1. Phylogeny  
   STRADβ (gene STRADB), also known as STLK6, ALS2CR2, and ILPIP, is a member of the STE20‐related pseudokinase subgroup within the human kinome and is evolutionarily conserved among vertebrates. Evidence from studies on STE20‐related kinases indicates that orthologs of STRAD exist in model organisms such as mouse and Drosophila, placing it among a group of kinases whose evolutionary history dates back to early eukaryotes (baas2003activationofthe pages 2-3, smith2021typeiibinders pages 1-3). STRADβ, like its paralog STRADα, shares structural features with the STE20 family but has accumulated key amino acid substitutions in its catalytic motifs, which distinguishes it as a pseudokinase with regulatory rather than enzymatic activity (baas2003activationofthe pages 2-3, trelford2024lkb1biologyassessing pages 2-4).
2. Reaction Catalyzed  
   Unlike canonical serine/threonine kinases, STRADβ does not catalyze the phosphorylation of protein substrates. Although it binds ATP, STRADβ lacks the critical catalytic residues—such as those within the DFG motif and the catalytic aspartate—required to transfer the γ‐phosphate from ATP to protein substrates (baas2003activationofthe pages 1-2, baas2003activationofthe pages 3-5). Instead, STRADβ functions as a pseudosubstrate within the LKB1–STRAD–MO25 complex, where its binding promotes a conformational change in LKB1 that facilitates LKB1 autophosphorylation and subsequent phosphorylation of downstream targets (baas2003activationofthe pages 3-5, trelford2024lkb1biologyassessing pages 2-4).
3. Cofactor Requirements  
   Canonical kinase activity typically requires the coordination of ATP with divalent metal ions such as Mg²⁺; however, STRADβ, being a pseudokinase, does not catalyze phosphoryl transfer and thus does not demonstrate a conventional cofactor requirement for catalytic activity. Although STRADβ retains the ability to bind ATP with reasonable affinity, no studies have established a requirement for Mg²⁺ or related cofactors in its regulatory function (baas2003activationofthe pages 2-3, smith2021typeiibinders pages 1-3).
4. Substrate Specificity  
   STRADβ does not possess intrinsic kinase activity and therefore has not been assigned a consensus substrate motif characteristic of catalytically active kinases. While STRADβ is phosphorylated by LKB1 on residues such as Thr329 and Thr419, it does not phosphorylate other substrates itself; its role is confined to acting as a scaffolding and regulatory subunit that influences LKB1’s substrate specificity (baas2003activationofthe pages 3-5, baas2003activationofthe pages 5-8, smith2021typeiibinders pages 13-15).
5. Structure  
   STRADβ is a protein of approximately 50 kDa that is composed almost entirely of a kinase‐like domain. This domain adopts the characteristic bilobal structure observed in protein kinases, with an N-terminal lobe consisting primarily of beta sheets and a C-terminal lobe that contains key secondary structural elements such as the αC helix. Despite its strong homology to active STE20 kinases, STRADβ lacks several critical catalytic residues—including a properly positioned DFG motif and the active site aspartate—which renders it catalytically inert yet structurally competent to bind ATP (baas2003activationofthe pages 2-3, bailey2014biochemicalanalysisof pages 29-33). Structural analyses, including homology modeling and crystallographic studies on related STRAD isoforms, reveal that STRADβ adopts a closed conformation typical of active kinases; this conformation is maintained even though the protein does not transfer phosphate groups (baas2003activationofthe pages 8-9, smith2021typeiibinders pages 3-4). Unique features of STRADβ include subtle alterations in its ATP-binding pocket and overall pseudocatalytic cleft that enable it to serve as a regulatory adaptor rather than a conventional kinase. In the context of the heterotrimeric complex with LKB1 and MO25, the structure of STRADβ facilitates a pseudosubstrate interaction with LKB1, promoting a conformational change that is essential for LKB1 activation (smith2021typeiibinders pages 8-10, trelford2024lkb1biologyassessing pages 2-4).
6. Regulation  
   Regulation of STRADβ is achieved principally through its participation in the LKB1–STRAD–MO25 complex rather than through its own catalytic activity. STRADβ binds ATP and adopts a closed, active-like conformation that is critical for its ability to interact with LKB1, effectively acting as a pseudosubstrate that induces conformational changes in LKB1 necessary for its autophosphorylation (baas2003activationofthe pages 3-5, baas2003activationofthe pages 8-9). LKB1, in turn, phosphorylates STRADβ on specific residues such as Thr329 and Thr419; however, mutagenesis studies have shown that these phosphorylation events are not required for STRADβ’s adaptor function or for the activation of LKB1 (baas2003activationofthe pages 5-8, baas2003activationofthe pages 3-5). Additionally, STRADβ’s interaction with MO25 is essential for the stabilization of the heterotrimeric complex, ensuring that LKB1 is maintained in an active conformation and efficiently localized to the cytoplasm where it can exert its tumor suppressor functions (trelford2024lkb1biologyassessing pages 2-4, rao2018repositioningofsomatic pages 9-10).
7. Function  
   STRADβ functions as a pseudokinase regulator that is required for the optimal activation of the tumor suppressor kinase LKB1. In the absence of intrinsic kinase activity, STRADβ facilitates the conversion of LKB1 into an active conformation by binding as a pseudosubstrate and promoting its autophosphorylation, an event that is critical for the downstream phosphorylation of substrates involved in cellular energy homeostasis, cell polarity, and growth control (baas2003activationofthe pages 1-2, baas2003activationofthe pages 3-5). Within the LKB1–STRAD–MO25 complex, STRADβ contributes to the cytoplasmic retention of LKB1 by enabling its interaction with nuclear export machinery; this cytoplasmic localization is necessary for LKB1’s ability to regulate cell cycle arrest and maintain cellular metabolism (baas2003activationofthe pages 8-9, trelford2024lkb1biologyassessing pages 2-4). Although STRADβ does not phosphorylate downstream targets itself, its role as an adaptor is indispensable for the propagation of LKB1-mediated signaling cascades that influence the activity of key kinases such as AMPK and various AMPK-related kinases (trelford2024lkb1biologyassessing pages 2-4, baas2003activationofthe pages 3-5).
8. Other Comments  
   Recent investigations have identified small-molecule type II inhibitors that target the unique pseudocatalytic cleft of STRAD by stabilizing its ‘GLR-out’ conformation, thus providing potential tools for modulating the assembly and function of the LKB1–STRAD–MO25 complex (smith2021typeiibinders pages 1-3, smith2021typeiibinders pages 13-15). STRADβ is alternatively designated as ALS2CR2, STLK6, and ILPIP, and these alternative names reflect its discovery in different biological contexts including studies of amyotrophic lateral sclerosis and chromosomal candidate gene analyses. Disruption of the STRAD–LKB1 interaction has been implicated in aberrant cell cycle regulation, with potential links to tumorigenesis in conditions such as Peutz–Jeghers syndrome due to compromised LKB1 function (baas2003activationofthe pages 1-2, trelford2024lkb1biologyassessing pages 14-15). Notably, despite its robust ATP binding, STRADβ’s lack of catalytic activity categorizes it as a non-enzymatic regulator, a characteristic that has spurred interest in its structural modulation via ATP-competitive compounds for therapeutic research (smith2021typeiibinders pages 22-25, trelford2024lkb1biologyassessing pages 14-15).
9. References
10. A. Baas, J. Boudeau, G. P. Sapkota, L. Smit, R. Medema, N. Morrice, D. Alessi, and H. Clevers, “Activation of the tumour suppressor kinase LKB1 by the STE20-like pseudokinase STRAD,” The EMBO Journal, vol. 22, pp. 3062–3072, Jun 2003. (baas2003activationofthe pages 1-2, baas2003activationofthe pages 2-3, baas2003activationofthe pages 3-5, baas2003activationofthe pages 5-8, baas2003activationofthe pages 8-9, baas2003activationofthe pages 9-10)
11. S. R. Rao, G. W. Kirschen, J. Szczurkowska, A. Di Antonio, J. Wang, S. Ge, and M. Shelly, “Repositioning of somatic Golgi apparatus is essential for the dendritic establishment of adult-born hippocampal neurons,” The Journal of Neuroscience, vol. 38, pp. 631–647, Dec 2018. (rao2018repositioningofsomatic pages 9-10)
12. R. H. B. Smith, Z. M. Khan, P. M.-U. Ung, A. P. Scopton, L. Silber, S. M. Mack, A. M. Real, A. Schlessinger, and A. C. Dar, “Type II binders targeting the ‘GLR-out’ conformation of the pseudokinase STRADα,” Biochemistry, vol. 60, pp. 289–302, Jan 2021. (smith2021typeiibinders pages 1-3, smith2021typeiibinders pages 3-4, smith2021typeiibinders pages 6-8, smith2021typeiibinders pages 8-10, smith2021typeiibinders pages 10-11, smith2021typeiibinders pages 11-13, smith2021typeiibinders pages 13-15, smith2021typeiibinders pages 20-22, smith2021typeiibinders pages 22-25)
13. C. B. Trelford and T. G. Shepherd, “LKB1 biology: assessing the therapeutic relevancy of LKB1 inhibitors,” Cell Communication and Signaling, Jun 2024. (trelford2024lkb1biologyassessing pages 1-2, trelford2024lkb1biologyassessing pages 2-4, trelford2024lkb1biologyassessing pages 5-7, trelford2024lkb1biologyassessing pages 14-15, trelford2024lkb1biologyassessing pages 16-17)

References

1. (baas2003activationofthe pages 1-2): A. Baas, J. Boudeau, Gopal P. Sapkota, L. Smit, R. Medema, N. Morrice, D. Alessi, and H. Clevers. Activation of the tumour suppressor kinase lkb1 by the ste20-like pseudokinase strad. The EMBO Journal, 22:3062-3072, Jun 2003. URL: https://doi.org/10.1093/emboj/cdg292, doi:10.1093/emboj/cdg292. This article has 489 citations.
2. (baas2003activationofthe pages 2-3): A. Baas, J. Boudeau, Gopal P. Sapkota, L. Smit, R. Medema, N. Morrice, D. Alessi, and H. Clevers. Activation of the tumour suppressor kinase lkb1 by the ste20-like pseudokinase strad. The EMBO Journal, 22:3062-3072, Jun 2003. URL: https://doi.org/10.1093/emboj/cdg292, doi:10.1093/emboj/cdg292. This article has 489 citations.
3. (baas2003activationofthe pages 3-5): A. Baas, J. Boudeau, Gopal P. Sapkota, L. Smit, R. Medema, N. Morrice, D. Alessi, and H. Clevers. Activation of the tumour suppressor kinase lkb1 by the ste20-like pseudokinase strad. The EMBO Journal, 22:3062-3072, Jun 2003. URL: https://doi.org/10.1093/emboj/cdg292, doi:10.1093/emboj/cdg292. This article has 489 citations.
4. (baas2003activationofthe pages 5-8): A. Baas, J. Boudeau, Gopal P. Sapkota, L. Smit, R. Medema, N. Morrice, D. Alessi, and H. Clevers. Activation of the tumour suppressor kinase lkb1 by the ste20-like pseudokinase strad. The EMBO Journal, 22:3062-3072, Jun 2003. URL: https://doi.org/10.1093/emboj/cdg292, doi:10.1093/emboj/cdg292. This article has 489 citations.
5. (baas2003activationofthe pages 8-9): A. Baas, J. Boudeau, Gopal P. Sapkota, L. Smit, R. Medema, N. Morrice, D. Alessi, and H. Clevers. Activation of the tumour suppressor kinase lkb1 by the ste20-like pseudokinase strad. The EMBO Journal, 22:3062-3072, Jun 2003. URL: https://doi.org/10.1093/emboj/cdg292, doi:10.1093/emboj/cdg292. This article has 489 citations.
6. (baas2003activationofthe pages 9-10): A. Baas, J. Boudeau, Gopal P. Sapkota, L. Smit, R. Medema, N. Morrice, D. Alessi, and H. Clevers. Activation of the tumour suppressor kinase lkb1 by the ste20-like pseudokinase strad. The EMBO Journal, 22:3062-3072, Jun 2003. URL: https://doi.org/10.1093/emboj/cdg292, doi:10.1093/emboj/cdg292. This article has 489 citations.
7. (rao2018repositioningofsomatic pages 9-10): Sneha Rao, Gregory W. Kirschen, J. Szczurkowska, Adrian Di Antonio, Jia Wang, S. Ge, and M. Shelly. Repositioning of somatic golgi apparatus is essential for the dendritic establishment of adult-born hippocampal neurons. The Journal of Neuroscience, 38:631-647, Dec 2018. URL: https://doi.org/10.1523/jneurosci.1217-17.2017, doi:10.1523/jneurosci.1217-17.2017. This article has 36 citations.
8. (smith2021typeiibinders pages 1-3): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
9. (smith2021typeiibinders pages 20-22): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
10. (smith2021typeiibinders pages 3-4): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
11. (smith2021typeiibinders pages 8-10): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
12. (trelford2024lkb1biologyassessing pages 2-4): Charles B. Trelford and Trevor G. Shepherd. Lkb1 biology: assessing the therapeutic relevancy of lkb1 inhibitors. Cell Communication and Signaling, Jun 2024. URL: https://doi.org/10.1186/s12964-024-01689-5, doi:10.1186/s12964-024-01689-5. This article has 12 citations and is from a peer-reviewed journal.
13. (bailey2014biochemicalanalysisof pages 29-33): F Bailey. Biochemical analysis of human cancer-associated pseudokinases. Unknown journal, 2014.
14. (smith2021typeiibinders pages 10-11): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
15. (smith2021typeiibinders pages 11-13): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
16. (smith2021typeiibinders pages 13-15): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
17. (smith2021typeiibinders pages 22-25): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
18. (smith2021typeiibinders pages 6-8): Ryan H. B. Smith, Zaigham M. Khan, Peter Man-Un Ung, Alex P. Scopton, Lisa Silber, Seshat M. Mack, Alexander M. Real, Avner Schlessinger, and Arvin C. Dar. Type ii binders targeting the “glr-out” conformation of the pseudokinase stradα. Biochemistry, 60:289-302, Jan 2021. URL: https://doi.org/10.1021/acs.biochem.0c00714, doi:10.1021/acs.biochem.0c00714. This article has 8 citations and is from a peer-reviewed journal.
19. (trelford2024lkb1biologyassessing pages 1-2): Charles B. Trelford and Trevor G. Shepherd. Lkb1 biology: assessing the therapeutic relevancy of lkb1 inhibitors. Cell Communication and Signaling, Jun 2024. URL: https://doi.org/10.1186/s12964-024-01689-5, doi:10.1186/s12964-024-01689-5. This article has 12 citations and is from a peer-reviewed journal.
20. (trelford2024lkb1biologyassessing pages 14-15): Charles B. Trelford and Trevor G. Shepherd. Lkb1 biology: assessing the therapeutic relevancy of lkb1 inhibitors. Cell Communication and Signaling, Jun 2024. URL: https://doi.org/10.1186/s12964-024-01689-5, doi:10.1186/s12964-024-01689-5. This article has 12 citations and is from a peer-reviewed journal.
21. (trelford2024lkb1biologyassessing pages 5-7): Charles B. Trelford and Trevor G. Shepherd. Lkb1 biology: assessing the therapeutic relevancy of lkb1 inhibitors. Cell Communication and Signaling, Jun 2024. URL: https://doi.org/10.1186/s12964-024-01689-5, doi:10.1186/s12964-024-01689-5. This article has 12 citations and is from a peer-reviewed journal.
22. (trelford2024lkb1biologyassessing pages 16-17): Charles B. Trelford and Trevor G. Shepherd. Lkb1 biology: assessing the therapeutic relevancy of lkb1 inhibitors. Cell Communication and Signaling, Jun 2024. URL: https://doi.org/10.1186/s12964-024-01689-5, doi:10.1186/s12964-024-01689-5. This article has 12 citations and is from a peer-reviewed journal.