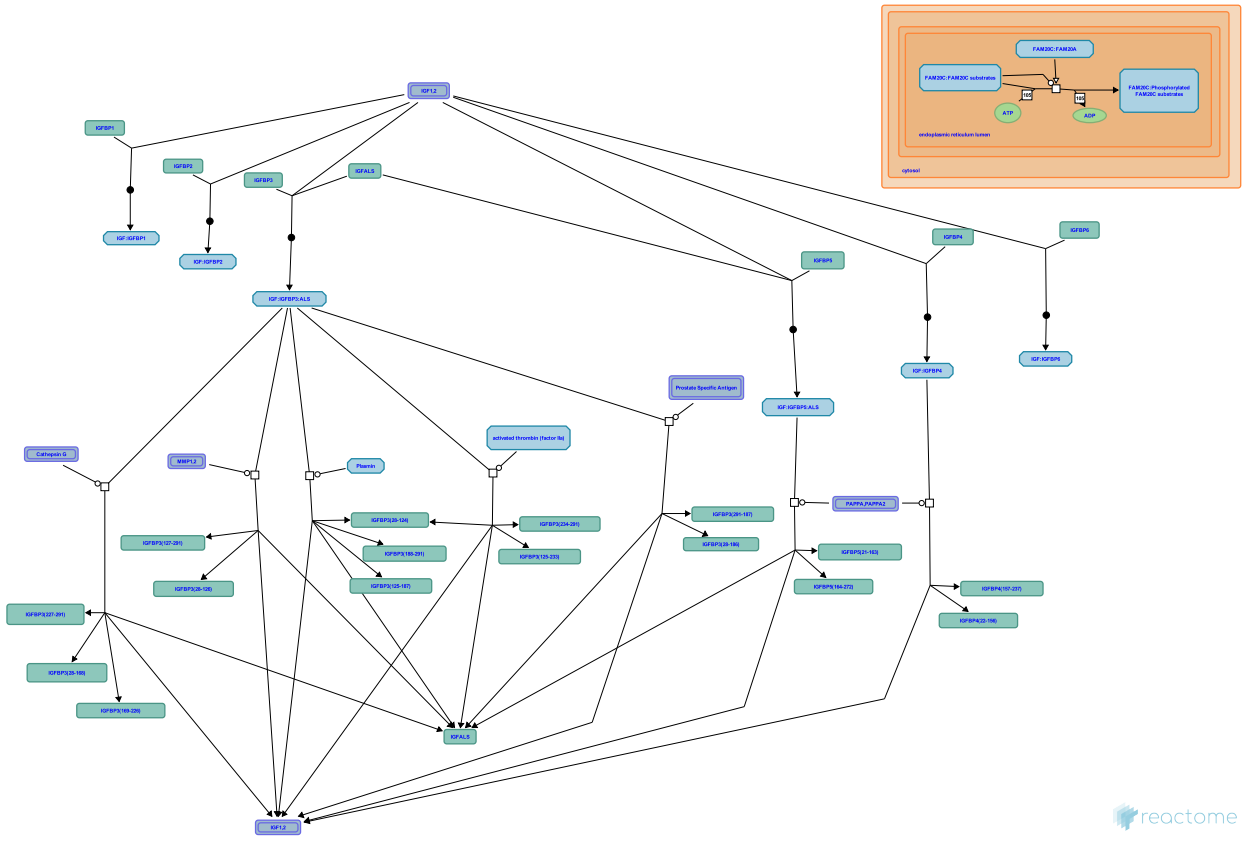
Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)



D'Eustachio, P., Gillespie, ME., Gopinathrao, G., Jupe, S., Matthews, L., May, B., Wiley, SE.

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

20/01/2021

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.

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. ↗

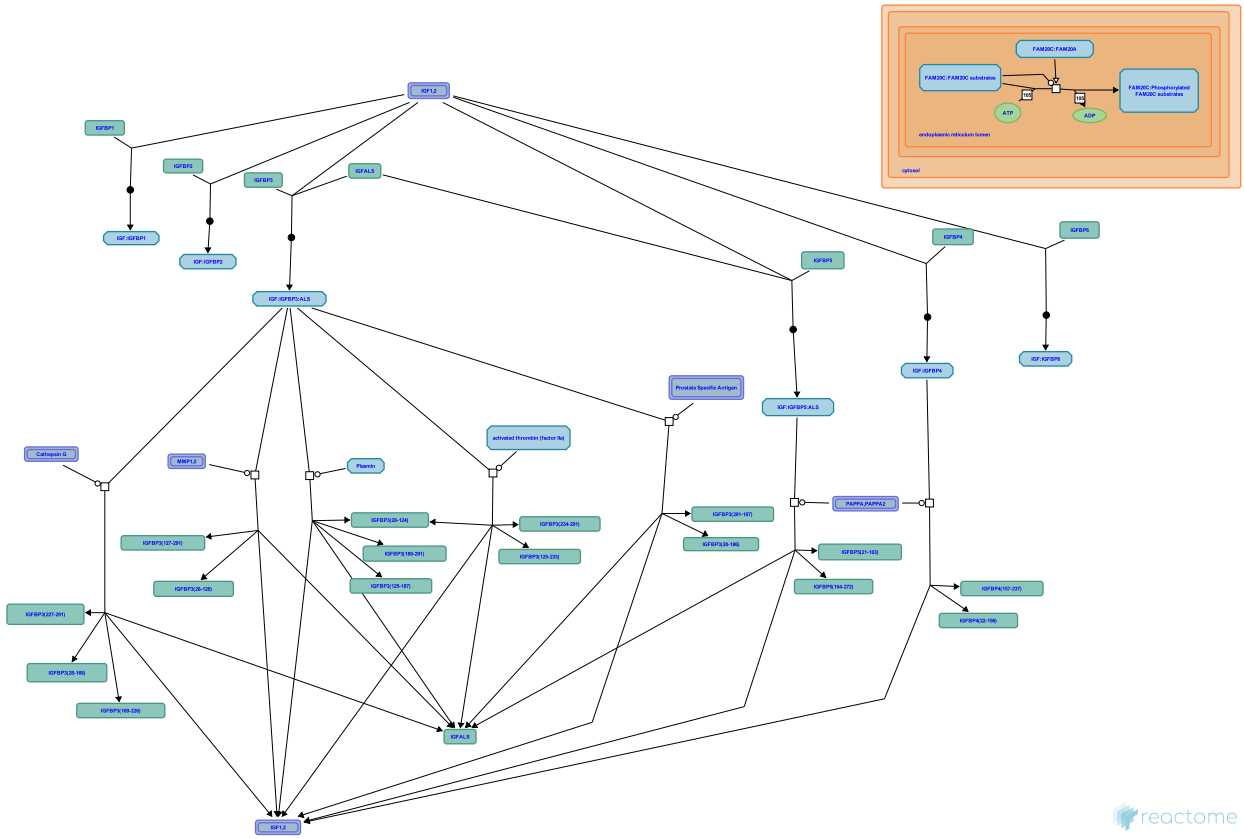
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) ↗

Stable identifier: R-HSA-381426

Compartments: extracellular region



The family of Insulin like Growth Factor Binding Proteins (IGFBPs) share 50% amino acid identity with conserved N terminal and C terminal regions responsible for binding Insulin like Growth Factors I and II (IGF I and IGF II). Most circulating IGFs are in complexes with IGFBPs, which are believed to increase the residence of IGFs in the body, modulate availability of IGFs to target receptors for IGFs, reduce insulin like effects of IGFs, and act as signaling molecules independently of IGFs.

About 75% of circulating IGFs are in 1500 220 KDa complexes with IGFBP3 and ALS. Such complexes are too large to pass the endothelial barrier. The remaining 20 25% of IGFs are bound to other IGFBPs in 40 50 KDa complexes. IGFs are released from IGF:IGFBP complexes by proteolysis of the IGFBP. IGFs become active after release, however IGFs may also have activity when still bound to some IGFBPs.

IGFBP1 is enriched in amniotic fluid and is produced in the liver under control of insulin (insulin suppresses production). IGFBP1 binding stimulates IGF function. It is unknown which if any protease degrades IGFBP1.

IGFBP2 is enriched in cerebrospinal fluid; its binding inhibits IGF function. IGFBP2 is not significantly degraded in circulation.

IGFB3, which binds most IGF in the body is enriched in follicular fluid and found in many other tissues. IGFBP 3 may be cleaved by plasmin, thrombin, Prostate specific Antigen (PSA, KLK3), Matrix Metalloprotease-1 (MMP1), and Matrix Metalloprotease-2 (MMP2). IGFBP3 also binds extracellular matrix and binding lowers its affinity for IGFs. IGFBP3 binding stimulates the effects of IGFs.

IGFBP4 acts to inhibit IGF function and is cleaved by Pregnancy associated Plasma Protein A (PAPPA) to release IGF.

IGFBP5 is enriched in bone matrix; its binding stimulates IGF function. IGFBP5 is cleaved by Pregnancy Associated Plasma Protein A2 (PAPPA2), ADAM9, complement C1s from smooth muscle, and thrombin. Only the cleavage site for PAPPA2 is known.

IGFBP6 is enriched in cerebrospinal fluid. It is unknown which if any protease degrades IGFBP6.

Literature references

Schneider, MR., Zhou, R., Hoeflich, A., Krebs, O., Schmidt, J., Mohan, S. et al. (2001). Insulin-like growth factor-binding protein-5 inhibits growth and induces differentiation of mouse osteosarcoma cells. *Biochem Biophys Res Commun, 288*, 435-42. ↗

Zhou, R., Diehl, D., Hoeflich, A., Lahm, H., Wolf, E. (2003). IGF-binding protein-4: biochemical characteristics and functional consequences. *J Endocrinol, 178*, 177-93. ↗

Mohan, S., Baylink, DJ. (2002). IGF-binding proteins are multifunctional and act via IGF-dependent and -independent mechanisms. *J Endocrinol, 175*, 19-31. ↗

Holly, J., Perks, C. (2006). The role of insulin-like growth factor binding proteins. *Neuroendocrinology, 83*, 154-60. ↗

Firth, SM., Baxter, RC. (2002). Cellular actions of the insulin-like growth factor binding proteins. *Endocr Rev, 23*, 824-54. ↗

Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

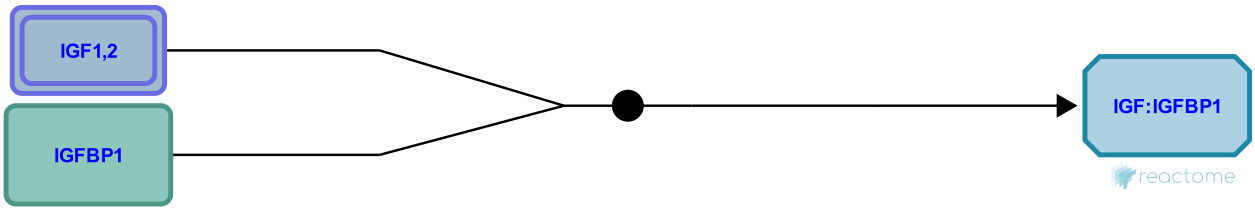
IGFBP1 binds IGF forming IGF:IGFBP1 ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381487

Type: binding

Compartments: extracellular region



IGFBP 1 binds IGF I or IGF II via the conserved N terminus and C terminus of IGFBP 1.

IGFBP 1 is enriched in amniotic fluid and is produced in the liver under control of insulin (insulin suppresses production). IGFBP 1 acts to stimulate IGF function. It is unknown which if any protease degrades IGFBP 1.

Literature references

Bach, LA., Hsieh, S., Sakano, K., Fujiwara, H., Perdue, JF., Rechler, MM. (1993). Binding of mutants of human insulin-like growth factor II to insulin-like growth factor binding proteins 1-6. *J Biol Chem, 268*, 9246-54. ↗

Arai, T., Parker, A., Busby W, Jr., Clemmons, DR. (1994). Heparin, heparan sulfate, and dermatan sulfate regulate formation of the insulin-like growth factor-I and insulin-like growth factor-binding protein complexes. *J Biol Chem, 269*, 20388-93. ↗

Bach, LA., Rechler, MM. (1996). Measurement of insulin-like growth factor (IGF)-II binding to purified IGF binding proteins 1-6: comparison of charcoal adsorption and high performance size exclusion chromatography. *Biochim Biophys Acta, 1313*, 79-88. ↗

Mohan, S., Baylink, DJ. (2002). IGF-binding proteins are multifunctional and act via IGF-dependent and -independent mechanisms. *J Endocrinol, 175*, 19-31. ↗

Juul, A., Dalgaard, P., Blum, WF., Bang, P., Hall, K., Michaelsen, KF. et al. (1995). Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the relation to IGF-I, IGF-II, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. *J Clin Endocrinol Metab, 80*, 2534-42. ↗

Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

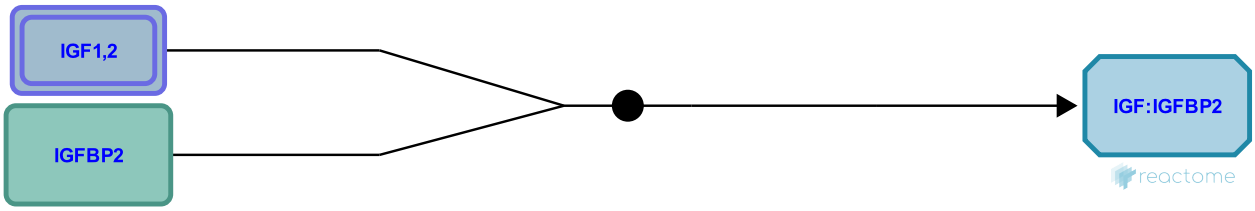
IGFBP2 binds IGF forming IGF:IGFBP2 ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381412

Type: binding

Compartments: extracellular region



IGFBP 2 binds IGF I or IGF II via the conserved N terminus and C terminus of IGFBP 2.

IGFBP 2 is enriched in cerebrospinal fluid and inhibits IGF function. IGFBP 2 is not significantly degraded in circulation.

Literature references

Binkert, C., Landwehr, J., Mary, JL., Schwander, J., Heinrich, G. (1989). Cloning, sequence analysis and expression of a cDNA encoding a novel insulin-like growth factor binding protein (IGFBP-2). *EMBO J, 8*, 2497-502. ↗

Bach, LA., Hsieh, S., Sakano, K., Fujiwara, H., Perdue, JF., Rechler, MM. (1993). Binding of mutants of human insulin-like growth factor II to insulin-like growth factor binding proteins 1-6. *J Biol Chem, 268*, 9246-54. ↗

Kuang, Z., Yao, S., McNeil, KA., Thompson, JA., Bach, LA., Forbes, BE. et al. (2007). Cooperativity of the N- and C-terminal domains of insulin-like growth factor (IGF) binding protein 2 in IGF binding. *Biochemistry, 46*, 13720-32. ↗

Arai, T., Parker, A., Busby W, Jr., Clemmons, DR. (1994). Heparin, heparan sulfate, and dermatan sulfate regulate formation of the insulin-like growth factor-I and insulin-like growth factor-binding protein complexes. *J Biol Chem, 269*, 20388-93. ↗

Juul, A., Dalgaard, P., Blum, WF., Bang, P., Hall, K., Michaelsen, KF. et al. (1995). Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the relation to IGF-I, IGF-II, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. *J Clin Endocrinol Metab, 80*, 2534-42. ↗

Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

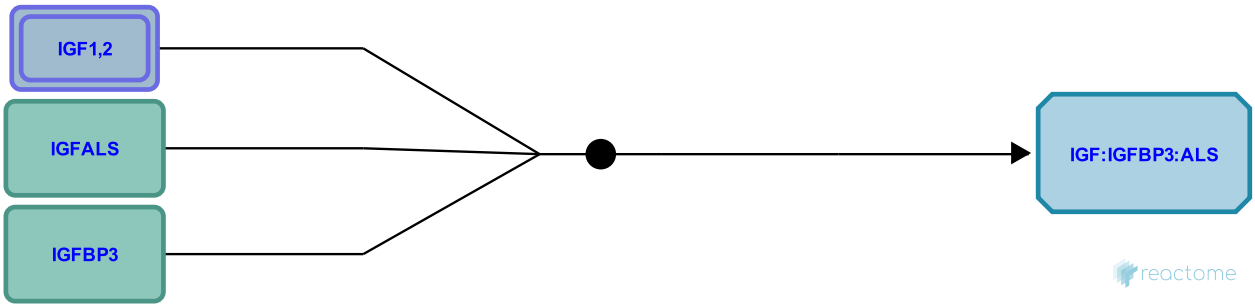
Formation of the IGF:IGFBP3:ALS complex ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381496

Type: binding

Compartments: extracellular region



IGFBP3 binds IGF I or IGF II via the conserved N terminus and C terminus of IGFBP 3. IGFBP3 also binds ALS via the C terminal portion of IGFBP3. The interaction is dependent on the glycosylation of ALS.

IGFBP3, which binds most IGF in the body, is enriched in follicular fluid and found in many other tissues. IGFBP3 may be cleaved by plasmin, thrombin, Prostate specific Antigen (PSA, KLK3), Matrix Metalloprotease-1 (MMP1), and Matrix Metalloprotease-2 (MMP2). IGFBP3 also binds extracellular matrix and binding lowers its affinity for IGFs. IGFBP3 stimulates the effects of IGFs.

Followed by: Prostate-specific Antigen proteolyzes IGF:IGFBP3:ALS , Matrix metalloproteinase proteolyzes IGF:IGFBP3:ALS, Cathepsin G proteolyzes IGF:IGFBP3:ALS, Plasmin proteolyzes IGF:IGFBP-3:ALS, Thrombin proteolyzes IGF:IGFBP3:ALS

Literature references

Baxter, RC., Martin, JL. (1989). Structure of the Mr 140,000 growth hormone-dependent insulin-like growth factor binding protein complex: determination by reconstitution and affinity-labeling. *Proc Natl Acad Sci U S A, 86*, 6898-902. ↗

Belgorosky, A., Rivarola, MA. (1999). Insulin-like growth factor binding protein (IGFBP)-3-bound IGF-I and IGFBP-3-bound IGF-II in growth hormone deficiency. *Horm Res, 52*, 60-5. ↗

Bach, LA., Hsieh, S., Sakano, K., Fujiwara, H., Perdue, JF., Rechler, MM. (1993). Binding of mutants of human insulin-like growth factor II to insulin-like growth factor binding proteins 1-6. *J Biol Chem, 268*, 9246-54. ↗

Arai, T., Parker, A., Busby W, Jr., Clemmons, DR. (1994). Heparin, heparan sulfate, and dermatan sulfate regulate formation of the insulin-like growth factor-I and insulin-like growth factor-binding protein complexes. *J Biol Chem, 269*, 20388-93. ↗

Bach, LA., Rechler, MM. (1996). Measurement of insulin-like growth factor (IGF)-II binding to purified IGF binding proteins 1-6: comparison of charcoal adsorption and high performance size exclusion chromatography. *Biochim Biophys Acta, 1313*, 79-88. ↗

Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

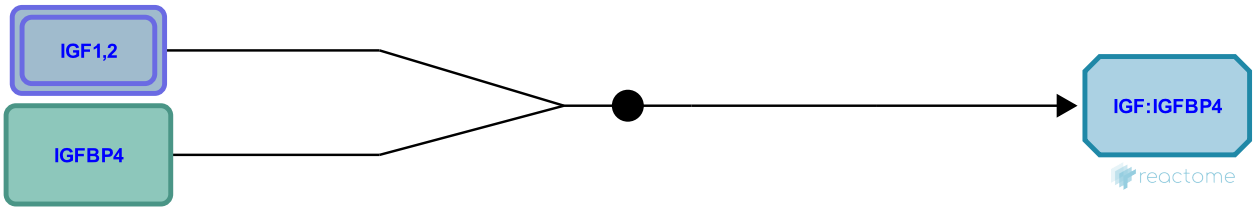
IGFBP4 binds IGF forming IGF:IGFBP4

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381543

Type: binding

Compartments: extracellular region



IGFBP 4 binds IGF I or IGF II via the conserved N terminus and C terminus of IGFBP 4.

Followed by: PAAP-A proteolyzes IGF:IGFBP4

Literature references

Bach, LA., Hsieh, S., Sakano, K., Fujiwara, H., Perdue, JF., Rechler, MM. (1993). Binding of mutants of human insulin-like growth factor II to insulin-like growth factor binding proteins 1-6. *J Biol Chem, 268*, 9246-54.

Arai, T., Parker, A., Busby W, Jr., Clemmons, DR. (1994). Heparin, heparan sulfate, and dermatan sulfate regulate formation of the insulin-like growth factor-I and insulin-like growth factor-binding protein complexes. *J Biol Chem, 269*, 20388-93.

Bach, LA., Rechler, MM. (1996). Measurement of insulin-like growth factor (IGF)-II binding to purified IGF binding proteins 1-6: comparison of charcoal adsorption and high performance size exclusion chromatography. *Biochim Biophys Acta, 1313*, 79-88.

Cianfarani, S., Frost, VJ., Savage, MO., Holly, JM. (1993). Glucose does not influence the insulin-like growth factor (JGF) binding to carrier proteins (IGFBPs): analysis of rat and human serum by western ligand blotting. *Experientia, 49*, 699-701.

Zhou, R., Diehl, D., Hoeflich, A., Lahm, H., Wolf, E. (2003). IGF-binding protein-4: biochemical characteristics and functional consequences. *J Endocrinol, 178*, 177-93.

Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

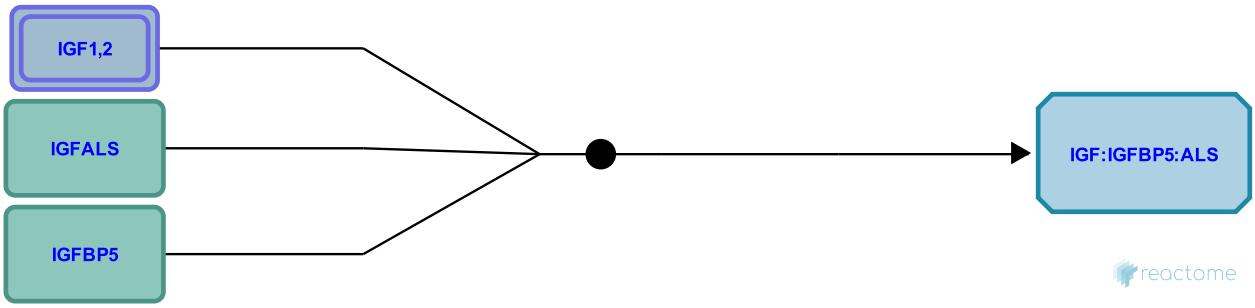
Formation of the IGF:IGFBP5:ALS complex ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381545

Type: binding

Compartments: extracellular region



IGFBP 5 binds IGF I or IGF II via the conserved N terminus and C terminus of IGFBP 5. IGFBP 5 also binds ALS via the central portion of IGFBP 5. About 55% of IGF:IGFBP 5 complexes contain ALS.

IGFBP 5 is enriched in bone matrix and acts to stimulate IGF function. IGFBP 5 is cleaved by Pregnancy associated Plasma Protein A2 (PAPP A2), ADAM 9, complement C1s from smooth muscle, and thrombin. Only the cleavage site for PAPP A2 is known.

About 55% of IGF:IGFBP 5 complexes contain ALS; 45% contain only IGF and IGFBP 5.

Followed by: PAPP-A2 proteolyzes IGF:IGFBP5:ALS

Literature references

Baxter, RC., Meka, S., Firth, SM. (2002). Molecular distribution of IGF binding protein-5 in human serum. *J Clin Endocrinol Metab, 87*, 271-6. ↗

Bach, LA., Hsieh, S., Sakano, K., Fujiwara, H., Perdue, JF., Rechler, MM. (1993). Binding of mutants of human insulin-like growth factor II to insulin-like growth factor binding proteins 1-6. *J Biol Chem, 268*, 9246-54. ↗

Arai, T., Parker, A., Busby W, Jr., Clemmons, DR. (1994). Heparin, heparan sulfate, and dermatan sulfate regulate formation of the insulin-like growth factor-I and insulin-like growth factor-binding protein complexes. *J Biol Chem, 269*, 20388-93. ↗

Bach, LA., Rechler, MM. (1996). Measurement of insulin-like growth factor (IGF)-II binding to purified IGF binding proteins 1-6: comparison of charcoal adsorption and high performance size exclusion chromatography. *Biochim Biophys Acta, 1313*, 79-88. ↗

Cianfarani, S., Frost, VJ., Savage, MO., Holly, JM. (1993). Glucose does not influence the insulin-like growth factor (JGF) binding to carrier proteins (IGFBPs): analysis of rat and human serum by western ligand blotting. *Experientia, 49*, 699-701. ↗

Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
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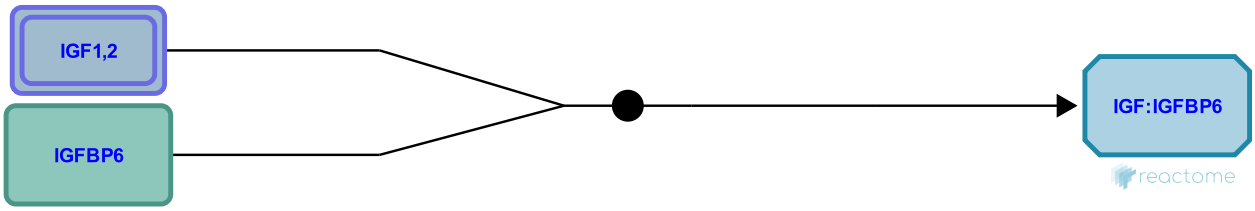
IGFBP6 binds IGF forming IGF:IGFBP6 ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381503

Type: binding

Compartments: extracellular region



IGFBP-6 binds IGF I or IGF II via the conserved N terminus and C terminus of IGFBP-6. IGFBP-6 binds IGF II with greater affinity than IGF I.

Literature references

Bach, LA., Hsieh, S., Sakano, K., Fujiwara, H., Perdue, JF., Rechler, MM. (1993). Binding of mutants of human insulin-like growth factor II to insulin-like growth factor binding proteins 1-6. *J Biol Chem, 268*, 9246-54. ↗

Bach, LA., Rechler, MM. (1996). Measurement of insulin-like growth factor (IGF)-II binding to purified IGF binding proteins 1-6: comparison of charcoal adsorption and high performance size exclusion chromatography. *Biochim Biophys Acta, 1313*, 79-88. ↗

Cianfarani, S., Frost, VJ., Savage, MO., Holly, JM. (1993). Glucose does not influence the insulin-like growth factor (JGF) binding to carrier proteins (IGFBPs): analysis of rat and human serum by western ligand blotting. *Experientia, 49*, 699-701. ↗

Headey, SJ., Leeding, KS., Norton, RS., Bach, LA. (2004). Contributions of the N- and C-terminal domains of IGF binding protein-6 to IGF binding. *J Mol Endocrinol, 33*, 377-86. ↗

Holly, J., Perks, C. (2006). The role of insulin-like growth factor binding proteins. *Neuroendocrinology, 83*, 154-60. ↗

Editions

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2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

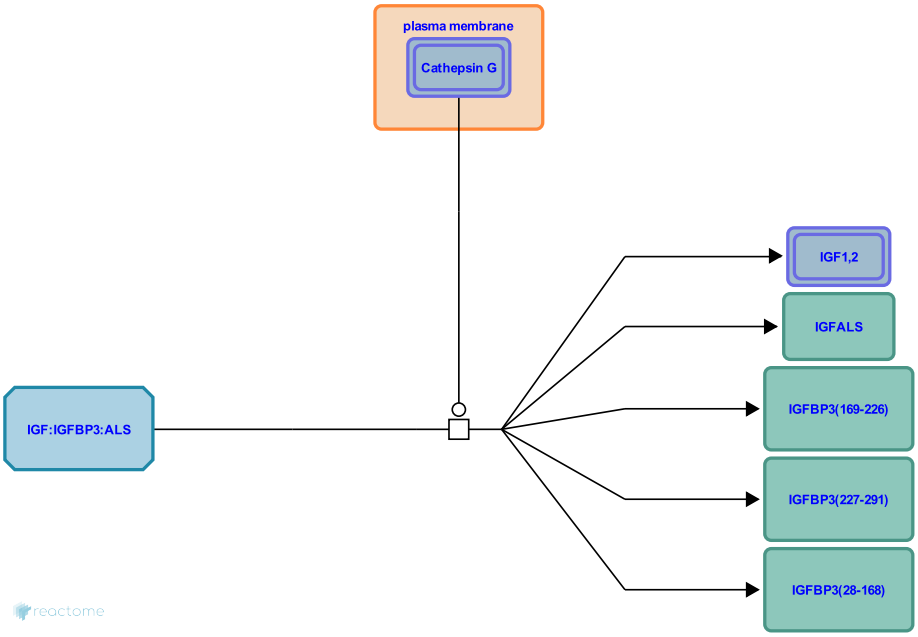
Cathepsin G proteolyzes IGF:IGFBP3:ALS ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381500

Type: transition

Compartments: extracellular region, plasma membrane



Cathepsin G cleaves IGFBP-3 between amino acids 168 and 169 and between amino acids 226 and 227, releasing IGF from the IGF:IGFBP-3:ALS Complex.

Preceded by: Formation of the IGF:IGFBP3:ALS complex

Literature references

Gibson, TL., Cohen, P. (1999). Inflammation-related neutrophil proteases, cathepsin G and elastase, function as insulin-like growth factor binding protein proteases. *Growth Horm IGF Res, 9*, 241-53. ↗

Editions

2008-11-20	Authored, Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.
2011-11-19	Edited	May, B.

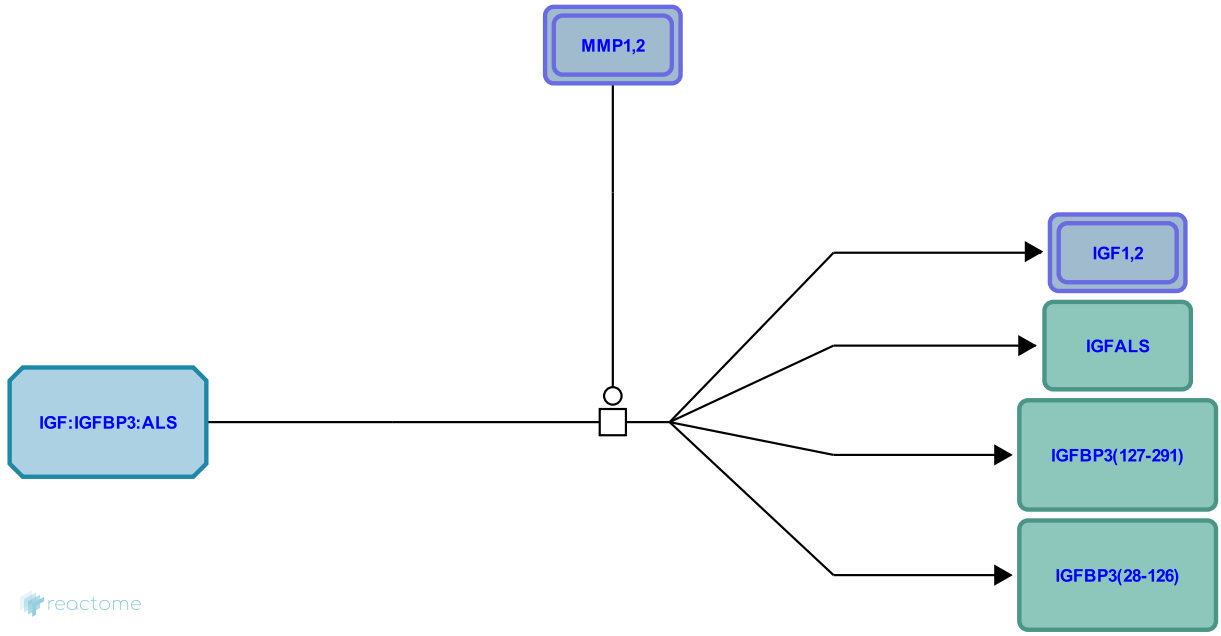
Matrix metalloproteinase proteolyzes IGF:IGFBP3:ALS ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381435

Type: transition

Compartments: extracellular region



Matrix Metalloprotease-1 and -2 cleave IGFBP-3 in the IGF:IGFBP-3:ALS Complex between amino acids 126 and 127, releasing IGF. The reaction has been demonstrated in vivo.

Preceded by: Formation of the IGF:IGFBP3:ALS complex

Literature references

Fowlkes, JL., Enghild, JJ., Suzuki, K., Nagase, H. (1994). Matrix metalloproteinases degrade insulin-like growth factor-binding protein-3 in dermal fibroblast cultures. *J Biol Chem, 269*, 25742-6. ↗

Rajah, R., Nachajon, RV., Collins, MH., Hakonarson, H., Grunstein, MM., Cohen, P. (1999). Elevated levels of the IGF-binding protein protease MMP-1 in asthmatic airway smooth muscle. *Am J Respir Cell Mol Biol, 20*, 199-208. ↗

Rajah, R., Katz, L., Nunn, S., Solberg, P., Beers, T., Cohen, P. (1995). Insulin-like growth factor binding protein (IGFBP) proteases: functional regulators of cell growth. *Prog Growth Factor Res, 6*, 273-84. ↗

Firth, SM., Baxter, RC. (2002). Cellular actions of the insulin-like growth factor binding proteins. *Endocr Rev, 23*, 824-54. ↗

Mohan, S., Baylink, DJ. (2002). IGF-binding proteins are multifunctional and act via IGF-dependent and -independent mechanisms. *J Endocrinol, 175*, 19-31. ↗

Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

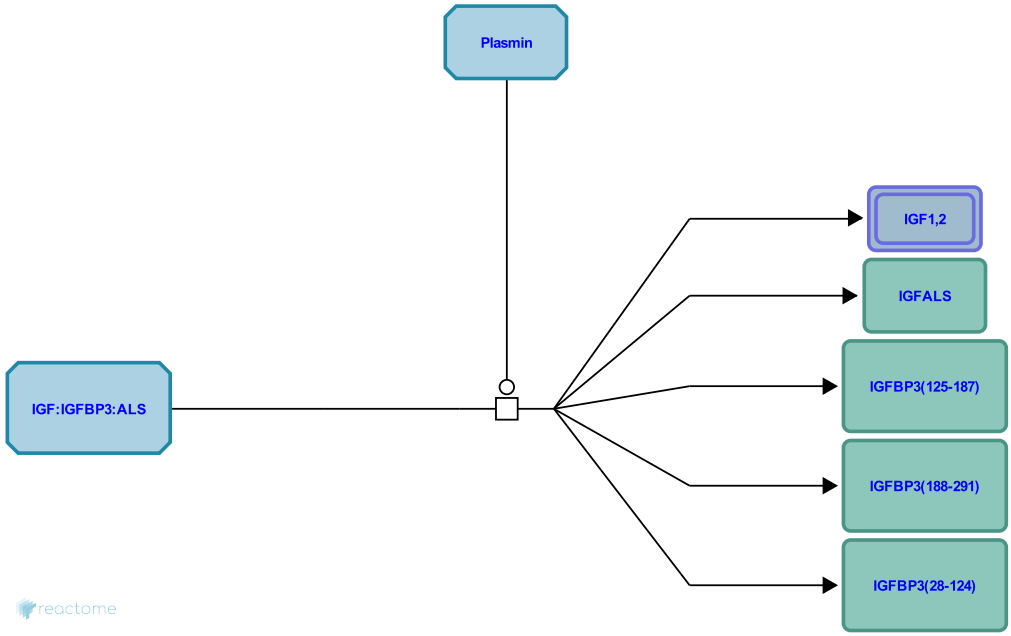
Plasmin proteolyzes IGF:IGFBP-3:ALS ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381461

Type: transition

Compartments: extracellular region



Plasmin cleaves IGFBP-3 in the IGF:IGFBP-3:ALS Complex between amino acids 124 and 125 and between amino acids 187 and 188, releasing IGF.

Preceded by: Formation of the IGF:IGFBP3:ALS complex

Literature references

Booth, BA., Boes, M., Dake, BL., Knudtson, KL., Bar, RS. (2002). IGFBP-3 binding to endothelial cells inhibits plasmin and thrombin proteolysis. *Am J Physiol Endocrinol Metab, 282*, E52-8. ↗

Angelloz-Nicoud, P., Lalou, C., Binoux, M. (1998). Prostate carcinoma (PC-3) cell proliferation is stimulated by the 22-25-kDa proteolytic fragment (1-160) and inhibited by the 16-kDa fragment (1-95) of recombinant human insulin-like growth factor binding protein-3. *Growth Horm IGF Res, 8*, 71-5. ↗

Angelloz-Nicoud, P., Harel, L., Binoux, M. (1996). Recombinant human insulin-like growth factor (IGF) binding protein-3 stimulates prostate carcinoma cell proliferation via an IGF-dependent mechanism. Role of serine proteases. *Growth Regul, 6*, 130-6. ↗

Angelloz-Nicoud, P., Binoux, M. (1995). Autocrine regulation of cell proliferation by the insulin-like growth factor (IGF) and IGF binding protein-3 protease system in a human prostate carcinoma cell line (PC-3). *Endocrinology, 136*, 5485-92. ↗

Lalou, C., Silve, C., Rosato, R., Segovia, B., Binoux, M. (1994). Interactions between insulin-like growth factor-I (IGF-I) and the system of plasminogen activators and their inhibitors in the control of IGF-binding protein-3 production and proteolysis in human osteosarcoma cells. *Endocrinology, 135*, 2318-26. ↗

Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

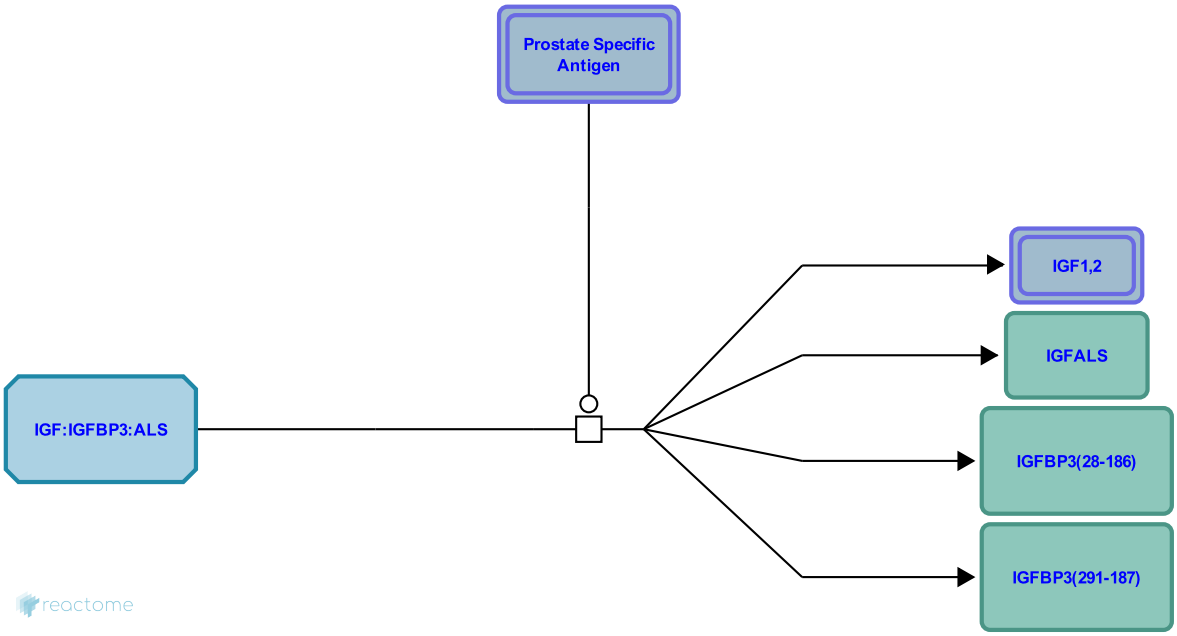
Prostate-specific Antigen proteolyzes IGF:IGFBP3:ALS ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381466

Type: transition

Compartments: extracellular region



Prostate specific Antigen (PSA, KLK3) cleaves IGFBP-3 in the IGF:IGFBP-3:ALS Complex between amino acids 186 and 187. Other cleavage sites were observed but not reproducibly. These may have been caused by impurities in the PSA preparation.

Preceded by: Formation of the IGF:IGFBP3:ALS complex

Literature references

Okabe, E., Kajihara, J., Usami, Y., Hirano, K. (1999). The cleavage site specificity of human prostate specific antigen for insulin-like growth factor binding protein-3. *FEBS Lett, 447*, 87-90. ↗

Fielder, PJ., Rosenfeld, RG., Graves, HC., Grandbois, K., Maack, CA., Sawamura, S. et al. (1994). Biochemical analysis of prostate specific antigen-proteolyzed insulin-like growth factor binding protein-3. *Growth Regul, 4*, 164-72. ↗

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Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.

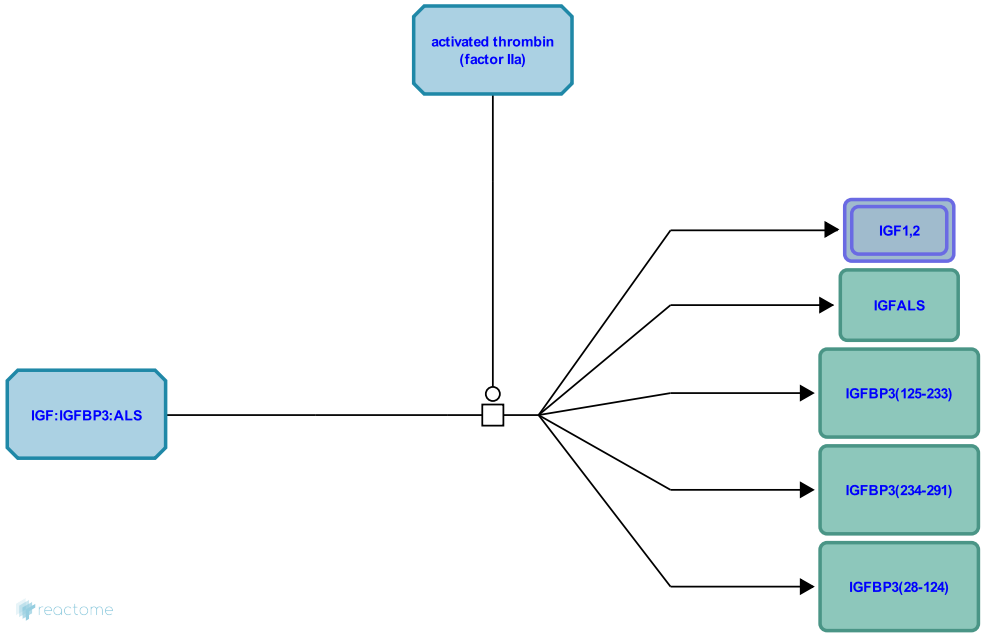
Thrombin proteolyzes IGF:IGFBP3:ALS ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381446

Type: transition

Compartments: extracellular region



Thrombin cleaves IGFBP-3 in the IGF:IGFBP-3:ALS Complex between amino acids 124 and 125 and between amino acids 233 and 234, releasing IGF.

Preceded by: Formation of the IGF:IGFBP3:ALS complex

Literature references

Booth, BA., Boes, M., Dake, BL., Knudtson, KL., Bar, RS. (2002). IGFBP-3 binding to endothelial cells inhibits plasmin and thrombin proteolysis. *Am J Physiol Endocrinol Metab, 282*, E52-8. ↗

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Mohan, S., Baylink, DJ. (2002). IGF-binding proteins are multifunctional and act via IGF-dependent and -independent mechanisms. *J Endocrinol, 175*, 19-31. ↗

Holly, J., Perks, C. (2006). The role of insulin-like growth factor binding proteins. *Neuroendocrinology, 83*, 154-60. ↗

Rajah, R., Katz, L., Nunn, S., Solberg, P., Beers, T., Cohen, P. (1995). Insulin-like growth factor binding protein (IGFBP) proteases: functional regulators of cell growth. *Prog Growth Factor Res, 6*, 273-84. ↗

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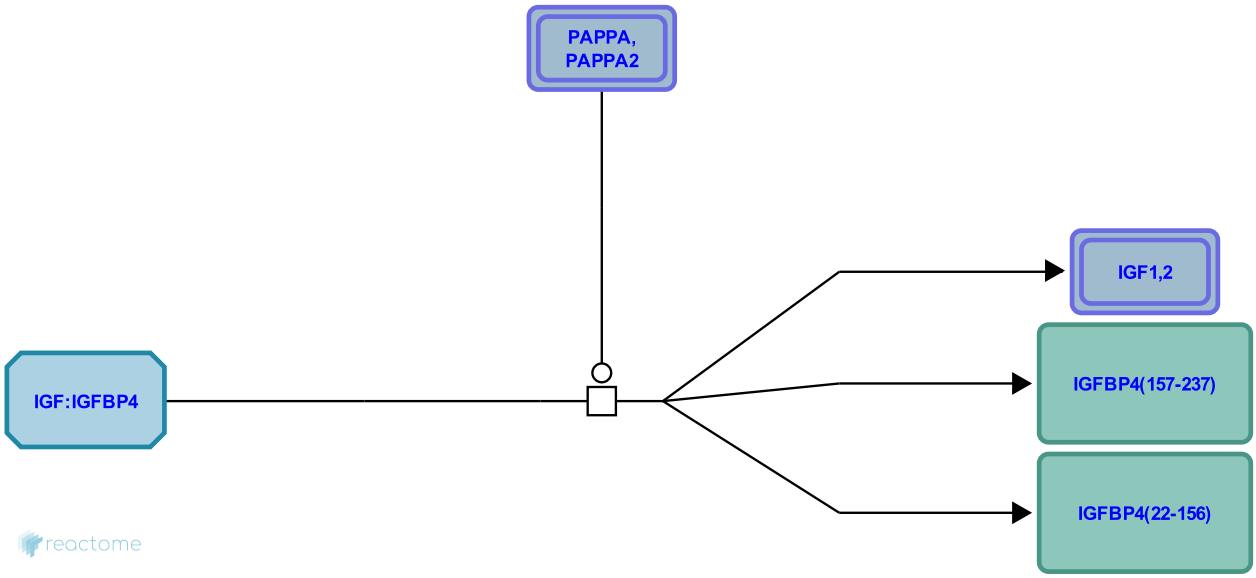
PAAP-A proteolyzes IGF:IGFBP4 ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381518

Type: transition

Compartments: extracellular region



Pregnancy associated Plasma Protein A (PPAP-A) cleaves IGFBP-4 in the IGF:IGFBP-4 Complex between amino acids 156 and 157, releasing IGF.

Preceded by: IGFBP4 binds IGF forming IGF:IGFBP4

Literature references

Laursen, LS., Overgaard, MT., Nielsen, CG., Boldt, HB., Hopmann, KH., Conover, CA. et al. (2002). Substrate specificity of the metalloproteinase pregnancy-associated plasma protein-A (PAPP-A) assessed by mutagenesis and analysis of synthetic peptides: substrate residues distant from the scissile bond are critical for proteolysis. *Biochem J, 367*, 31-40. ↗

Byun, D., Mohan, S., Yoo, M., Sexton, C., Baylink, DJ., Qin, X. (2001). Pregnancy-associated plasma protein-A accounts for the insulin-like growth factor (IGF)-binding protein-4 (IGFBP-4) proteolytic activity in human pregnancy serum and enhances the mitogenic activity of IGF by degrading IGFBP-4 in vitro. *J Clin Endocrinol Metab, 86*, 847-54. ↗

Laursen, LS., Kjaer-Sorensen, K., Andersen, MH., Oxvig, C. (2007). Regulation of insulin-like growth factor (IGF) bioactivity by sequential proteolytic cleavage of IGF binding protein-4 and -5. *Mol Endocrinol, 21*, 1246-57. ↗

Gyrup, C., Oxvig, C. (2007). Quantitative analysis of insulin-like growth factor-modulated proteolysis of insulin-like growth factor binding protein-4 and -5 by pregnancy-associated plasma protein-A. *Biochemistry, 46*, 1972-80. ↗

Qin, X., Byun, D., Lau, KH., Baylink, DJ., Mohan, S. (2000). Evidence that the interaction between insulin-like growth factor (IGF)-II and IGF binding protein (IGFBP)-4 is essential for the action of the IGF-II-dependent IGFBP-4 protease. *Arch Biochem Biophys, 379*, 209-16. ↗

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2008-11-20	Edited	Gopinathrao, G., May, B.
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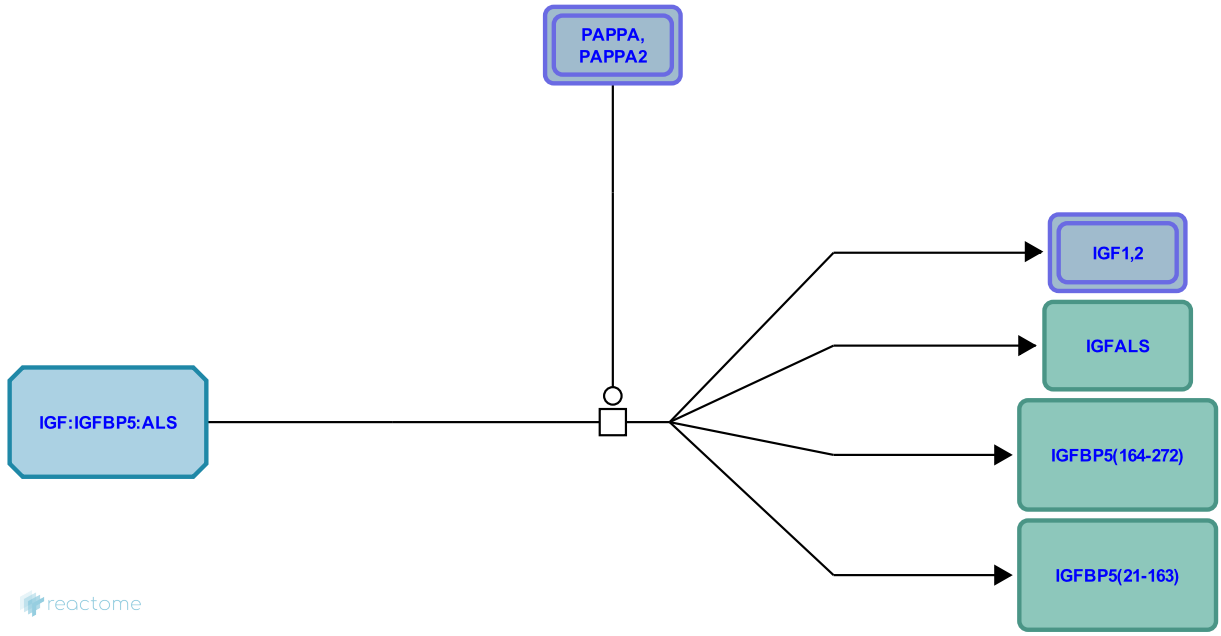
PAPP-A2 proteolyzes IGF:IGFBP5:ALS ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-381537

Type: transition

Compartments: extracellular region



Both Pregnancy Associated Plasma Protein A (PAPP-A) and A2 (PAPP-A2) cleave IGFBP-5 in the IGF-:IGFBP-5:ALS Complex between amino acids 163 and 164, releasing IGF. PPAP-A has also been shown to cleave IGFBP-5 that is not complexed with IGF.

Preceded by: Formation of the IGF:IGFBP5:ALS complex

Literature references

Overgaard, MT., Boldt, HB., Laursen, LS., Sottrup-Jensen, L., Conover, CA., Oxvig, C. (2001). Pregnancy-associated plasma protein-A2 (PAPP-A2), a novel insulin-like growth factor-binding protein-5 proteinase. *J Biol Chem, 276*, 21849-53. ↗

Laursen, LS., Overgaard, MT., Søe, R., Boldt, HB., Sottrup-Jensen, L., Giudice, LC. et al. (2001). Pregnancy-associated plasma protein-A (PAPP-A) cleaves insulin-like growth factor binding protein (IGFBP)-5 independent of IGF: implications for the mechanism of IGFBP-4 proteolysis by PAPP-A. *FEBS Lett, 504*, 36-40. ↗

Firth, SM., Baxter, RC. (2002). Cellular actions of the insulin-like growth factor binding proteins. *Endocr Rev, 23*, 824-54. ↗

Baxter, RC., Meka, S., Firth, SM. (2002). Molecular distribution of IGF binding protein-5 in human serum. *J Clin Endocrinol Metab, 87*, 271-6. ↗

Schneider, MR., Zhou, R., Hoeflich, A., Krebs, O., Schmidt, J., Mohan, S. et al. (2001). Insulin-like growth factor-binding protein-5 inhibits growth and induces differentiation of mouse osteosarcoma cells. *Biochem Biophys Res Commun, 288*, 435-42. ↗

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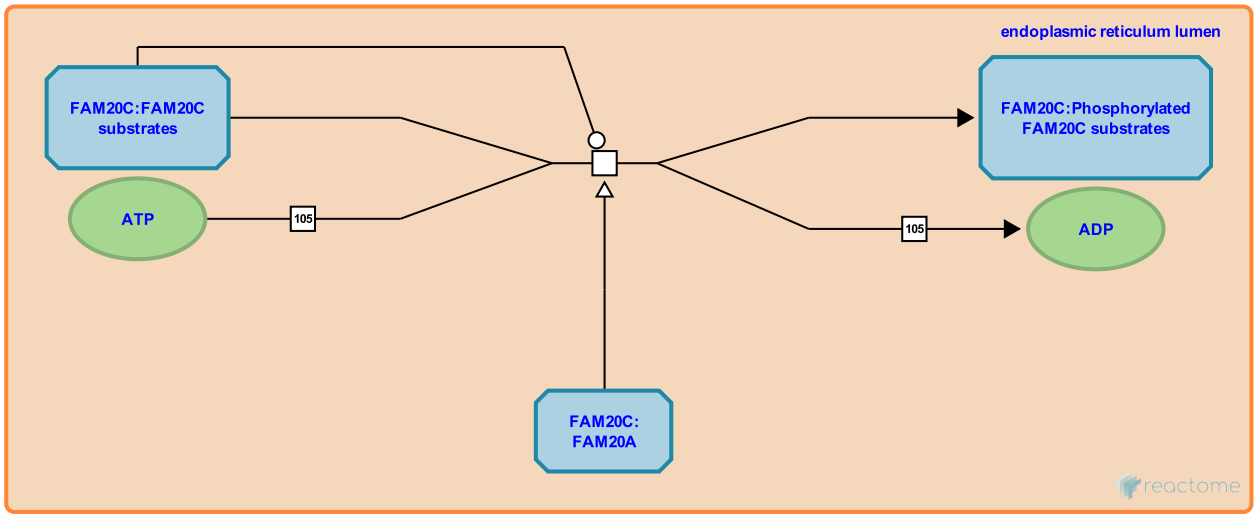
FAM20C phosphorylates FAM20C substrates ↗

Location: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)

Stable identifier: R-HSA-8952289

Type: transition

Compartments: endoplasmic reticulum lumen



Extracellular serine/threonine protein kinase FAM20C is an extracellular kinase that can phosphorylate a broad range of secreted protein. FAM20C is bound and allosterically activated by the pseudokinase FAM20A (Tagliabracchi et al. 2012, 2015, Cui et al. 2015).

Loss of function mutations in Fam20C cause Raine Syndrome, an osteosclerotic bone dysplasia (Faundes et al. 2014).

Literature references

Tagliabracci, VS., Wiley, SE., Guo, X., Kinch, LN., Durrant, E., Wen, J. et al. (2015). A Single Kinase Generates the Majority of the Secreted Phosphoproteome. *Cell, 161*, 1619-32. ↗

Editions

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2017-01-23	Reviewed	Wiley, SE.

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