Navaneethakrishnan S, Rosales JL, Lee KL. Cdk5: A Mediator of Mptp Opening. J Cancer Treatment Diagn.(2020);4(2):12-13

Journal of Cancer Treatment and Diagnosis

Journal of Cancer Treatment & Diagnosis

Commentary Open Access

Cdk5: A Mediator of Mptp Opening

Saranya NavaneethaKrishnan[1], Jesusa L. Rosales[1], Ki-Young Lee[1]*

[1]Department of Cell Biology & Anatomy, Arnie Charbonneau Cancer and Alberta Children's Hospital Research Institutes, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Article Info

Article Notes
Received: April 27, 2020
Accepted: May 29, 2020

***Correspondence:**
Dr. Ki-Young Lee, Department of Cell Biology and Anatomy, Cumming School of Medicine, University of Calgary, Calgary, AB, T2N 4N1, Canada; Telephone No: (403) 220-8723; Fax No: (403) 283-8727; E-mail: kylee@ucalgary.ca.

Keywords:
Sarcomatoid Transformation
Epithelial to Mesenchymal Transition

Mitochondrial Ca^{2+} concentration ($[Ca^{2+}]_{mt}$) regulates cellular functions as diverse as bioenergetic processes and apoptosis[1]. Ca^{2+} uptake by mitochondria via the mitochondrial Ca^{2+} uniporter (MCU) causes an increase in respiratory rate by activating dehydrogenases and electron carriers required for ATP production[2]. However, prolonged accumulation of mitochondrial Ca^{2+} results in sustained opening of the mitochondrial permeability transition pore (mPTP) which causes cell death[3]. In fact, mPTP is a Ca^{2+}-dependent and cyclosporin A-sensitive large conductance channel in the inner mitochondrial membrane (IMM). It plays a role in mitochondrial Ca^{2+} homeostasis and other physiological as well as pathological functions[3]. Thus, although mPTP serves as a mitochondrial Ca^{2+} extrusion channel, prolonged mPTP opening induces increased production of reactive oxygen species (ROS), mitochondrial depolarization and caspase-mediated apoptosis[4,5].

Our previous studies in breast cancer cells demonstrate that Cdk5 depletion by siRNA triggers mPTP opening that leads to ROS increase, mitochondrial depolarization, mitochondrial fragmentation and intrinsic apoptosis. These events are accompanied by a rise in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$)[6]. These phenotypes were recapitulated in primary mouse embryonic fibroblasts (MEFs) from *Cdk5*$^{-/-}$ mice[7], which exhibit perinatal mortality (i.e. 64% die *in utero* and newborns are dead or weak and die within 12 hours after birth)[8]. Treatment of Cdk5-depleted breast cancer cells[6] or *Cdk5*$^{-/-}$ MEFs[7] with an mPTP inhibitor, cyclosporine A (CsA) or sanglifehrin A (SfA), reverses mPTP-mediated mitochondrial dysfunction and apoptosis[6], suggesting that Cdk5 acts as a modulator of mPTP opening[7].

Mitochondria associate with endoplasmic reticulum (ER) via the Cdk5-containing mitochondria-associated ER membrane (MAM). A MAM-targeting motif in Cdk5 has not been reported. However, since the Cdk5 activator, p35, contains an N-terminal myristoylation signal motif that allows targeting of the Cdk5/p35 complex to cellular membranes, we speculate that Cdk5 localizes to MAMs through p35. The versatile MAMs are fundamental for Ca^{2+} and lipid transfer between mitochondria and ER. Approximately 5 to 20% of mitochondrial surface is physically in contact with the ER, and contact distances range from 10 to 30 nm[9]. As the mitochondrial Ca^{2+} uptake machinery has low affinity to Ca^{2+}, MAM microdomains facilitate efficient 1,4,5-trisphosphate receptor (IP3R)-mediated Ca^{2+} transfer from the ER to the adjacent mitochondria[10]. Interestingly, loss of Cdk5 in MAMs significantly increases the number and lengths of ER-mitochondrial contact sites as well as the percentage of ER-mitochondria contact sites with a distance of <30 nm, leading to

increased Ca^{2+} transfer from the ER to the mitochondria, elevation of $[Ca^{2+}]_{mt}$ and subsequent mPTP opening[7]. The fact that mPTP opening due to Cdk5 loss is completely blocked by inhibition of either ER Ca^{2+} release with xestospongin c (XeC) or mitochondrial Ca^{2+} uptake with ruthenium red (RuR)[7] further supports our view that mPTP opening is regulated by *Cdk5*. Since the regulatory function of Cdk5 is mostly attributed to its kinase activity, whether such activity is required for Cdk5 control of mPTP opening is currently under investigation.

It is interesting that Cdk5 loss induces apoptosis in breast cancer cells[6] but not in *Cdk5*$^{-/-}$ MEFs[7]. Further analysis on how Cdk5 regulates ER-mitochondria tethering and intracellular Ca^{2+} signaling in normal and diseased conditions could provide clues on how loss of Cdk5 leads to mitochondria-associated apoptosis in cancer cells.

Acknowledgements

This work was supported by a grant from the NSERC (RGPIN/06270-2019) to KYL and an Alberta Cancer Foundation graduate studentship to SN.

Author contributions

SN drafted the manuscript. JLR and KYL critically revised the manuscript for important intellectual content and wrote the final version of the manuscript

Disclosure of conflicts of interest

The authors declare no competing financial interests.

References

1. Duchen MR. Mitochondria and calcium: from cell signalling to cell death. The Journal of physiology. 2000; 529 Pt 1: 57-68.
2. Finkel T, Menazza S, Holmstrom KM, et al. The ins and outs of mitochondrial calcium. Circulation research. 2015; 116(11): 1810-1819.
3. Rasola A, Bernardi P. The mitochondrial permeability transition pore and its involvement in cell death and in disease pathogenesis. Apoptosis : an international journal on programmed cell death. 2007; 12(5): 815-833.
4. Saotome M, Katoh H, Yaguchi Y, et al. Transient opening of mitochondrial permeability transition pore by reactive oxygen species protects myocardium from ischemia-reperfusion injury. American journal of physiology Heart and circulatory physiology. 2009; 296(4): H1125-1132.
5. Hausenloy D, Wynne A, Duchen M, et al. Transient mitochondrial permeability transition pore opening mediates preconditioning-induced protection. Circulation. 2004; 109(14): 1714-1717.
6. NavaneethaKrishnan S, Rosales JL, Lee KY. Loss of Cdk5 in breast cancer cells promotes ROS-mediated cell death through dysregulation of the mitochondrial permeability transition pore. Oncogene. 2018; 37(13): 1788-1804.
7. NavaneethaKrishnan S, Rosales JL, Lee KY. mPTP opening caused by Cdk5 loss is due to increased mitochondrial Ca(2+) uptake. Oncogene. 2020; 39(13): 2797-2806.
8. Ohshima T, Ward JM, Huh CG, et al. Targeted disruption of the cyclin-dependent kinase 5 gene results in abnormal corticogenesis, neuronal pathology and perinatal death. Proc Natl Acad Sci U S A. 1996; 93(20): 11173-11178.
9. Csordas G, Renken C, Varnai P, et al. Structural and functional features and significance of the physical linkage between ER and mitochondria. The Journal of cell biology. 2006; 174(7): 915-921.
10. Rizzuto R, Pinton P, Carrington W, et al. Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca2+ responses. Science. 1998; 280(5370): 1763-1766.