



HAL
open science

LIM Kinases: From Molecular to Pathological Features

Hélène Bénédetti, Béatrice Vallée

► **To cite this version:**

Hélène Bénédetti, Béatrice Vallée. LIM Kinases: From Molecular to Pathological Features. Cells, 2023, 12 (12), pp.1649. 10.3390/cells12121649 . hal-04208415

HAL Id: hal-04208415

<https://hal.science/hal-04208415>

Submitted on 15 Sep 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

LIM Kinases: From Molecular to Pathological Features

Hélène Bénédicti  and Béatrice Vallée * 

Centre de Biophysique Moléculaire, UPR4301, CNRS, University of Orleans and INSERM, CEDEX 2, 45071 Orleans, France; helene.benedetti@cnrs-orleans.fr

* Correspondence: beatrice.vallee@cnrs-orleans.fr; Tel.: +33-(0)2-38-25-76-11

LIM kinases (LIMKs), LIMK1 and LIMK2, are atypical kinases, as they are the only two members of the LIM kinase family harbouring two LIM domains at their N-terminus and a kinase domain at their C-terminus. They are dual kinases able to phosphorylate serine, threonine and tyrosine due to their non-canonical catalytic site. They play a crucial role in cytoskeleton remodelling through the independent regulation of the actin filament and microtubule turnover. Initially, LIMKs were described as downstream effectors of the signalling pathway controlled by small Rho GTPases. Along this pathway, LIMKs phosphorylate cofilin, an actin-depolymerizing factor, leading to its inhibition and actin filament stabilization. The molecular actors of LIMK implication into microtubule dynamics remain unknown. Therefore, many studies on LIMKs have focused on their role involved in cell division, differentiation and migration as aspects of cytoskeleton remodelling.

However, many partners of LIMKs have been identified over the last years, positioning them at the heart of an impressive network of signalling pathways. Along this line, the implications of LIMKs in numerous pathologies have inspired interest in their role as potential relevant therapeutic targets. Many small molecule inhibitors targeting their kinase active site have been developed without success during the clinical stage. As such, it appears crucial to have a better understanding of these kinases to develop new efficient therapies. This Special Issue focuses on these different aspects of LIMKs, presenting an interesting overview of this field and opening new exciting perspectives.

Villalonga et al. [1] propose a broad overview of the LIMK gene and protein organization, as well as their implication in many physiological and pathological processes. They also depicted LIMK partners, substrates and regulators, establishing a detailed scheme of their molecular interactome.

Berabez et al. [2] focus on small molecule inhibitors targeting LIMK kinase activity, and discuss their chemical structure–biological activity relationship. They concentrate on inhibitors that have successfully reached the stage of preclinical assays on animal models of different diseases. They emphasize the failure of these compounds to reach the clinical stage.

Chatterjee et al. [3] highlight the structural features of LIMKs, describing their conformational changes due to ligand binding. They underscore the atypical catalytic mechanism of these kinases, with a focus on substrate recognition and LIMK regulation. They also propose new therapeutic strategies to target these kinases without restricting the field of investigation to their kinase activity.

Ribba et al. [4] shed light on the less known role of LIMKs in embryonic development. They depicted LIMK tissue expression during development, and utilize studies on animal models with loss- or gain-of function mutations in LIMKs and the inhibitors targeting LIMKs in order to better understand their functions.

Park et al. [5] focus on a recently described function of LIMKs in male urogenital system. Indeed, these kinases are involved in several processes crucial for proper urogenital function, such as smooth muscle contraction and spermatogenesis, but also with roles in pathological phenomena, such as cavernosal fibrosis and erectile dysfunction. Therefore, LIMKs may be new therapeutic targets against different urogenital disorders.



Citation: Bénédicti, H.; Vallée, B. LIM Kinases: From Molecular to Pathological Features. *Cells* **2023**, *12*, 1649. <https://doi.org/10.3390/cells12121649>

Received: 9 June 2023

Accepted: 14 June 2023

Published: 16 June 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Brion et al. [6] draw attention to the implication of LIMKs in osteosarcoma, a bone cancer mainly affecting children and adolescents. Many patients still die from this disease and the survival rates have increased minimally over the last decades; find new therapies against this cancer is an emergency. LIMKs may be one of these new therapeutic targets, as many recent papers described their implication in osteosarcoma. These data are well depicted in this review.

It would also have been interesting to focus on other characteristics of these LIMKs; however, these topics will be briefly mentioned, as limited relevant information has been collated in this Special Issue.

LIMK regulation by miRNA is a well-documented topic in the literature. More than 30 miRNAs targeting LIMKs have been described to regulate their expression, leading to their downregulation and playing a role in various diseases such as cancers, neural pathologies, etc. Long non-coding RNA (LncRNA) and circRNA have also been shown to regulate LIMKs.

Recently, LIMKs have been shown to play a role in viral infections of HIV, Herpes Simplex, Ebola, Rift Valley fever and Venezuelan Equine Encephalitis viruses, and more studies on this topic would be fruitful [7–9].

Furthermore, many papers discuss computational calculations, virtual screening, molecular docking and dynamic simulations, and comparative analysis of different kind of inhibitors (type I, II or III) in order to improve the approach concerning the development of small molecule inhibitors targeting LIMKs [10–13]. Many efforts are dedicated to this field to improve the pharmacological properties of these molecules and reflect the emergency of finding new compounds in order to selectively target these kinases, with the ultimate goal to reach clinical stages.

The field of research concerning the LIM kinases is still widely open, and many discoveries remain to be achieved to gain a better understanding of these multitasking kinases. We hope you will have interest and enthusiasm to read these well-documented reviews, and that you will widely increase your knowledge on these amazing LIMKs!

Funding: This research was funded by the Centre National de la Recherche Scientifique, the Ministère de l'Enseignement Supérieur et de la Recherche, University of Orleans, La Ligue contre le Cancer (grant number PM/FP/202-251, comités d'Eure et Loire et du Loiret), the French Association Neurofibromatosis et Recklinghausen, the French Agence Nationale de la recherche (grant number ANR-19-CE18-0016-02), and the region Centre Val de Loire.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Villalonga, E.; Mosrin, C.; Normand, T.; Girardin, C.; Serrano, A.; Žunar, B.; Doudeau, M.; Godin, F.; Bénédicti, H.; Vallée, B. LIM Kinases, LIMK1 and LIMK2, Are Crucial Node Actors of the Cell Fate: Molecular to Pathological Features. *Cells* **2023**, *12*, 805. [[CrossRef](#)] [[PubMed](#)]
2. Berabez, R.; Routier, S.; Bénédicti, H.; Plé, K.; Vallée, B. LIM Kinases, Promising but Reluctant Therapeutic Targets: Chemistry and Preclinical Validation In Vivo. *Cells* **2022**, *11*, 2090. [[CrossRef](#)] [[PubMed](#)]
3. Chatterjee, D.; Preuss, F.; Dederer, V.; Knapp, S.; Mathea, S. Structural Aspects of LIMK Regulation and Pharmacology. *Cells* **2022**, *11*, 142. [[CrossRef](#)] [[PubMed](#)]
4. Ribba, A.S.; Fraboulet, S.; Sadoul, K.; Lafanechère, L. The Role of LIM Kinases during Development: A Lens to Get a Glimpse of Their Implication in Pathologies. *Cells* **2022**, *11*, 403. [[CrossRef](#)] [[PubMed](#)]
5. Park, J.; Kim, S.W.; Cho, M.C. The Role of LIM Kinase in the Male Urogenital System. *Cells* **2021**, *11*, 78. [[CrossRef](#)] [[PubMed](#)]
6. Brion, R.; Regnier, L.; Mullard, M.; Amiaud, J.; Rédini, F.; Verrecchia, F. LIM Kinases in Osteosarcoma Development. *Cells* **2021**, *10*, 3542. [[CrossRef](#)] [[PubMed](#)]
7. Manetti, F. HIV-1 proteins join the family of LIM kinase partners. New roads open up for HIV-1 treatment. *Drug Discov. Today* **2012**, *17*, 81–88. [[CrossRef](#)] [[PubMed](#)]
8. Wen, X.; Ding, L.; Wang, J.J.; Qi, M.; Hammonds, J.; Chu, H.; Chen, X.; Hunter, E.; Spearman, P. ROCK1 and LIM kinase modulate retrovirus particle release and cell-cell transmission events. *J. Virol.* **2014**, *88*, 6906–6921. [[CrossRef](#)] [[PubMed](#)]
9. Yi, F.; Guo, J.; Dabbagh, D.; Spear, M.; He, S.; Kehn-Hall, K.; Fontenot, J.; Yin, Y.; Bibian, M.; Park, C.M.; et al. Discovery of Novel Small-Molecule Inhibitors of LIM Domain Kinase for Inhibiting HIV-1. *J. Virol.* **2017**, *91*, e02418-16. [[CrossRef](#)] [[PubMed](#)]

10. Collins, R.; Lee, H.; Jones, D.H.; Elkins, J.M.; Gillespie, J.A.; Thomas, C.; Baldwin, A.G.; Jones, K.; Waters, L.; Paine, M.; et al. Comparative Analysis of Small-Molecule LIMK1/2 Inhibitors: Chemical Synthesis, Biochemistry, and Cellular Activity. *J. Med. Chem.* **2022**, *65*, 13705–13713. [[CrossRef](#)] [[PubMed](#)]
11. Hanke, T.; Mathea, S.; Woortman, J.; Salah, E.; Berger, B.T.; Tumber, A.; Kashima, R.; Hata, A.; Kuster, B.; Müller, S.; et al. Development and Characterization of Type I, Type II, and Type III LIM-Kinase Chemical Probes. *J. Med. Chem.* **2022**, *65*, 13264–13287. [[CrossRef](#)] [[PubMed](#)]
12. Nagarajan, H.; Samdani, A.; Umashankar, V.; Jeyakanthan, J. Deciphering the conformational transitions of LIMK2 active and inactive states to ponder specific druggable states through microsecond scale molecular dynamics simulation. *J. Comput. Aided Mol. Des.* **2022**, *36*, 459–482. [[CrossRef](#)] [[PubMed](#)]
13. Singh, R.; Pokle, A.V.; Ghosh, P.; Ganeshpurkar, A.; Swetha, R.; Singh, S.K.; Kumar, A. Pharmacophore-based virtual screening, molecular docking and molecular dynamics simulations study for the identification of LIM kinase-1 inhibitors. *J. Biomol. Struct. Dyn.* **2022**, 1–15. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.