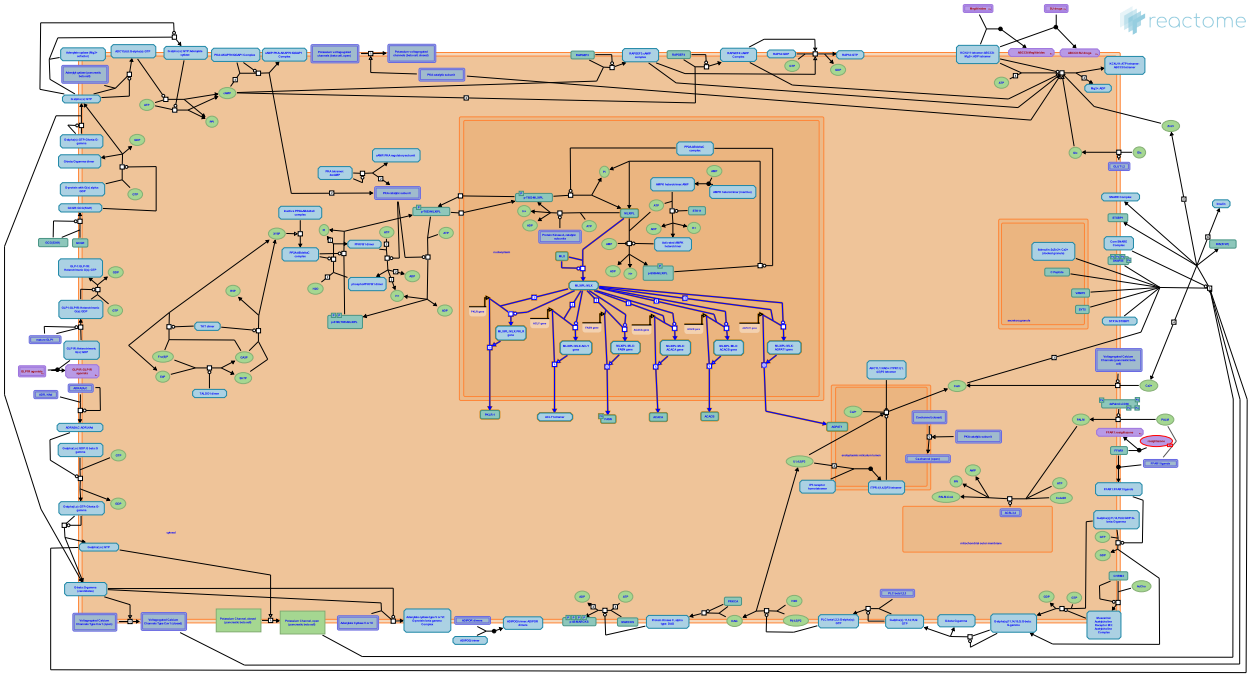
ChREBP activates metabolic gene expression



D'Eustachio, P., Gopinathrao, G., Hill, DP.

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

21/09/2024

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

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. ↗

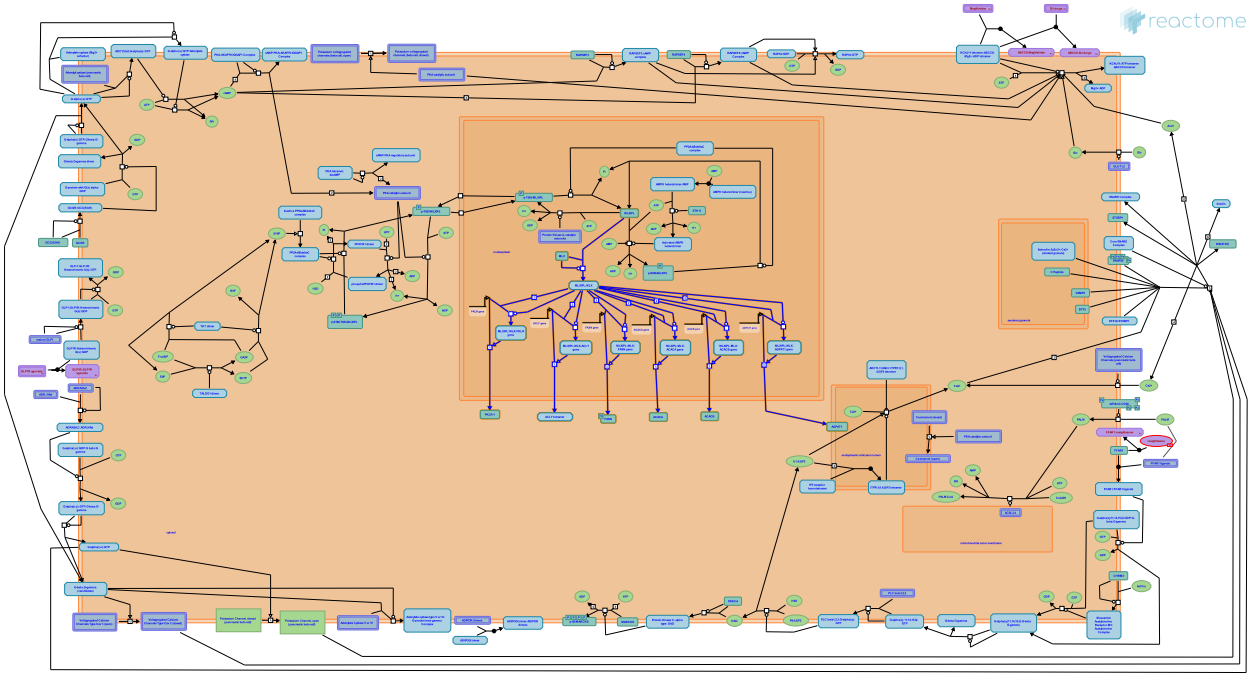
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

ChREBP activates metabolic gene expression ↗

Stable identifier: R-HSA-163765

Compartments: nucleoplasm, cytosol, endoplasmic reticulum membrane



ChREBP (Carbohydrate Response Element Binding Protein) is a large multidomain protein containing a nuclear localization signal near its amino terminus, polyproline domains, a basic helix-loop-helix-leucine zipper domain, and a leucine-zipper-like domain (Uyeda et al., 2002). Its dephosphorylation in response to molecular signals associated with the well-fed state allows it to enter the nucleus, interact with MLX protein, and bind to ChRE DNA sequence motifs near Acetyl-CoA carboxylase, Fatty acid synthase, and Pyruvate kinase (L isoform) genes (Ishi et al.2004). This sequence of events is outlined schematically in the picture below (adapted from Kawaguchi et al. (2001) - copyright (2001) National Academy of Sciences, U.S.A.).

Literature references

Uyeda, K., Horton, JD., Iizuka, K., Liang, G., Bruick, RK. (2004). Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis. *Proc Natl Acad Sci U S A, 101*, 7281-6. ↗

Uyeda, K., Kabashima, T., Kawaguchi, T., Takenoshita, M. (2001). Glucose and cAMP regulate the L-type pyruvate kinase gene by phosphorylation/dephosphorylation of the carbohydrate response element binding protein. *Proc Natl Acad Sci U S A, 98*, 13710-5. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2005-05-13	Authored	Gopinathrao, G.
2024-02-12	Reviewed	Hill, DP.

Formation of ChREBP:MLX heterodimer ↗

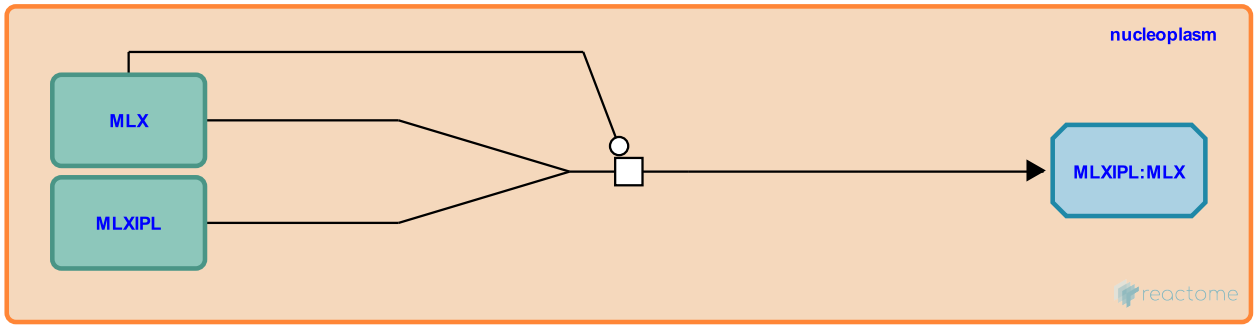
Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-163666

Type: transition

Compartments: nucleoplasm

Inferred from: Formation of mChREBP:mMlx complex (Mus musculus)



Dephosphorylation of ChREBP protein enables it to enter the nucleus, where it binds MLX protein to form a heterodimer that acts as a transcription factor to enable the expression of genes like PKLR, ACLY, FASN, ACACA, ACACB, and AGPAT associated with metabolism in the well-fed state (Ma et al. 2005).

Followed by: MLXIPL:MLX binds ACACB gene promoter, MLXIPL:MLX binds FASN gene promoter, MLXIPL:MLX binds ACACA gene promoter, MLXIPL:MLX binds ACLY gene promoter, MLXIPL:MLX binds AGPAT1 gene promoter, MLXIPL:MLX binds PKLR gene promoter

Literature references

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2024-02-12	Reviewed	Hill, DP.

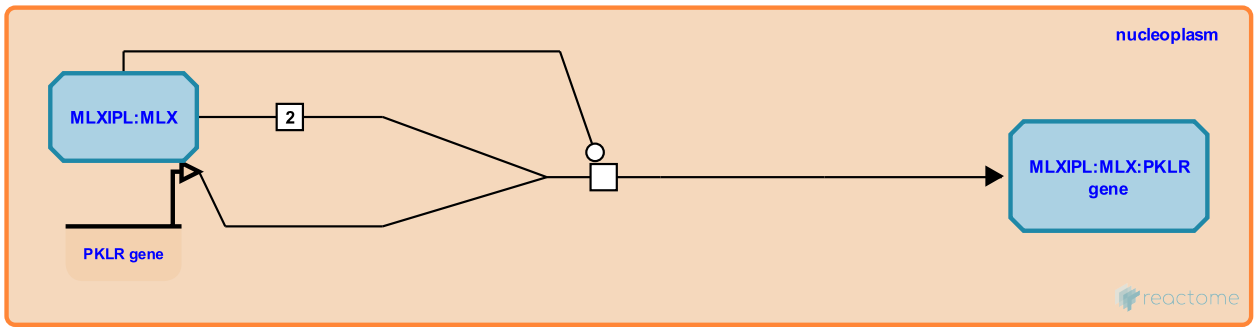
MLXIPL:MLX binds PKLR gene promoter ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-9856539

Type: transition

Compartments: nucleoplasm



As part of the physiological response to high dietary carbohydrate intake, two copies of the MLXIPL:MLX (ChREBP:MLX) complex bind to the carbohydrate response element (ChoRE) in the promoter of the PKLR (pyruvate kinase) gene (Ma et al. 2005, 2006, 2007; Stoeckman et al. 2004).

Preceded by: Formation of ChREBP:MLX heterodimer

Followed by: Transcriptional activation of PKLR gene by ChREBP:MLX

Literature references

Ma, L., Towle, HC., Stoeckman, AK. (2004). Mlx is the functional heteromeric partner of the carbohydrate response element-binding protein in glucose regulation of lipogenic enzyme genes. *J Biol Chem, 279*, 15662-9. ↗

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2023-12-19	Edited	D'Eustachio, P.
2023-12-20	Authored	D'Eustachio, P.
2024-02-12	Reviewed	Hill, DP.

Transcriptional activation of PKLR gene by ChREBP:MLX ↗

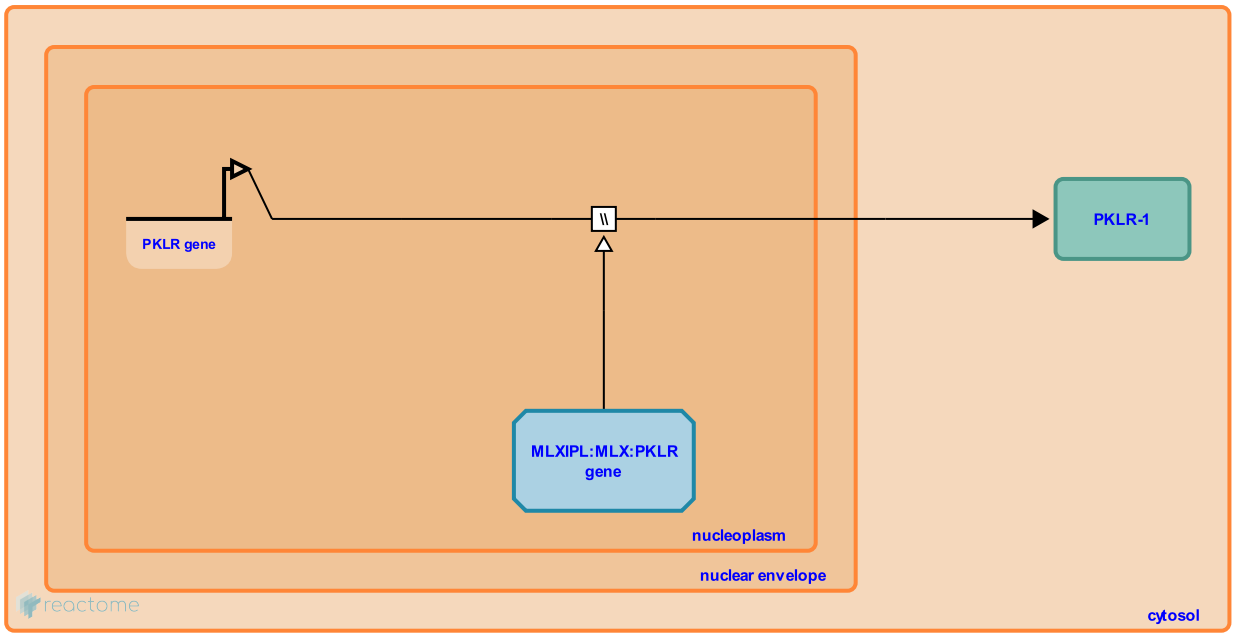
Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-163669

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Transcriptional activation of pyruvate kinase L isoform gene by mChREBP:mMLX (Mus musculus)



The PKLR (pyruvate kinase) gene, activated by binding of MLXIPL:MLX (ChREBP:MLX) to its promoter region, is transcribed and the resulting mRNA is translated to yield PKLR protein (Ma et al. 2005, 2006, 2007). Additional regulatory effects of polyunsaturated fatty acids on PKLR gene expression suggested by studies of animal models (Dentin et al. 2005; Xu et al. 2006) have not been annotated here.

Preceded by: MLXIPL:MLX binds PKLR gene promoter

Literature references

Benhamed, F., Girard, J., Viollet, B., Pégorier, JP., Vaulont, S., Postic, C. et al. (2005). Polyunsaturated fatty acids suppress glycolytic and lipogenic genes through the inhibition of ChREBP nuclear protein translocation. *J Clin Invest, 115*, 2843-54. ↗

Christian, B., Xu, J., Jump, DB. (2006). Regulation of rat hepatic L-pyruvate kinase promoter composition and activity by glucose, n-3 polyunsaturated fatty acids, and peroxisome proliferator-activated receptor-alpha agonist. *J Biol Chem, 281*, 18351-62. ↗

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2024-02-12	Reviewed	Hill, DP.

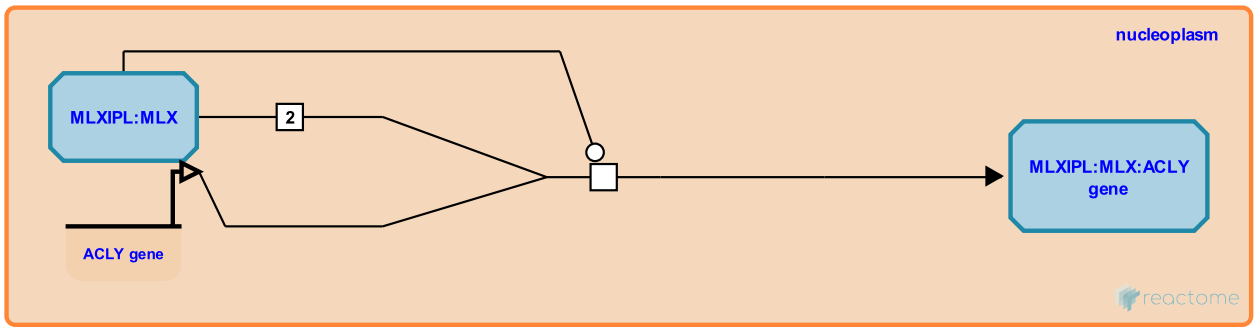
MLXIPL:MLX binds ACLY gene promoter ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-9856549

Type: transition

Compartments: nucleoplasm



As part of the physiological response to high dietary carbohydrate intake, two copies of the MLXIPL:MLX (ChREBP:MLX) complex bind to the carbohydrate response element (ChoRE) in the promoter of the ACLY (ATP citrate synthase) gene (Ma et al. 2005, 2006, 2007; Stoeckman et al. 2004).

Preceded by: Formation of ChREBP:MLX heterodimer

Followed by: Transcriptional activation of Citrate lyase monomer gene by ChREBP:MLX

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2023-12-19	Edited	D'Eustachio, P.
2023-12-20	Authored	D'Eustachio, P.
2024-02-12	Reviewed	Hill, DP.

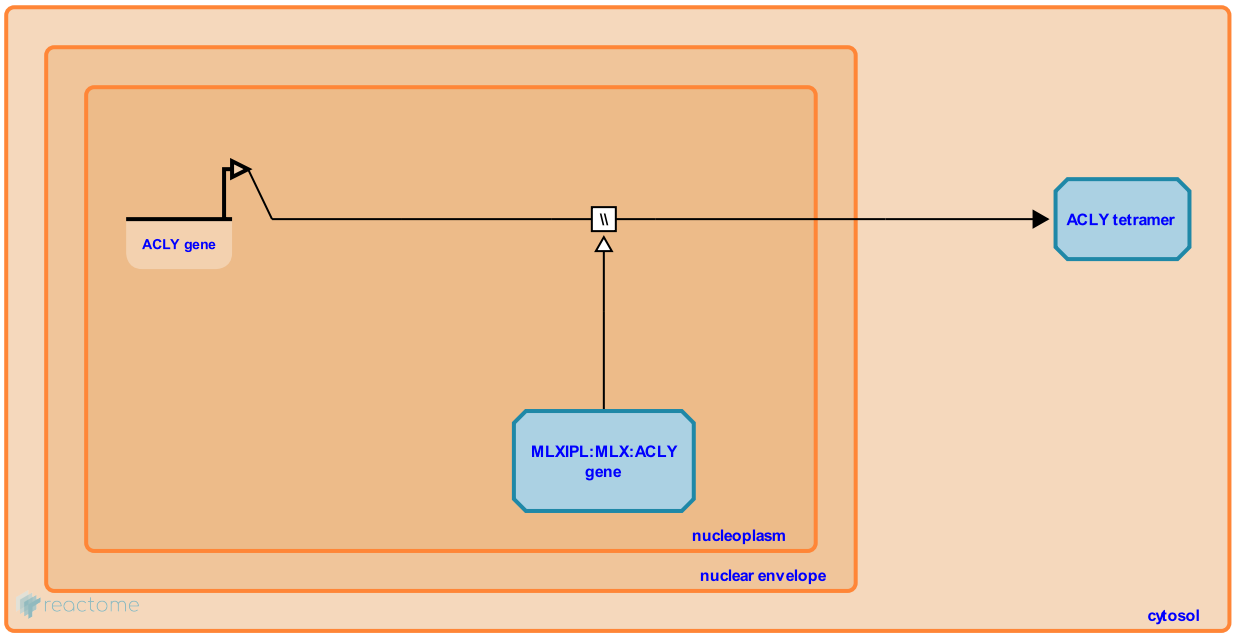
Transcriptional activation of Citrate lyase monomer gene by ChREBP:MLX ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-163770

Type: omitted

Compartments: nucleoplasm, cytosol



The ACLY (ATP citrate synthase) gene, activated by binding of MLXIPL:MLX (ChREBP:MLX) to its promoter region, is transcribed and the resulting mRNA is translated to yield ACLY protein (Ma et al. 2005, 2006, 2007).

Preceded by: MLXIPL:MLX binds ACLY gene promoter

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

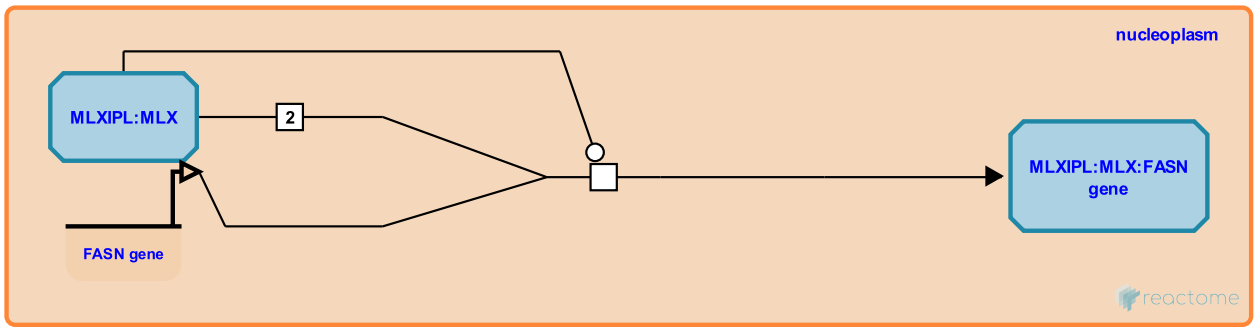
MLXIPL:MLX binds FASN gene promoter ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-9856546

Type: transition

Compartments: nucleoplasm



As part of the physiological response to high dietary carbohydrate intake, two copies of the MLXIPL:MLX (ChREBP:MLX) complex bind to the carbohydrate response element (ChoRE) in the promoter of the FASN (Fatty acid synthase) gene (Ma et al. 2006, 2006, 2007; Stoeckman et al. 2004).

Preceded by: Formation of ChREBP:MLX heterodimer

Followed by: Transcriptional activation of FASN monomer gene by ChREBP:MLX

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2023-12-19	Edited	D'Eustachio, P.
2023-12-20	Authored	D'Eustachio, P.
2024-02-12	Reviewed	Hill, DP.

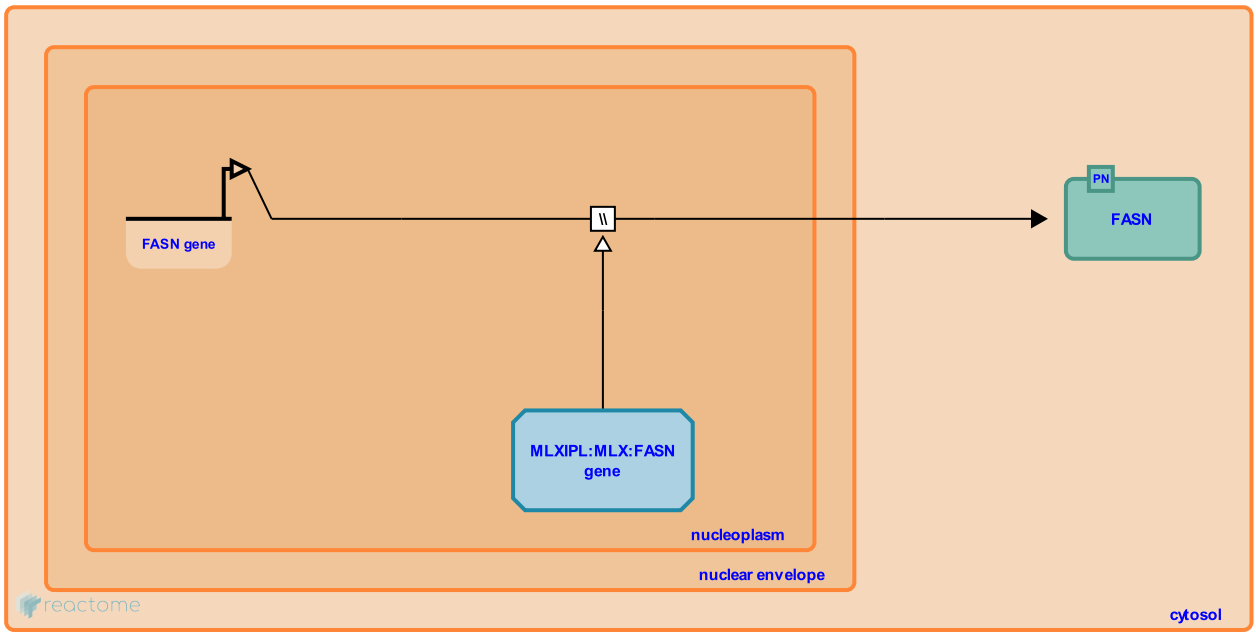
Transcriptional activation of FASN monomer gene by ChREBP:MLX ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-163733

Type: omitted

Compartments: nucleoplasm, cytosol



The ACLY (ATP citrate synthase) gene, activated by binding of MLXIPL:MLX (ChREBP:MLX) to its promoter region, is transcribed and the resulting mRNA is translated to yield ACLY protein (Ma et al. 2005, 2006, 2007).

Preceded by: MLXIPL:MLX binds FASN gene promoter

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2024-02-12	Reviewed	Hill, DP.

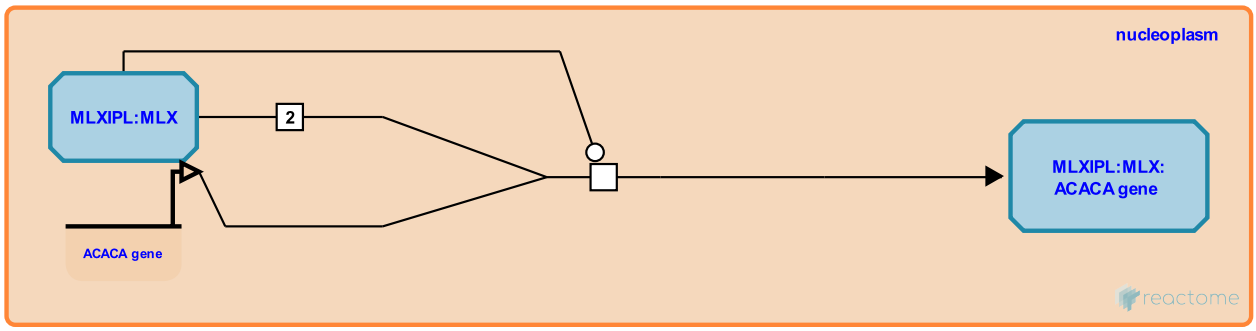
MLXIPL:MLX binds ACACA gene promoter ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-9856550

Type: transition

Compartments: nucleoplasm



As part of the physiological response to high dietary carbohydrate intake, two copies of the MLXIPL:MLX (ChREBP:MLX) complex bind to the carbohydrate response element (ChoRE) in the promoter of the ACACA (Acetyl-CoA carboxylase 1) gene (Ma et al. 2005, 2006, 2007; Stoeckman et al. 2004).

Preceded by: Formation of ChREBP:MLX heterodimer

Followed by: Transcriptional activation of ACACA by ChREBP:MLX

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2023-12-19	Edited	D'Eustachio, P.
2023-12-20	Authored	D'Eustachio, P.
2024-02-12	Reviewed	Hill, DP.

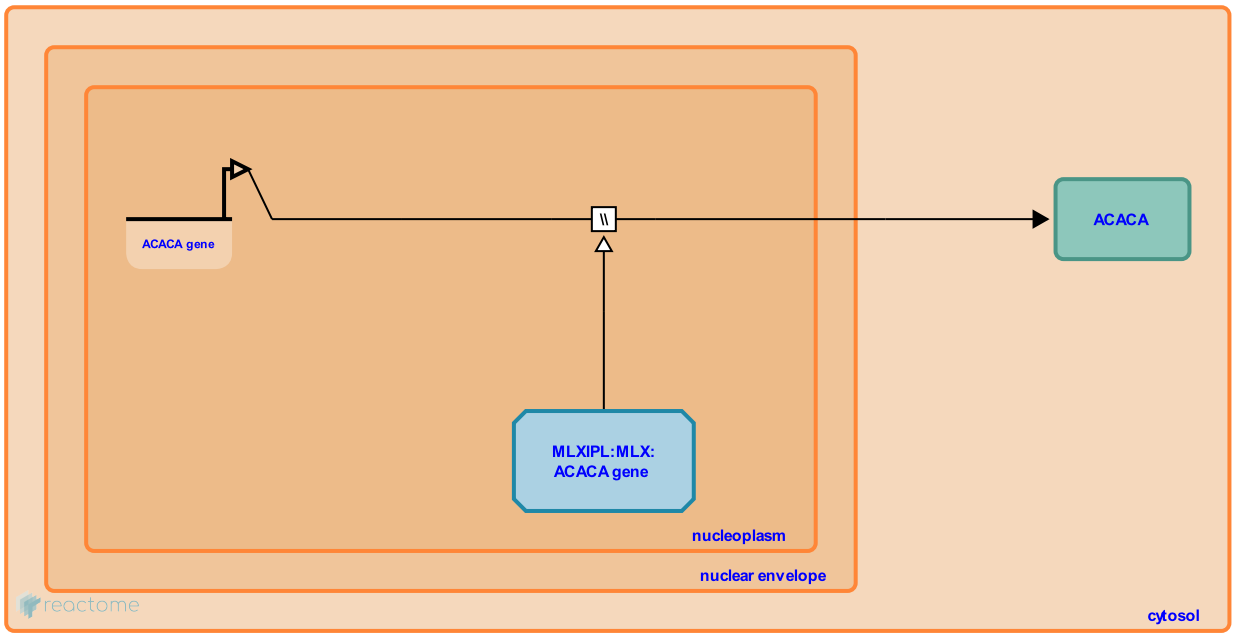
Transcriptional activation of ACACA by ChREBP:MLX ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-163743

Type: omitted

Compartments: nucleoplasm, cytosol



The ACACA (Acetyl-CoA carboxylase 1) gene, activated by binding of MLXIPL:MLX (ChREBP:MLX) to its promoter region, is transcribed and the resulting mRNA is translated to yield ACACA protein (Ma et al. 2005, 2006, 2007).

Preceded by: MLXIPL:MLX binds ACACA gene promoter

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2024-02-12	Reviewed	Hill, DP.

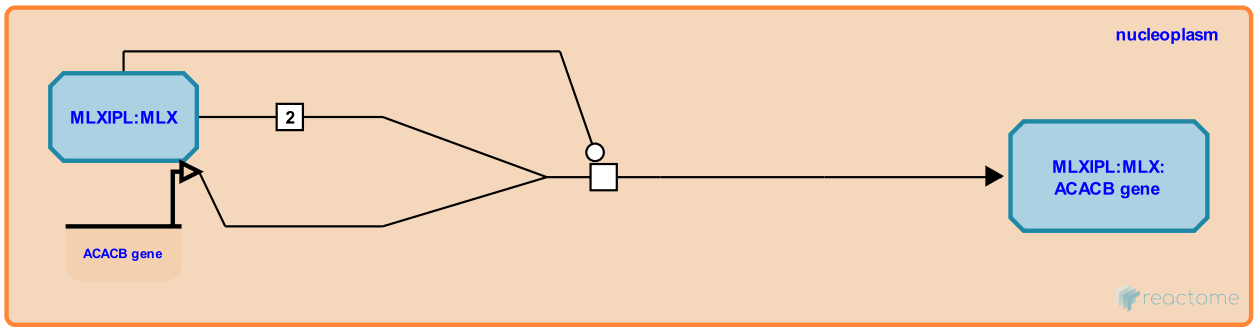
MLXIPL:MLX binds ACACB gene promoter ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-9856548

Type: transition

Compartments: nucleoplasm



As part of the physiological response to high dietary carbohydrate intake, two copies of the MLXIPL:MLX (ChREBP:MLX) complex bind to the carbohydrate response element (ChoRE) in the promoter of the ACACB (Acetyl-CoA carboxylase 2) gene (Ma et al. 2005, 2006, 2007; Stoeckman et al. 2004).

Preceded by: Formation of ChREBP:MLX heterodimer

Followed by: Transcriptional activation of ACACB by ChREBP:MLX

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2023-12-19	Edited	D'Eustachio, P.
2023-12-20	Authored	D'Eustachio, P.
2024-02-12	Reviewed	Hill, DP.

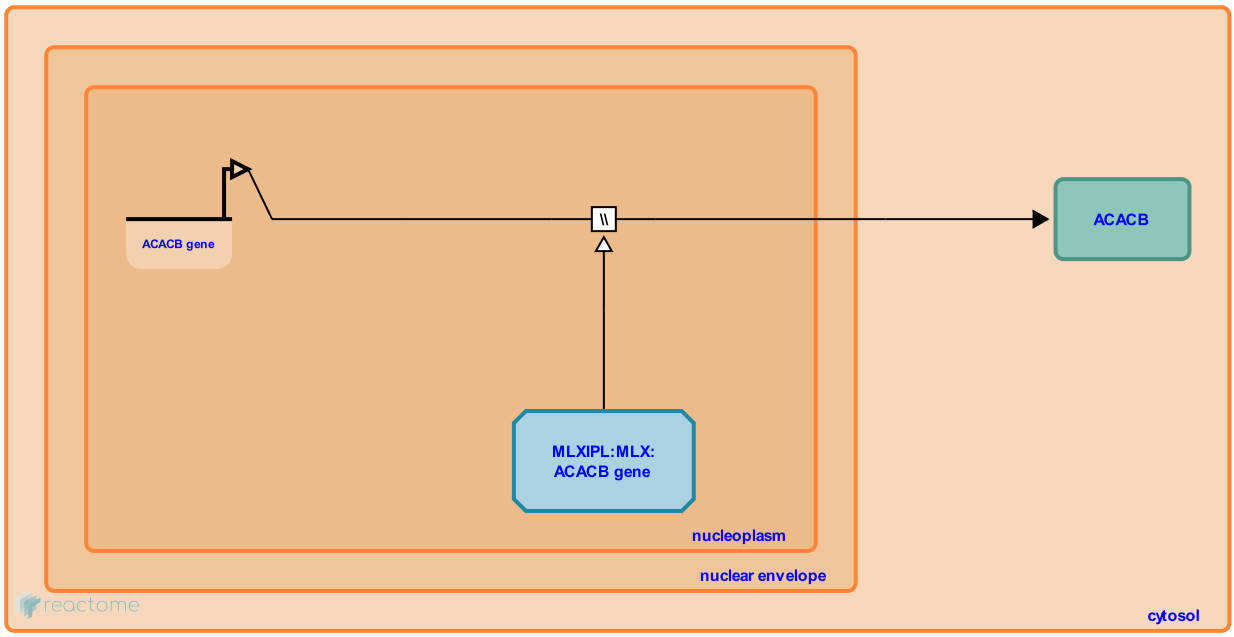
Transcriptional activation of ACACB by ChREBP:MLX ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-9856605

Type: omitted

Compartments: nucleoplasm, cytosol



The ACACB (Acetyl-CoA carboxylase 2) gene, activated by binding of MLXIPL:MLX (ChREBP:MLX) to its promoter region, is transcribed and the resulting mRNA is translated to yield ACACB protein (Ma et al. 2005, 2006, 2007).

Preceded by: MLXIPL:MLX binds ACACB gene promoter

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2023-12-19	Edited	D'Eustachio, P.
2023-12-20	Authored	D'Eustachio, P.
2024-02-12	Reviewed	Hill, DP.

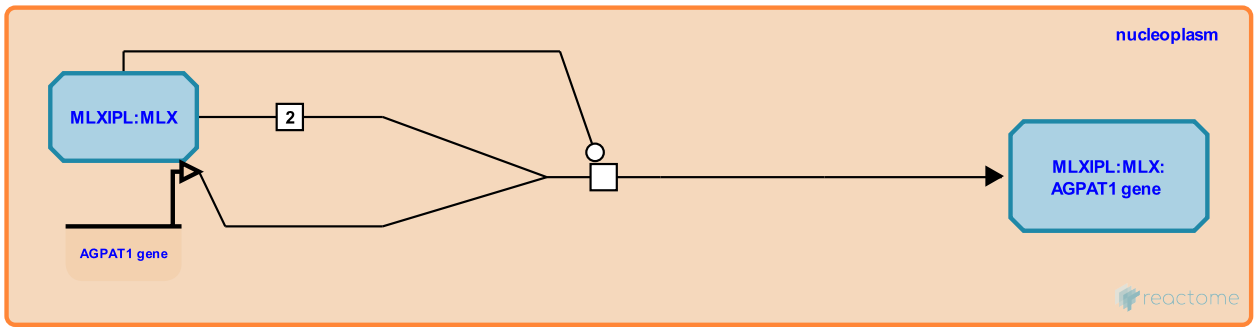
MLXIPL:MLX binds AGPAT1 gene promoter ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-9856604

Type: transition

Compartments: nucleoplasm



As part of the physiological response to high dietary carbohydrate intake, two copies of the MLXIPL:MLX (ChREBP:MLX) complex bind to the carbohydrate response element (ChoRE) in the promoter of the AGPAT1 (1-acyl-sn-glycerol-3-phosphate acyltransferase alpha) gene (Ma et al. 2005, 2006, 2007; Stoeckman et al. 2004).

Preceded by: Formation of ChREBP:MLX heterodimer

Followed by: Transcriptional activation of AGPAT1 by ChREBP:MLX

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

Towle, HC., Ma, L., Robinson, LN. (2006). ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem., 281*, 28721-30. ↗

Ma, L., Tsatsos, NG., Towle, HC. (2005). Direct role of ChREBP.Mlx in regulating hepatic glucose-responsive genes. *J Biol Chem, 280*, 12019-27. ↗

Editions

2023-12-19	Edited	D'Eustachio, P.
2023-12-20	Authored	D'Eustachio, P.
2024-02-12	Reviewed	Hill, DP.

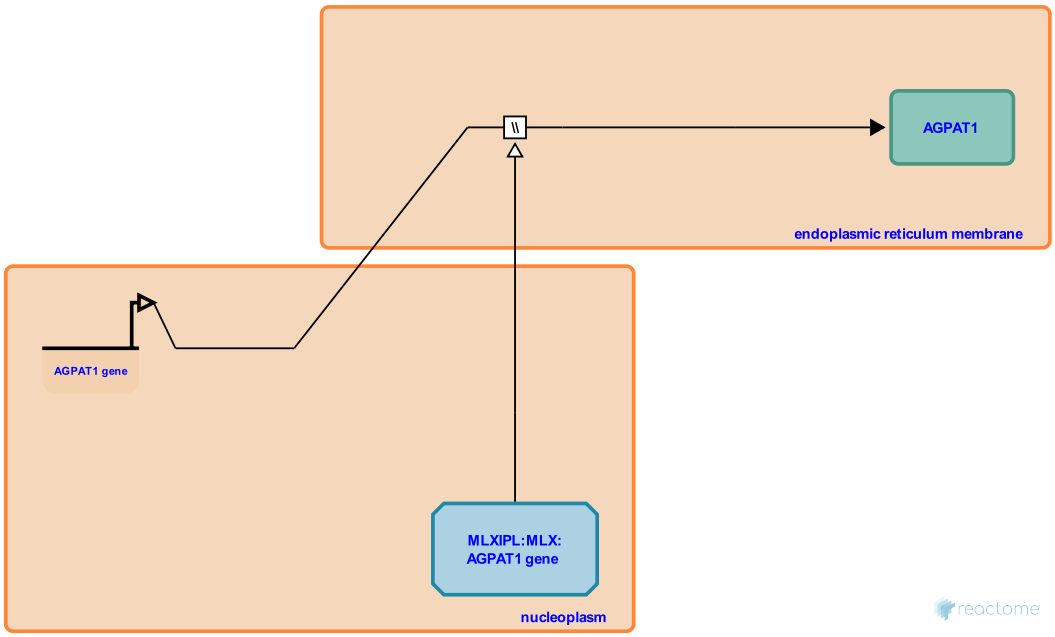
Transcriptional activation of AGPAT1 by ChREBP:MLX ↗

Location: ChREBP activates metabolic gene expression

Stable identifier: R-HSA-163748

Type: omitted

Compartments: endoplasmic reticulum membrane, nucleoplasm



The AGPAT1 (1-acyl-sn-glycerol-3-phosphate acyltransferase alpha) gene, activated by binding of MLXIPL:MLX (ChREBP:MLX) to its promoter region, is transcribed and the resulting mRNA is translated to yield ACACB protein (Ma et al. 2005, 2006, 2007).

Preceded by: MLXIPL:MLX binds AGPAT1 gene promoter

Literature references

Sham, YY., Towle, HC., Ma, L., Walters, KJ. (2007). A critical role for the loop region of the basic helix-loop-helix/leucine zipper protein Mlx in DNA binding and glucose-regulated transcription. *Nucleic Acids Res., 35*, 35-44. ↗

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