Hinke, SA., Cali, JJ., Pipeleers, D., Schuit, F. (2003). Type VIII adenylyl cyclase in rat beta cells: coincidence signal detector/generator for glucose and GLP-1. *Diabetologia, 46*, 1383-93. ↗

Doyle, ME., Egan, JM. (2007). Mechanisms of action of glucagon-like peptide 1 in the pancreas. *Pharmacol Ther, 113*, 546-93. ↗

Winzell, MS., Ahren, B. (2007). G-protein-coupled receptors and islet function-implications for treatment of type 2 diabetes. *Pharmacol Ther, 116*, 437-48. ↗

Editions

2009-05-28	Authored, Edited	May, B.
2009-06-02	Reviewed	Gillespie, ME.

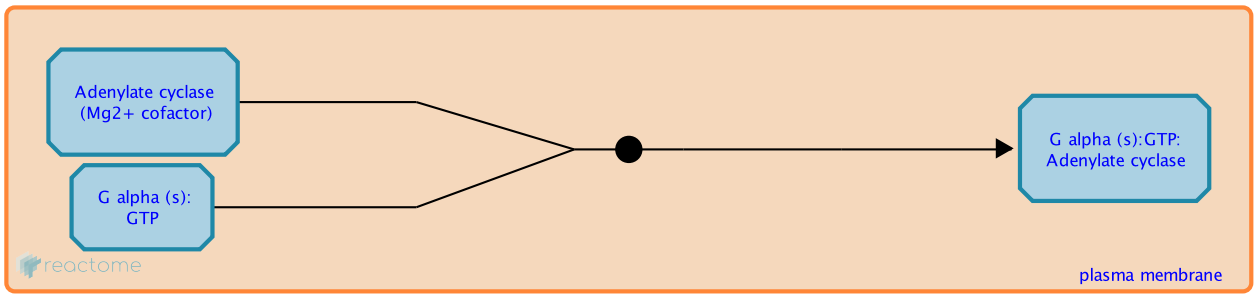
G alpha (s) activates adenylate cyclase ↗

Location: Glucagon signaling in metabolic regulation

Stable identifier: R-HSA-163617

Type: binding

Compartments: plasma membrane



G(s)-alpha:GTP binds to inactive adenylate cyclase, causing a conformational transition in adenylate cyclase exposing the catalytic site and activating it.

Preceded by: Glucagon:GCGR mediates GTP-GDP exchange

Literature references

Tesmer, JJ., Sunahara, RK., Gilman, AG., Sprang, SR. (1997). Crystal structure of the catalytic domains of adenylyl cyclase in a complex with Gsalpha.GTPgammaS. *Science, 278*, 1907-16. ↗

Dessauer, CW., Chen-Goodspeed, M., Chen, J. (2002). Mechanism of Galpha i-mediated inhibition of type V adenylyl cyclase. *J. Biol. Chem., 277*, 28823-9. ↗

Editions

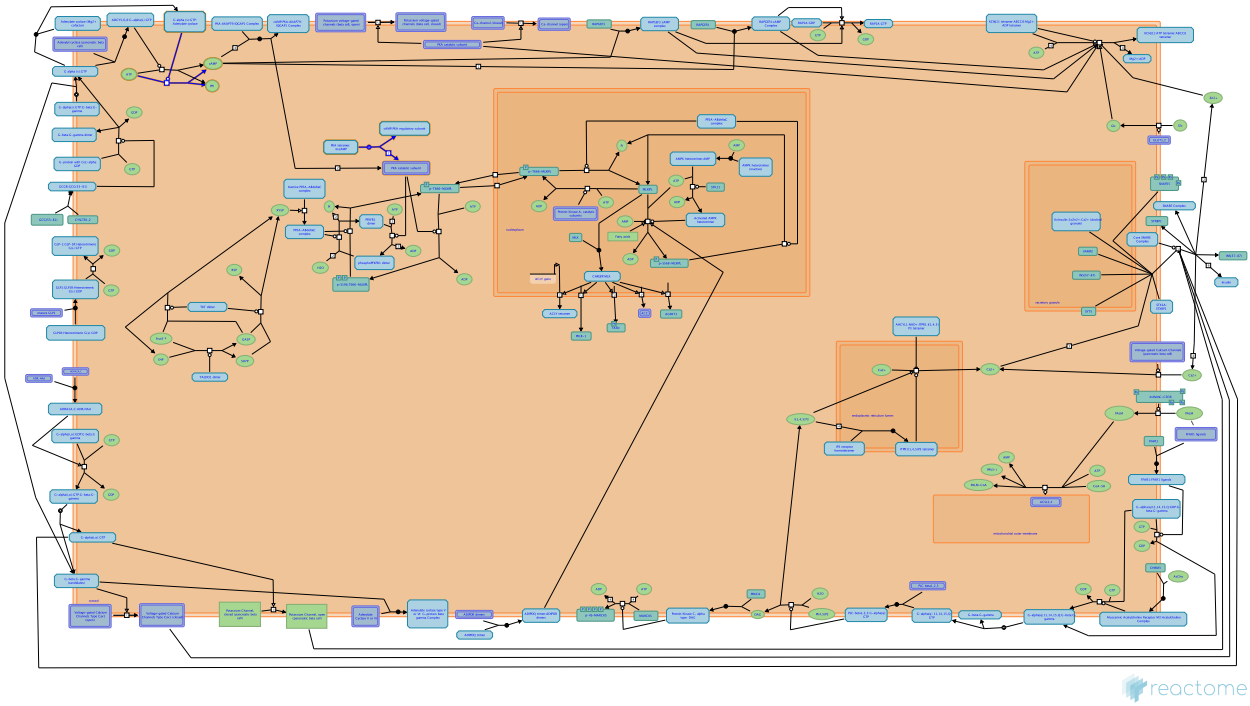
2009-03-09	Authored	Jupe, S.
2009-06-03	Reviewed	Akkerman, JW.
2009-08-11	Edited	May, B.
2017-07-10	Revised	Varusai, TM.

PKA activation in glucagon signalling ↗

Location: Glucagon signaling in metabolic regulation

Stable identifier: R-HSA-164378

Compartments: plasma membrane



Adenylate cyclase catalyses the synthesis of cyclic AMP (cAMP) from ATP. In the absence of cAMP, protein kinase A (PKA) exists as inactive tetramers of two catalytic subunits and two regulatory subunits. cAMP binding to PKA tetramers causes them to dissociate and release their catalytic subunits as active monomers. Four isoforms of the regulatory subunit are known, that differ in their tissue specificity and functional characteristics, but the specific isoform activated in response to glucagon signaling has not yet been identified.

Editions

2005-05-19	Authored	Gopinathrao, G., D'Eustachio, P.

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