

# Homeodomain-interacting protein kinase 2 (HIPK2)

Subjects: **Biochemistry & Molecular Biology**

Contributor: Giovanna Maria Pierantoni

Homeodomain-interacting protein kinase 2 (HIPK2) is a serine-threonine kinase that phosphorylates various transcriptional and chromatin regulators, thus modulating numerous important cellular processes, such as proliferation, apoptosis, DNA damage response, and oxidative stress. The role of HIPK2 in the pathogenesis of cancer and fibrosis is well established, and evidence of its involvement in the physiological homeostasis of multiple organs has been recently emerging.

HIPK2

myopathic changes

knock-out mice

kinase

mouse model

## 1. Introduction

Homeodomain-interacting protein kinase 2 (HIPK2) is a member of a protein family that includes four nuclear serine-threonine kinases (HIPK1, HIPK2, HIPK3, and HIPK4) [1]. Originally identified as corepressors of homeodomain transcription factors, HIPKs are able to phosphorylate and modulate the activity of various transcriptional regulators and chromatin modifiers, thus playing an important role in embryonic development, and in a multitude of cellular processes [2]. HIPKs also act as transcriptional coregulators in important signal transduction pathways, such as Wnt/β-catenin, TGF-β, MAPK, Notch, Salvador–Warts–Hippo, and androgen receptor (AR), contributing to their cross-talk [3][4]. HIPK2 is the best characterized member of the family and is actively involved in the regulation of cell proliferation, apoptosis, DNA damage response, cytokinesis, transcription, and protein stability [5][6][7][8][9][10][11]. HIPK2 expression and activity are tightly regulated by post-translational modifications and miRNAs, and its functions strongly depend on the cellular context, and on its subcellular localization, which can be nuclear and/or cytoplasmic [8][9][10].

Because of their important role in the regulation of cell proliferation and survival, HIPK proteins have traditionally been linked to the pathogenesis of cancer and fibrosis, which are often associated with deregulated activity or expression of HIPKs [12]. In particular, HIPK2 is considered a bona fide tumor suppressor, primarily because of its involvement in DNA damage repair, induction of apoptosis, and regulation of cell proliferation [4][5][6][7][8][9][10][11][12][13]. Indeed, *Hipk2*<sup>-/-</sup> mice are more susceptible to skin chemical carcinogenesis [11], and HIPK2 expression is down-regulated in breast, thyroid, and colon carcinomas [14][15]. HIPK2 is also involved in signaling pathways crucial for the induction of kidney and lung fibrosis [12].

The relevant physiological role of HIPK2 emerged also from the phenotype of *Hipk2*-null (*Hipk2*-KO) mice. *Hipk2* genetic ablation affects the mouse body size, being *Hipk2*-KO mice significantly smaller than their wild-type

littermates, as well as the proliferation of different cell types, including fetal liver cells [16], mouse embryo fibroblasts (MEFs) [17][18], bone marrow [19], and sensory neurons [20]. Moreover, *Hipk2*-KO mice show several neuronal defects, including a reduction of midbrain dopamine neuron survival [21] and apoptosis of cerebellar Purkinje cells, associated with several psychomotor behavioral abnormalities [22].

Recent findings suggest that HIPK2 may be important also for the biology of cardiac and skeletal muscle cells. In particular, the involvement of HIPK2 in heart pathophysiology is suggested by the evidence that a reduction of HIPK2 in cardiomyocytes leads to cardiac dysfunction in mice and that cardiac HIPK2 expression is significantly reduced in human end-stage ischemic cardiomyopathy, in comparison with non-failing myocardium [23]. On the other hand, HIPK2 expression strongly increases after skeletal muscle contusion in neutrophils, macrophages, and myofibroblasts [24]. Finally, we recently reported that the double KO of HIPK2 and high-mobility group A1 (HMGA1), a chromatin non-histone protein previously identified as HIPK2 interactor and substrate, causes perinatal death due to respiratory failure, associated with impaired lung development and reduction in surfactant proteins, as well as reduced expression of thyroid differentiation markers [25].

All these data suggest a pleiotropic involvement of HIPK2 in the physiological homeostasis of different organs and tissues and, potentially, in the pathogenesis of multiple diseases. On this basis, to confirm the importance of HIPK2 in the above-mentioned organs and tissues, and try to identify other organs or tissues whose homeostasis may depend on HIPK2, we performed a systematic morphological analysis of *Hipk2*-KO mice. Post-mortem examination and histological analysis revealed that *Hipk2* loss causes neuronal alterations throughout the central nervous system (CNS), a myopathic phenotype, and cardiac fibrosis associated with increased cardiomyocyte size.

## 2. Current Insights

In general, the evidence that all the observed phenotypic features of the KO mice are relatively mild may be due to the functional redundancy of the different HIPK family members. In fact, *Hipk1* displays a very high homology degree to *Hipk2*, and the two genes play overlapping roles in mediating cell proliferation and apoptosis in response to morphogenetic and genotoxic signals during mouse development, as evidenced by embryonic lethality following their double KO [14]. The combination of *Hipk2* constitutive KO with an organ-specific *Hipk1*-KO (in the cerebellum, in the heart, or in muscle cells) may unleash much more severe phenotypes, revealing more information about the role and the functional interaction of these two HIPK proteins *in vivo*. Similarly, it is important to take into account that HIPK2 activity is strictly dependent on the functional interaction with its phosphorylation targets. For this reason, the ablation or mutation of one of these targets may contribute to causing a stronger phenotype.

## References

1. Kim, Y.H.; Choi, C.Y.; Lee, S.J.; Conti, M.A.; Kim, Y. Homeodomain-interacting protein kinases, a novel family of co-repressors for homeodomain transcription factors. *J. Biol. Chem.* 1998, 273, 25875–25879.

2. Rinaldo, C.; Prodromo, A.; Siepi, F.; Soddu, S. HIPK2: A multitalented partner for transcription factors in DNA damage response and development. *Biochem. Cell Biol.* 2007, 85, 411–418.
3. Schmitz, M.L.; Rodriguez-Gil, A.; Hornung, J. Integration of stress signals by homeodomain interacting protein kinases. *Biol. Chem.* 2014, 395, 375–386.
4. Hofmann, T.G.; Glas, C.; Bitomsky, N. HIPK2: A tumour suppressor that controls DNA damage-induced cell fate and cytokinesis. *Bioessays* 2013, 35, 55–64.
5. D’Orazi, G.; Rinaldo, C.; Soddu, S. Updates on HIPK2: A resourceful oncosuppressor for clearing cancer. *J. Exp. Clin. Cancer Res.* 2012, 31, 63.
6. Conte, A.; Pierantoni, G.M. Regulation of HIPK proteins by MicroRNAs. *MicroRNA* 2015, 4, 148–157.
7. Conte, A.; Pierantoni, G.M. Update on the regulation of HIPK1, HIPK2 and HIPK3 protein kinases by microRNAs. *MicroRNA* 2018, 7, 178–186.
8. Valente, D.; Bossi, G.; Moncada, A.; Tornincasa, M.; Indelicato, S.; Piscuoglio, S.; Karamitopoulou, E.D.; Bartolazzi, A.; Pierantoni, G.M.; Fusco, A.; et al. HIPK2 deficiency causes chromosomal instability by cytokinesis failure and increases tumorigenicity. *Oncotarget* 2015, 6, 10320–10334.
9. Wei, G.; Ku, S.; Ma, G.K.; Saito, S.; Tang, A.A.; Zhang, J.; Mao, J.H.; Appella, E.; Balmain, A.; Huang, E.J. HIPK2 represses beta-catenin-mediated transcription, epidermal stem cell expansion, and skin tumorigenesis. *Proc. Natl. Acad. Sci. USA* 2007, 104, 13040–13045.
10. Ritter, O.; Schmitz, M.L. Differential intracellular localization and dynamic nucleocytoplasmic shuttling of homeodomain-interacting protein kinase family members. *Biochim. Biophys. Acta Mol. Cell Res.* 2019, 1866, 1676–1686.
11. Pierantoni, G.M.; Fedele, M.; Pentimalli, F.; Benvenuto, G.; Pero, R.; Viglietto, G.; Santoro, M.; Chiariotti, L.; Fusco, A. High mobility group I (Y) proteins bind HIPK2, a serine-threonine kinase protein which inhibits cell growth. *Oncogene* 2001, 20, 6132–6141.
12. Xiao, W.; Jing, E.; Bao, L.; Fan, Y.; Jin, Y.; Wang, A.; Bauman, D.; Li, Z.; Zheng, Y.L.; Liu, R.; et al. Tubular HIPK2 is a key contributor to renal fibrosis. *JCI Insight* 2020, 5, e136004.
13. D’Orazi, G.; Cecchinelli, B.; Bruno, T.; Manni, I.; Higashimoto, Y.; Saito, S.; Gostissa, M.; Coen, S.; Marchetti, A.; Del Sal, G.; et al. Homeodomain- interacting protein kinase-2 phosphorylates p53 at Ser 46 and mediates apoptosis. *Nat. Cell Biol.* 2002, 4, 11–19.
14. Pierantoni, G.M.; Bulfone, A.; Pentimalli, F.; Fedele, M.; Iuliano, R.; Santoro, M.; Chiariotti, L.; Ballabio, A.; Fusco, A. The homeodomain-interacting protein kinase 2 gene is expressed late in embryogenesis and preferentially in retina, muscle, and neural tissues. *Biochem. Biophys. Res. Commun.* 2002, 290, 942–947.

15. Lavra, L.; Rinaldo, C.; Ulivieri, A.; Luciani, E.; Fidanza, P.; Giacomelli, L.; Bellotti, C.; Ricci, A.; Trovato, M.; Soddu, S.; et al. The loss of the p53 activator HIPK2 is responsible for galectin-3 overexpression in well differentiated thyroid carcinomas. *PLoS ONE* 2011, 6, e20665.
16. Hattangadi, S.M.; Burke, K.A.; Lodish, H.F. Homeodomain-interacting protein kinase 2 plays an important role in normal terminal erythroid differentiation. *Blood* 2010, 115, 4853–4861.
17. Isono, K.; Nemoto, K.; Li, Y.; Takada, Y.; Suzuki, R.; Katsuki, M.; Nakagawara, A.; Koseki, H. Overlapping roles for homeodomain-interacting protein kinases hipk1 and hipk2 in the mediation of cell growth in response to morphogenetic and genotoxic signals. *Mol. Cell. Biol.* 2006, 26, 2758–2771.
18. Rinaldo, C.; Moncada, A.; Gradi, A.; Ciuffini, L.; D'Eliseo, D.; Siepi, F.; Prodoso, A.; Giorgi, A.; Pierantoni, G.M.; Trapasso, F.; et al. HIPK2 controls cytokinesis and prevents tetraploidization by phosphorylating histone H2B at the midbody. *Mol. Cell* 2012, 47, 87–98.
19. Iacovelli, S.; Ciuffini, L.; Lazzari, C.; Bracaglia, G.; Rinaldo, C.; Prodoso, A.; Bartolazzi, A.; Sacchi, A.; Soddu, S. HIPK2 is involved in cell proliferation and its suppression promotes growth arrest independently of DNA damage. *Cell Prolif.* 2009, 42, 373–384.
20. Wiggins, A.K.; Wei, G.; Doxakis, E.; Wong, C.; Tang, A.A.; Zang, K.; Luo, E.J.; Neve, R.L.; Reichardt, L.F.; Huang, E.J. Interaction of Brn3a and HIPK2 mediates transcriptional repression of sensory neuron survival. *J. Cell Biol.* 2004, 167, 257–267.
21. Zhang, J.; Pho, V.; Bonasera, S.J.; Holtzman, J.; Tang, A.T.; Hellmuth, J.; Tang, S.; Janak, P.H.; Tecott, L.H.; Huang, E.J. Essential function of HIPK2 in TGFbeta-dependent survival of midbrain dopamine neurons. *Nat. Neurosci.* 2007, 10, 77–86.
22. Anzilotti, S.; Tornincasa, M.; Gerlini, R.; Conte, A.; Brancaccio, P.; Cuomo, O.; Bianco, G.; Fusco, A.; Annunziato, L.; Pierantoni, G.M.; et al. Genetic ablation of homeodomain-interacting protein kinase 2 selectively induces apoptosis of cerebellar Purkinje cells during adulthood and generates an ataxic-like phenotype. *Cell Death Dis.* 2015, 6, e2004.
23. Guo, Y.; Sui, J.Y.; Kim, K.; Zhang, Z.; Qu, X.A.; Nam, Y.J.; Willette, R.N.; Barnett, J.V.; Knollmann, B.C.; Force, T.; et al. Cardiomyocyte Homeodomain-Interacting Protein Kinase 2 Maintains Basal Cardiac Function via Extracellular Signal-Regulated Kinase Signaling. *Circulation* 2019, 140, 1820–1833.
24. Zhang, M.; Zhang, M.Z.; Wen, S.H.; Sun, Y.F.; Jiang, P.H.; Wang, L.L.; Zhao, R.; Wang, C.L.; Jiang, S.K.; Guan, D.W. The distribution and Time-dependent expression of HIPK2 during the repair of contused skeletal muscle in mice. *Histol. Histopathol.* 2019, 34, 745–753.
25. Gerlini, R.; Amendola, E.; Conte, A.; Valente, V.; Tornincasa, M.; Credendino, S.C.; Cammarota, F.; Gentile, C.; Di Guida, L.; Paladino, S.; et al. Double knock-out of Hmga1 and Hipk2 genes

causes perinatal death associated to respiratory distress and thyroid abnormalities in mice. *Cell Death Dis.* 2019, 10, 747.

---

Retrieved from <https://encyclopedia.pub/entry/history/show/31527>