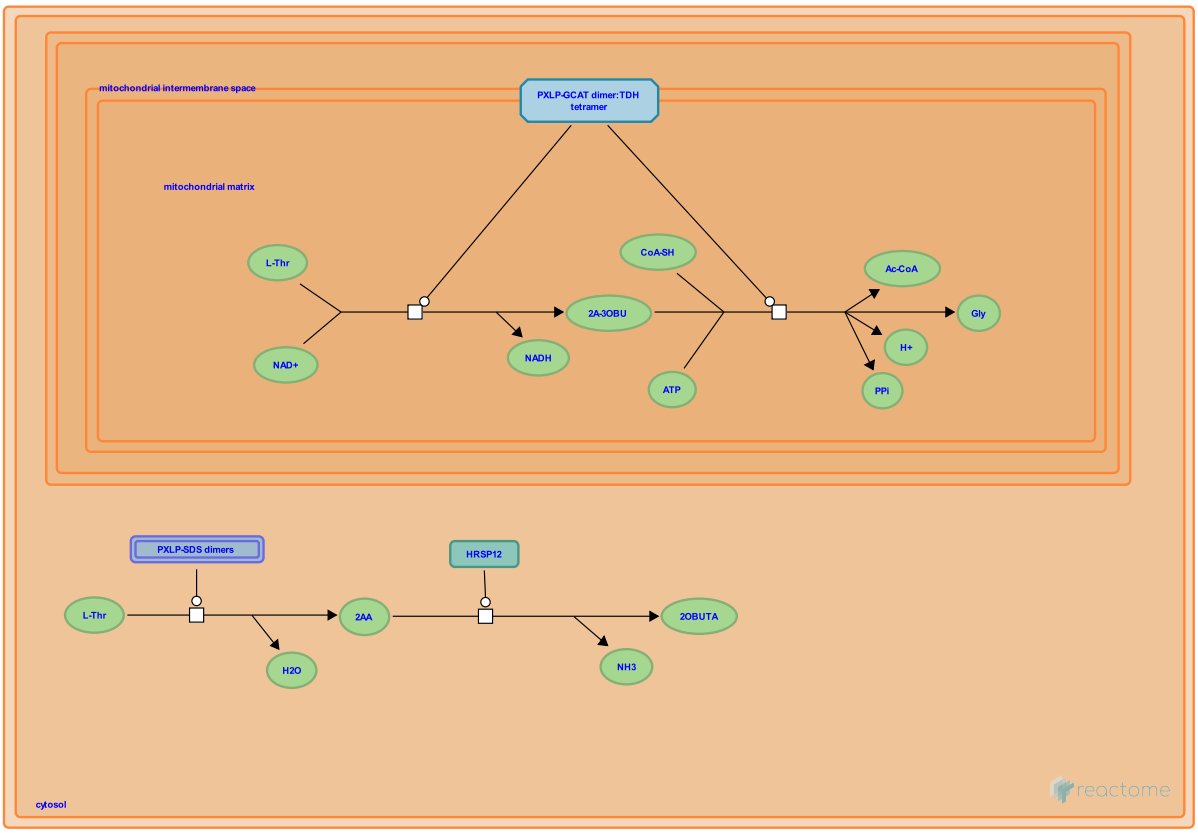
Threonine catabolism



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29/04/2024

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. ↗

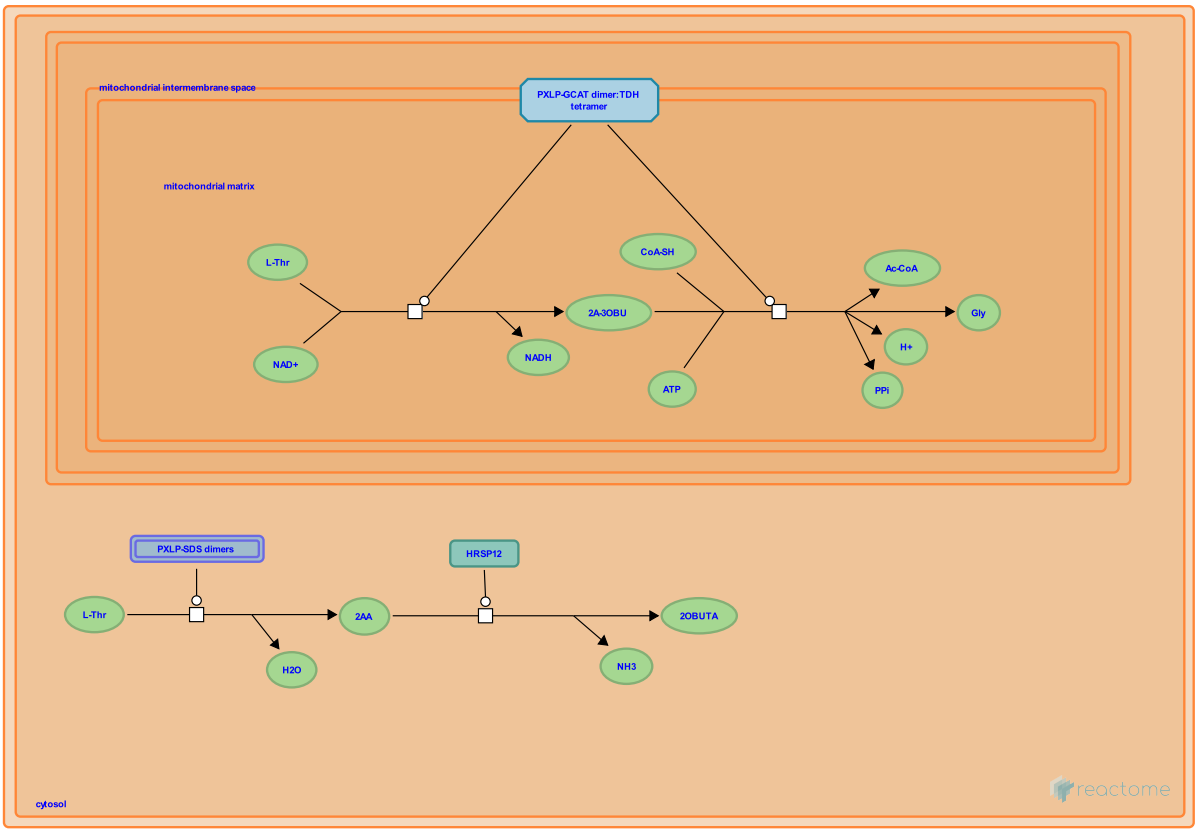
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Threonine catabolism ↗

Stable identifier: R-HSA-8849175



The degradation of L-threonine to glycine in both prokaryotes and eukaryotes takes place through a two-step biochemical pathway in mitochondria (Dale 1978). In the first step, L-threonine is oxidised to 2-amino-3-oxobutanoate. This reaction is catalysed by mitochondrial L-threonine 3-dehydrogenase tetramer (TDH tetramer). In the second step, mitochondrial 2-amino-3-ketobutyrate coenzyme A ligase (GCAT, aka KBL) catalyses the reaction between 2-amino-3-oxobutanoate and coenzyme A to form glycine and acetyl-CoA. GCAT resides on the mitochondrial inner membrane in dimeric form and requires pyridoxal 5-phosphate (PXLP) as cofactor. GCAT is thought to exist on the mitochondrial inner membrane in complex with TDH. With these two enzymes located together, it stops the rapid and spontaneous decarboxylation of 2A-3OBU to aminoacetone and carbon dioxide and instead, results in glycine formation (Tressel et al. 1986).

Literature references

Dale, RA. (1978). Catabolism of threonine in mammals by coupling of L-threonine 3-dehydrogenase with 2-amino-3-oxobutyrate-CoA ligase. *Biochim. Biophys. Acta, 544*, 496-503. ↗

Davis, L., Zieske, LR., Thompson, R., Menendez, MI., Tressel, T. (1986). Interaction between L-threonine dehydrogenase and aminoacetone synthetase and mechanism of aminoacetone production. *J. Biol. Chem., 261*, 16428-37. ↗

Editions

2015-12-14	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

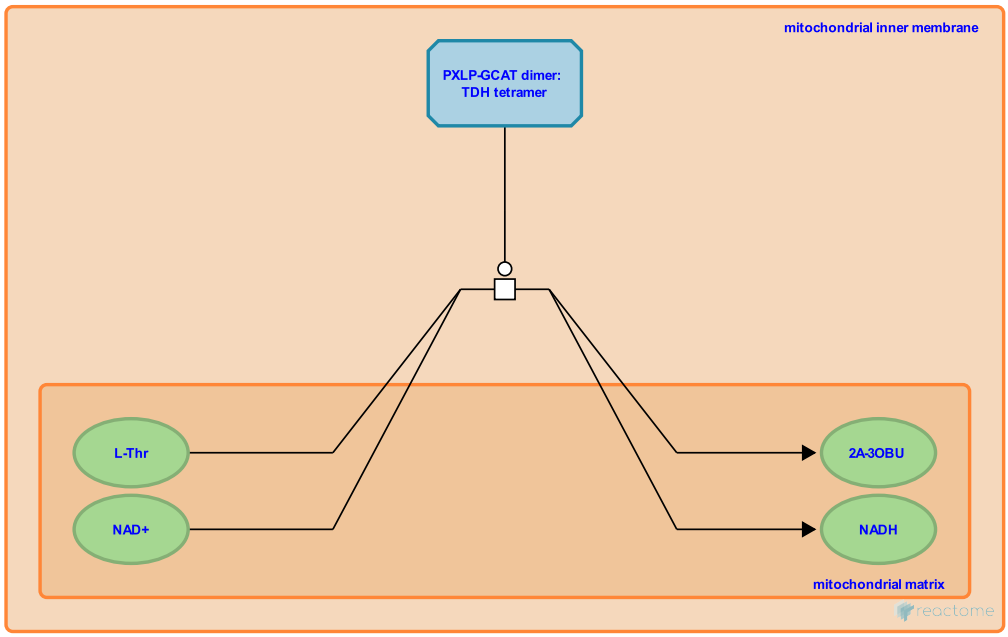
TDH tetramer oxidises L-Thr to 2A-3OB ↗

Location: Threonine catabolism

Stable identifier: R-HSA-6798667

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix



The degradation of L-threonine to glycine in both prokaryotes and eukaryotes takes place through a two-step biochemical pathway. In the first step, L-threonine (L-Thr) is oxidised to 2-amino-3-oxobutanoate (2A-3OBU) using NAD+ as acceptor. This reaction is catalysed by mitochondrial L-threonine 3-dehydrogenase (TDH) (Edgar 2002). The human activity is inferred from the characterised porcine Tdh (Edgar 2002b, Kao & Davis 1994). TDH is thought to exist as a tetramer on the mitochondrial inner membrane in complex with dimeric 2-amino-3-ketobutyrate coenzyme A ligase (GCAT), the second enzyme in this pathway (Tressel et al. 1986). With these two enzymes located together, it stops the rapid and spontaneous decarboxylation of 2A-3OBU to aminoacetone and carbon dioxide and instead, results in glycine formation.

Followed by: PXLP-GCAT dimer ligates CoASH to 2A-3OB to form Gly and Ac-CoA

Literature references

Edgar, AJ. (2002). The human L-threonine 3-dehydrogenase gene is an expressed pseudogene. *BMC Genet., 3*, 18. ↗

Davis, L., Kao, YC. (1994). Purification and structural characterization of porcine L-threonine dehydrogenase. *Protein Expr. Purif., 5*, 423-31. ↗

Davis, L., Zieske, LR., Thompson, R., Menendez, MI., Tressel, T. (1986). Interaction between L-threonine dehydrogenase and aminoacetone synthetase and mechanism of aminoacetone production. *J. Biol. Chem., 261*, 16428-37. ↗

Edgar, AJ. (2002). Molecular cloning and tissue distribution of mammalian L-threonine 3-dehydrogenases. *BMC Biochem., 3*, 19. ↗

Editions

2015-09-21	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

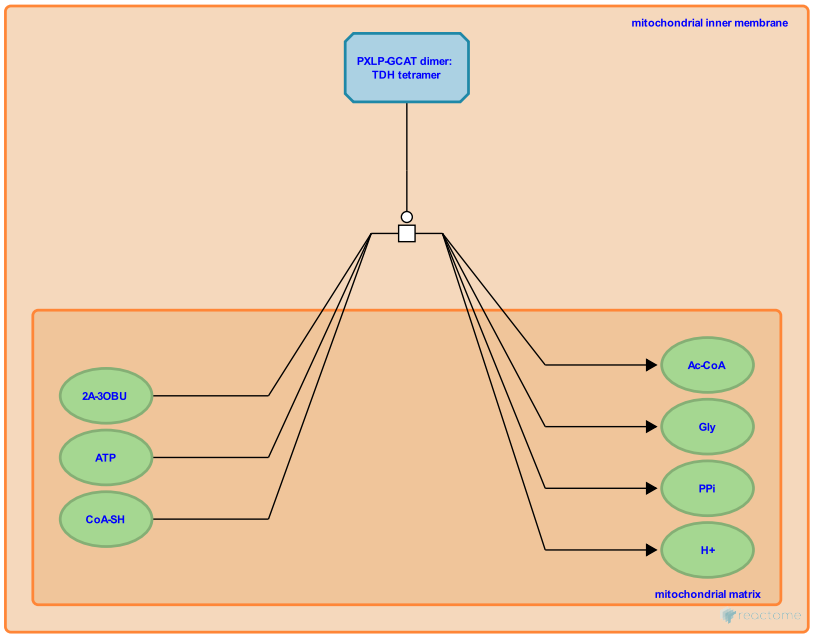
PXLP-GCAT dimer ligates CoASH to 2A-3OB to form Gly and Ac-CoA ↗

Location: Threonine catabolism

Stable identifier: R-HSA-6798345

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix



The degradation of L-threonine to glycine in both prokaryotes and eukaryotes takes place through a two-step biochemical pathway. In the second step, mitochondrial 2-amino-3-ketobutyrate coenzyme A ligase (GCAT, aka KBL) catalyses the reaction between 2-amino-3-oxobutanoate (2A-3OBU) and coenzyme A (CoA-SH) to form glycine (Gly) and acetyl-CoA (Ac-CoA) (Edgar & Polak 2000). GCAT resides on the mitochondrial inner membrane and requires pyridoxal 5-phosphate (PXLP) as cofactor. It is strongly expressed in heart, brain, liver and pancreas. Dimeric GCAT:PXLP is thought to exist on the mitochondrial inner membrane in complex with tetrameric L-threonine 3-dehydrogenase (TDH), the first enzyme in this pathway (Tressel et al. 1986). With these two enzymes located together, it stops the rapid and spontaneous decarboxylation of 2A-3OBU to aminoacetone and carbon dioxide and instead, results in glycine formation.

Preceded by: TDH tetramer oxidises L-Thr to 2A-3OB

Literature references

Davis, L., Zieske, LR., Thompson, R., Menendez, MI., Tressel, T. (1986). Interaction between L-threonine dehydrogenase and aminoacetone synthetase and mechanism of aminoacetone production. *J. Biol. Chem., 261*, 16428-37. ↗

Edgar, AJ., Polak, JM. (2000). Molecular cloning of the human and murine 2-amino-3-ketobutyrate coenzyme A ligase cDNAs. *Eur. J. Biochem., 267*, 1805-12. ↗

Editions

2015-09-18	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

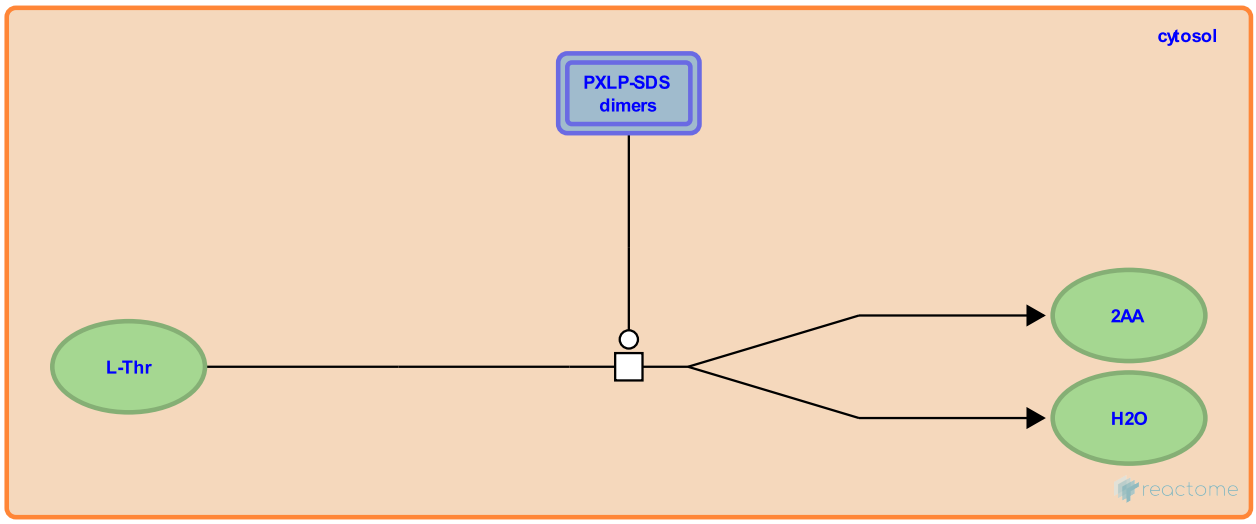
SDS dimers:PXLP dehydrate L-Thr to 2AA ↗

Location: Threonine catabolism

Stable identifier: R-HSA-9014627

Type: transition

Compartments: cytosol



Various PXLP-dependent enzymes can catalyse α, β-elimination reactions of amino acid substrates, ultimately yielding α-keto (or 2-oxo-) acid products. However, these enzymes, such as L-serine dehydratase/L-threonine deaminase (SDS aka TDH), only form the enamine intermediate as the remainder of the reaction occurs in solution with the enamine intermediate tautomerising to the imine form, which then spontaneously hydrolyzes to the final α-keto acid product (Downs & Ernst 2015). SDS can dehydrate L-threonine (L-Thr) to form the intermediate enamine 2-aminoacrylate (2AA), which can damage the pyridoxal 5'-phosphate cofactor (PXLP) of various enzymes, causing inactivation and significant cellular damage if allowed to accumulate (Lambrecht et al. 2013). SDS exists as a homodimer and requires PXLP for activity (Sun et al. 2005). An isoform of SDS, serine dehydratase-like (SDSL aka SDH2), is found in human cancer cell lines and possesses lower catalytic activity than SDS (Yamada et al. 2008).

Followed by: HRSP12 deaminates 2AA to 2OBUTA

Literature references

Bartlam, M., Rao, Z., Pang, H., Liu, Y., Sun, L. (2005). Crystal structure of the pyridoxal-5'-phosphate-dependent serine dehydratase from human liver. *Protein Sci., 14*, 791-8. ↗

Yamada, T., Ogawa, H., Kasuya, T., Takata, Y., Komoto, J., Takusagawa, F. et al. (2008). A catalytic mechanism that explains a low catalytic activity of serine dehydratase like-1 from human cancer cells: crystal structure and site-directed mutagenesis studies. *Biochim. Biophys. Acta, 1780*, 809-18. ↗

Editions

2017-08-02	Authored, Edited	Jassal, B.
2018-02-28	Reviewed	Downs, M., Cooper, JL.

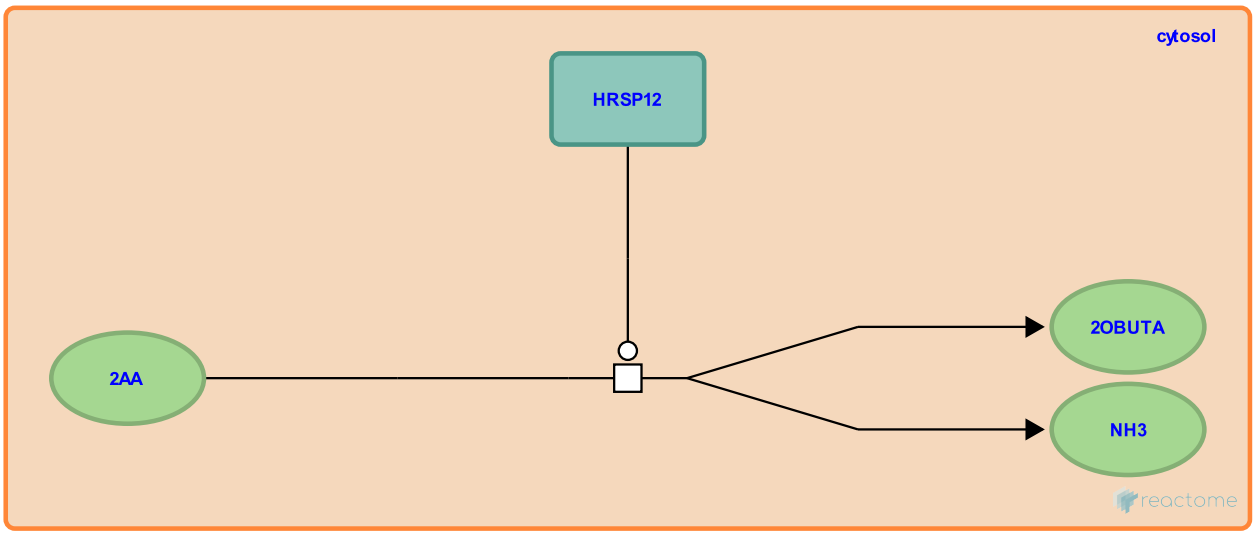
HRSP12 deaminates 2AA to 2OBUTA ↗

Location: Threonine catabolism

Stable identifier: R-HSA-9014641

Type: transition

Compartments: cytosol



The toxic enamine/imine intermediates generated by pyridoxal 5'-phosphate (PXLP) containing enzymes can cause severe cellular damage if allowed to accumulate (Downs & Ernst 2015). 2-iminobutanoate/2-iminopropanoate deaminase (RIDA aka HRSP12) is a widely conserved protein that prevents 2AA accumulation by facilitating its conversion to the stable metabolite 2-oxobutanoate (2OBUTA aka 2-ketobutyrate) (Cooper et al. 2011, Lambrecht et al. 2012, 2013, Niehaus et al. 2015).

Preceded by: SDS dimers:PXLP dehydrate L-Thr to 2AA

Literature references

Downs, DM., Flynn, JM., Lambrecht, JA. (2012). Conserved YjgF protein family deaminates reactive enamine/imine intermediates of pyridoxal 5'-phosphate (PLP)-dependent enzyme reactions. *J. Biol. Chem., 287*, 3454-61. ↗

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Editions

2017-08-02	Authored, Edited	Jassal, B.
2018-02-28	Reviewed	Downs, M., Cooper, JL.

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