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Mitochondrial sirtuins in cancer

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Genet. Mol. Res. 20 (4): gmr33110
Received June 4, 2021
Accepted June 18, 2021
Published June 25, 2021

ABSTRACT. All living beings require energy and the ultimate source for this energy in eukaryotes are mitochondria – originally an organelle of bacterial origin and eventually incorporated into the cytoplasm. Mitochondrial bioenergetics and dynamics are essential for the maintenance of cellular and metabolic homeostasis and any imbalance can result in diseases such as cancer. The mitochondrial matrix is a vital site for many enzymes responsible for mitochondrial function. Three members of the sirtuin family (*SIRT3*, *SIRT4* and *SIRT5*) localize into the mitochondrial matrix and are, like all sirtuins, dependent on NAD+. They regulate various cellular processes such as cell cycle, gene expression, energy homeostasis and post translational processes, for example deacetylation, ADP-ribosylation, etc. Studies so far suggest that mitochondrial sirtuins (mtSirts) can act both as tumor promotor and suppressor, and therefore play contrasting roles in various cancers.

Key words: Mitochondria; Mitochondrial sirtuins; Cancer; Tumour suppressor; Tumour promoter

DESCRIPTION

The sirtuin family consists of seven members: SIRT1-7 which require nicotinamide adenine dinucleotide (NAD+) for their activity [1]. They localize into different compartments performing diverse functional roles. *SIRT1*, 6 and 7 localize in the nucleus, *Sirt2* in the cytoplasm and *SIRT3*, *4*, and *5* mostly in mitochondria. Intriguingly, both functionally and structurally all members are highly conserved [2]. Sirtuins belong to the class III family of histone deacetylase (HDAC) and can control the transcription of various genes [3]. In addition, they also perform various other post translational modifications (PTMs) using different acyl groups such as desuccinylation, demalonylation, decrotonylation, etc. to specific proteins and protein residues resulting in metabolic and biochemical regulation [4]. The three mitochondrial members of the sirtuin family (*SIRT3*, *SIRT4* and *SIRT5*) in addition to those above-mentioned processes perform an additional role in maintaining mitochondrial fitness, dynamics and metabolic regulation. Moreover, mitochondrial cell signaling is extremely important in the context of cancer as cancer cells require constant energy through mitochondria or glycolysis in order to grow and proliferate. Several studies suggested that mitochondrial sirtuins can act both as tumor promotors and suppressors in several cancers. Some of them are discussed below:

The role of *SIRT3* in cancer

SIRT3 is involved in various cancer entities, however, its role is controversial. In breast cancer, *SIRT3* expression levels are much lower than in normal tissue thereby activating the SRC/FAK signaling which enhances cancer progression through metastasis [5]. In contrast, *SIRT3* overexpression decreases Reactive Oxygen Species (ROS) and can influence the metabolic shift from glycolysis to oxidative phosphorylation (Oxphos) during aerobic respiration and thus acts as a tumor suppressor [6]. Furthermore, *SIRT3* can activate mitochondrial ATP synthase subunit ATP5O and enhance ATP production resulting in enhanced Oxphos [7]. In neuroblastoma, *SIRT3* is highly expressed and decrease of its levels increases mitochondrial membrane potential collapse through increase of ROS, suggesting *SIRT3* to be a tumor promotor [8]. In lung and liver cancer, *SIRT3* expression is downregulated and its exogenous overexpression suppressed the proliferation of liver cancer cells by activating the p53 pathway [9,10], In case of ovarian cancer, *SIRT3* levels are also low and overexpression of *SIRT3* reduces ovarian cancer cell proliferation [11], A similar mechanism has been reported in pancreatic cancer where decreased levels of *SIRT3* activate the malate-aspartate complex leading to higher production of ATP and thereby fueling the growth of cancer cells [12], In gastric cancer the role of *SIRT3* is contradictory as both elevated and decreased levels of *SIRT3* were reported [13,14]. In colorectal cancer, higher *SIRT3* levels deacetylate the serine hydroxymethyltransferase 2 (SHMT2), thereby enhancing serine consumption and cancer progression [15]. In prostate cancer, *SIRT3* performs as a tumor suppressor as its low expression facilitates the acetylation of mitochondrial acotinase 2 (ACO2) which activates lipogenesis and promotes prostate cancer growth [16]. In contrast to the above-described cancer species, in thyroid cancer and esophageal cancer, *SIRT3* levels are higher than in normal tissue. In the former, *SIRT3* activates the catenin pathway and in the latter *SIRT3* decreases the levels of p21 and BAX [17,18], Thus, in majority of the cancers *SIRT3* acts a tumor suppressor by influencing different mitochondrial and cellular processes and pathways while in some it can also act as a tumour promoter. However, there are still detailed studies required in order to identify the downstream targets.

The role of *SIRT4* in cancer

Lower *SIRT4* levels increase glycolysis activity supporting cancer cell proliferation and survival in various types of cancer cells including breast cancer cells [19], neuroblastoma [20] pancreatic [21] and liver cancer

[22]. In contrast, increasing *SIRT4* expression halted the growth of neuroblastoma cells through decreased ATP production [23] characterizing *SIRT4* as a tumor suppressor. On the other hand, in lung cancer, *SIRT4* levels are much higher than in normal cells. Jeong et al. demonstrated that *Sirt4* knockout mice develop lung cancer randomly through increased glutamine signaling [24] while in gastric cancer *SIRT4* acted as tumor suppressor. *SIRT4* levels were significantly lower and overexpression of *SIRT4* arrested the cell cycle checkpoint G1 in gastric cancer [21]. In both colorectal and prostate cancer, *SIRT4* expression levels were lower than in normal tissue. Over-expression of *SIRT4* inhibited glutamine metabolism in the former while in the latter it inhibited the expression of the mitochondrial inner membrane protein ANT2 [25] A similar mechanism was observed in thyroid cancer as well as in leukemia where overexpression of *SIRT4* inhibited glutamate dehydrogenase (GDH) and obstructed glutamine signaling leading to decreased proliferation of cancer cells [22]. Thus, *SIRT4* can also act as tumor suppressor and thereby hinder cancer cell proliferation.

The role of *SIRT5* in cancer

Contrasting to *SIRT3* and *SIRT4*, *SIRT5* levels are increased in breast cancer and neuroblastoma. They protect cells by decreasing apoptosis and ROS levels. In liver cancer, a study showed that *SIRT5* acted as tumor suppressor as it was downregulated and as a result *ACOX1* was succinylated and activated fueling cancer cells while another study demonstrated that *SIRT5* was upregulated which then activated E2F1, a cell cycle control check point protein [26]. Higher *SIRT5* levels were also observed in ovarian cancer which reduced ROS levels and promoted tumor progression. Similarly, in lung cancer higher *SIRT5* levels activated *NRF2* and *SOD1* leading to rapid tumor progression while the reverse mechanism was found in gastric cancer where lower *SIRT5* levels activated cyclin dependent kinase (CDK2) supporting cancer progression. Higher *SIRT5* expression was also observed in colorectal and prostate cancer. *SIRT5* demalonylated lactate dehydrogenase B (LDHB) and deglutarylated glutamate dehydrogenase 1 (GLUD1) [23] activating those enzymes resulting in a higher accumulation of lactate and glutamate which facilitated colorectal cancer growth. In prostate cancer *SIRT5* stimulated cyclin D1 and hijacked cell cycle processes and thereby promoted the proliferation of prostate cancer cells [27]. In renal cell carcinoma a higher level of *SIRT5* was found which desuccinylated succinate dehydrogenase (SDHA), a nuclearly encoded component of respiration complex II, supporting cancer development [28]. Taken together, *SIRT5* acts as a tumor promotor in most of the analysed cancer types.

CONCLUSION

Mitochondrial sirtuins (mtSirts) play a critical role in the mitochondrial and metabolic regulation of cellular homeostasis. mtSirts interact with various substrates that are responsible for cancer progression and thus a better understanding of the function and mechanisms of action of mtSirts can provide a deeper insight of their importance in cancer biology. Further research should explore both upstream and downstream targets of mtSirts which would better characterize their dual nature of being both “tumor activator” as well as “tumor promotor”. Furthermore, *via* these new insights mitochondrial sirtuins could pose novel molecular targets for cancer management.

REFERENCES

1. MICHAN, S. and SINCLAIR, D. (2007). Sirtuins in mammals: Insights into their biological function. *The Biochemical Journal*
2. Kupis, W., Pałyga, J. and Tomal, E (2016). The role of sirtuins in cellular homeostasis. *Journal of Physiology and Biochemistry*.
3. Fiorino, E., Giudici, M. and Ferrari. The sirtuin class of histone deacetylases: Regulation and roles in lipid metabolism. *IUBMB Life*
4. Teixeira, C. S. S., Cerqueira, N. M. F. S. A.). A Molecular Perspective on Sirtuin Activity. *IJMS*

5. Lee, J. J., van de Ven, R. A. H. and Zaganjor. Inhibition of epithelial cell migration and Src/FAK signaling by *SIRT3*. *Proc Natl*

6. Pinteric, M., Podgorski, Sobocanec and Popovic Hadzija. De novo expression of transfected sirtuin 3 enhances susceptibility of human MCF-7 breast cancer cells to hyperoxia treatment. *Free Radic Res*

7. Yang, W., Nagasawa, K., Münch, C. and Xu, Y. (2016). Mitochondrial Sirtuin Network Reveals Dynamic *SIRT3*-Dependent Deacetylation in Response to Membrane Depolarization. *Cell*

8. Zhang Meng, *SIRT3* Protects Rotenone-induced Injury in SH-SY5Y Cells by Promoting Autophagy through the LKB1-AMPK-mTOR Pathway.

9. Liu, Y., Liu, Y. L. and Cheng, W. The expression of *SIRT3* in primary hepatocellular carcinoma and the mechanism of its tumor suppressing effects.

10. Xiao K. (2013). *Sirt3* is a tumor suppressor in lung adenocarcinoma cells. *Oncology Reports*

11. Li, J., Yue, H. and Yu, H. (2019). Development and validation of *SIRT3*-related nomogram predictive of overall survival in patients with serous ovarian cancer. *J Ovarian Res*

12. Yang, H., Zhou, L., Shi, Q. and Zhao, Y et al. *SIRT3*-dependent GOT2 acetylation status affects the malate-aspartate NADH shuttle activity and pancreatic tumor growth. *EMBO J*

13. Cui, Y., Qin, L. and Wu, J. *SIRT3* enhances glycolysis and proliferation in *SIRT3*-expressing gastric cancer cells. *PLoS One*

14. Wang, L., Wang, W. Y., and Cao, L. P. (2015). *SIRT3* inhibits cell proliferation in human gastric cancer through down-regulation of Notch-1.

15. Wei, Z., Song, J.and Wang, G. (2018). Deacetylation of serine hydroxymethyl-transferase 2 by *SIRT3* promotes colorectal carcinogenesis. *Nat Commun*

16. Dessai, A. S., Dominguez, M. P. and Chen, U. (2021). Transcriptional repression of *SIRT3* potentiates mitochondrial aconitase activation to drive aggressive prostate cancer to the bone. *Cancer Research*

17. Wang, S., Chen, X., Zhang, Z., and Wu, Z et al. MicroRNA-1225-5p inhibits the development and progression of thyroid cancer via targeting sirtuin.

18. Yang, M., Yang, C., and Pei, Y (2014). Effects of downregulation of *SIRT3* expression on proliferation and apoptosis in esophageal squamous cell carcinoma EC9706 cells and its molecular mechanisms. *Biomed Mater Eng*

19. Shi, Q., Liu, T.and Zhang, X. (2016). Decreased sirtuin 4 expression is associated with poor prognosis in patients with invasive breast cancer. *Oncol Lett*

20. Wang, Y., Guo, Y., Gao, J., and Yuan, X et al. (2018). Tumor-suppressive function of *SIRT4* in neuroblastoma through mitochondrial damage.

21. Hu, Q., Qin, Y., Ji, S and Xu, W. et al. (2019). UHRF1 promotes aerobic glycolysis and proliferation via suppression of *SIRT4* in pancreatic cancer. *Cancer Lett*

22. Chen, Z., Lin, J., Feng, S. and Chen, X et al. *SIRT4* inhibits the proliferation, migration, and invasion abilities of thyroid cancer cells by inhibiting glutamine metabolism.

23. Wang, Y. Q., Wang, H. L and Xu, J.et al, (2018). Sirtuin5 contributes to colorectal carcinogenesis by enhancing glutaminolysis in a deglutarylation-dependent manner. *Nat Commun*

24. Jeong, S. M., Xiao, C., Finley and L. W., Lahusen et al, (2013). *SIRT4* has tumor-suppressive activity and regulates the cellular metabolic response to DNA damage by inhibiting mitochondrial glutamine metabolism. *Cancer Cell*

25. Li, T., Li, Y., Liu, T and Hu, B. et al. (2020). Mitochondrial PAK6 inhibits prostate cancer cell apoptosis via the PAK6-*SIRT4*-ANT2 complex. *Theranostics*,

26. Chang, L., Xi, L and Liu, Y (2018). *SIRT5* promotes cell proliferation and invasion in hepatocellular carcinoma by targeting E2F1. *Mol Med Rep*,

27. Guan, J., Jiang, X., Gai, J. and, Sun, X.et al. (2020). Sirtuin 5 regulates the proliferation, invasion and migration of prostate cancer cells through acetyl-CoA acetyltransferase 1. *Journal of Cellular and Molecular Medicine*.

28. Ma, Y., Qi, Y., Wang, L and Zheng, Z.et al. (2019). *SIRT5*-mediated SDHA desuccinylation promotes clear cell renal cell carcinoma tumorigenesis. *Free Radic Biol Med*