

Mitochondrial Shaping Protein Mitofusin 2: Will a Paradoxical Molecule become a Reliable Cancer Therapeutic Target?

Antonella Cormio*

Department of Biosciences, Biotechnology and Biopharmaceutics, University of Bari, Bari, Italy

Corresponding author: Dr. Cormio Antonella, Department of Biosciences, Biotechnologies and Biopharmaceutics, University of Bari, Via Orabona, 4, 70125, Bari, Italy, Tel: +390805443377; E-mail: antonella.cormio@uniba.it

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Introduction

The past decade has witnessed an explosion of knowledge regarding how mitochondrial shape and dynamics impact mitochondrial function and their role in several diseases including cancer.

Mitochondrial shape can shift between small, fragmented units and larger networks of elongated mitochondria by means of coordinated fission and fusion processes [1]. Fusion is mediated by mitofusin-1 (Mfn1) and mitofusin-2 (Mfn2) proteins in the outer mitochondrial membrane and by optic atrophy 1 (Opa1) protein in the inner mitochondrial membrane. Fission is mediated by cytosolic dynamin related protein 1 (Drp1) and mitochondrial fission1 protein (Fis1) [1]. Mfn2 is also present in the endoplasmic reticulum (ER) and controls ER morphology and its tethering to mitochondria [2].

Mitochondrial dynamics is highly integrated with mitochondrial autophagy (mitophagy), with which it plays a role in regulating mitochondrial quality control. Upon fission, mitochondria can be segregated into polarized and depolarized daughter mitochondria. While polarized daughter mitochondria can undergo fusion, depolarized mitochondria are targeted by mitophagic proteins to degradation [3,4]. Mitophagy promotes turnover of dysfunctional mitochondria that would otherwise hamper the cell homeostasis [5,6].

It has been reported that Mfn2 depletion induces mitochondrial dysfunction [7-10] leading to a decrease of: 1) mitochondrial membrane potential; 2) cellular oxygen consumption; 3) oxidation of glucose, pyruvate, and fatty acids; 5) expression of mitochondrial respiratory complexes subunits with consequent decrease in their enzymatic activity.

Mfn2 is also involved in cell cycle [11], cell proliferation [12] and in apoptosis [13]. Mfn2 overexpression increases the mitochondrial Bax/Bcl-2 ratio thus resulting into a pro-apoptotic effect [13] and depletion of DRP1 causes increased apoptosis in human colon cancer cells [14]. Altered mitochondrial dynamics including a reduced Mfn2 expression were therefore expected in cancer cells; as a matter of fact, Mfn2 expression has been found to be significantly lower in

bladder cancer, hepatocellular carcinoma, endometrial cancer and breast cancer than in nearby non-neoplastic tissues [15-18].

In breast cancer patients reduced Mfn2 expression is also associated with poor prognosis; moreover, Mfn2 knockout promotes cell viability, colony formation, and invasion of cancer cells in vitro and in vivo through inhibition of mTORC2/Akt signaling [18].

Patients with hepatocellular carcinoma (HCC) frequently show loss of heterozygosity in the Mfn2 gene [19] and a significant correlation between reduced Mfn2 expression and poorer prognosis [20]. Conversely, Mfn2 overexpression induces in hepatocellular carcinoma cells apoptosis, reduced mitochondrial membrane potential ($\Delta\Psi_m$), reduced endoplasmic reticulum (ER) calcium ion Ca^{2+} concentrations, and elevated intracellular reactive oxygen species (ROS) and mitochondrial Ca^{2+} concentrations [20]. It was also demonstrated that Mfn2 is repressed by microRNA miR-761, which was found to be upregulated in hepatocellular carcinoma, and that the inhibitor of miR-761 repressed tumor growth and metastasis both in vivo and in vitro by upregulating Mfn2 [21].

Finally in bladder cancer, Mfn2 overexpression was found to inhibit cell proliferation by arresting the transition of the cell cycle from the G1 to S phase, and to induce apoptosis by upregulating active caspase-3 and increasing cleavage of poly (ADP-ribose) polymerase PARP [15]. Mfn2 therefore seems to be a potential tumor suppressor gene that promotes apoptosis and inhibits the proliferation of cancer cells; this makes Mfn2 a promising therapeutic target. Unfortunately, the finding that other cancers exhibit Mfn2 overexpression has cooled down some enthusiasm. In patients with lung cancer Mfn2 was overexpressed and its knockdown interrupted cell cycle distribution, inhibited cell proliferation and cell invasion [22]. Similarly, in patients with gastric cancer an overexpression of Mfn2 was found to be positively associated with depth of invasion, stage and vascular invasion, resulting in lower survival rate and invasion [significantly lower disease-free survival rate; moreover, Mfn2 knockdown suppressed cell proliferation] [23]. The role of Mfn2 seems to be controversial in gastric cancer since in a

previous study a decrease of Mfn2 expression was reported in tumor tissue than in nearby non-neoplastic [24].

A potential explanation for this paradoxical effect of Mfn2 in different cancer types has come out from microarray analysis showing that Mfn2 knockdown has opposite impact on different oncogenes such as RAP1A, RALB and ITGA2 and therefore may have an anti- or a pro-tumor effect depending on specific environmental conditions and type of tumor [22].

Research is therefore moving towards molecules that can modulate Mfn2 expression. Melatonin, resveratrol, metformin, MitoQ and SS31 have been shown to increase Mfn2 expression and mitochondrial fusion restoring mitochondrial function; conversely, doxorubicin has been shown to decrease Mfn2 expression and stimulate fission [25]. Therefore, these molecules could represent new drugs to treat several diseases characterized by altered mitochondrial dynamics, including cancer.

In conclusion, Mfn2 is an example of the complexity of cancer biology, whereby the same molecule can exert a pro- or anti-tumor effect depending on type of tumor and microenvironmental conditions. Independently its paradoxical behavior, Mfn2 has shown to play a relevant role in cancer development and progression as well as to represent an extremely interesting potential therapeutic target.

References

- Mishr P, Chan DC (2016) Metabolic regulation of mitochondrial dynamics. *J Cell Biol* 212: 379e387.
- de Brito OM, Scorrano L (2008) Mitofusin 2 tethers endoplasmic reticulum to mitochondria. *Nature* 456: 605-610.
- Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, et al. (2008) Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *EMBO J* 27: 433-446.
- Arnoult D, Rismanchi N, Grodet A, Roberts RG, Seeburg DP, et al. (2005) Bax/Bak-dependent release of DDP/TIMM8a promotes Drp1-mediated mitochondrial fission and mitoptosis during programmed cell death. *Curr Biol* 15: 2112-2118.
- Chen H, Chomyn A, Chan DC (2005) Disruption of fusion results in mitochondrial heterogeneity and dysfunction. *J Biol Chem* 280: 26185-26192.
- Gomes LC, Di Benedetto G, Scorrano L (2011) During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. *Nat Cell Biol* 13: 589-598.
- Bach D, Pich S, Soriano FX, Vega N, Baumgartner B, et al. (2003) Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism. A novel regulatory mechanism altered in obesity. *J Biol Chem* 278: 17190-17199.
- Chen H, Chomyn A, Chan DC (2005) Disruption of fusion results in mitochondrial heterogeneity and dysfunction. *J Biol Chem* 280: 26185-26192.
- Loiseau D, Chevrollier A, Verny C, Guillet V, Gueguen N, et al. (2007) Mitochondrial coupling defect in Charcot-Marie-Tooth type 2A disease. *Ann Neurol* 61: 315-323.
- Pich S, Bach D, Briones, Liesa PM, Camps M, et al. (2005) The Charcot-Marie-Tooth type 2A gene product, Mfn2, up-regulates fuel oxidation through expression of OXPHOS system. *Hum Mol Genet* 14: 1405-1415.
- Mitra K, Wunder C, Roysam B, Lin G, Lippincott-Schwartz J (2009) Organization of the mitochondrial network is sophisticatedly controlled across the different phases of the cell cycle. A hyperfused mitochondrial state achieved at G1-S regulates cyclin E buildup and entry into S phase. *Proc Natl Acad Sci USA* 106: 11960-11965.
- Chen KH, Dasgupta A, Ding J, Indig FE, Ghosh P, et al. (2014) Role of mitofusin 2 (Mfn2) in controlling cellular proliferation. *FASEB J* 28: 382-394.
- Guo X, Chen KH, Guo Y, Liao H, Tang J, et al. (2007) Mitofusin 2 triggers vascular smooth muscle cell apoptosis via mitochondrial death pathway. *Circ Res* 101: 1113-1122.
- Inoue-Yamauchi A, Oda H (2012) Depletion of mitochondrial fission factor DRP1 causes increased apoptosis in human colon cancer cells. *Biochem Biophys Res Commun* 421: 81-85.
- Jin B, Fu G, Pan H, Cheng X, Zhou L, et al. (2011) Anti-tumour efficacy of mitofusin-2 in urinary bladder carcinoma. *Med. Oncol* 28: S373-S380.
- Wang W, Lu J, Zhu F, Wei J, Jia C, et al. (2012) Pro-apoptotic and anti-proliferative effects of mitofusin-2 via Bax signaling in hepatocellular carcinoma cells. *Med Oncol* 29: 70-76.
- Cormio A, Musicco C, Gasparre G, Cormio G, Pesce V, et al. (2017) Increase in proteins involved in mitochondrial fission, mitophagy, proteolysis and antioxidant response in type I endometrial cancer as an adaptive response to respiratory complex I deficiency. *Biochem Biophys Res Commun* 41: 85-90.
- Xu K, Chen G, Li X, Wu X, Chang Z, et al. (2017) MFN2 suppresses cancer progression through inhibition of mTORC2/Akt signaling. *Sci Rep* 7: 41718.
- Qu L, Chen H, Wang G, Wei J (2013) Frequent losses of heterozygosity in the mitofusin 2 gene in hepatocellular carcinoma: their relationship to clinicopathological features. *Tumori* 99: 697-701.
- Wang W, Xie Q, Zhou X, Yao J, Zhu X et al. (2015) Mitofusin-2 triggers mitochondria Ca²⁺ influx from the endoplasmic reticulum to induce apoptosis in hepatocellular carcinoma cells. *Cancer Lett* 358: 47-58.
- Zhou X, Zhang L, Zheng B, Yan Y, Zhang Y, et al. (2016) MicroRNA-761 is upregulated in and regulates tumorigenesis by targeting Mitofusin-2. *Cancer Sci* 107: 424-432.
- Lou Y, Li R, Liu J, Zhang Y, Zhang X, et al. (2015) Mitofusin-2 over-expresses and leads to dysregulation of cell cycle and cell invasion in lung adenocarcinoma. *Med Oncol* 32: 132.
- Fang CL, Sun DP, Chen HK, Lin CC, Hung ST, et al. (2017) Overexpression of mitochondrial GTPase MFN2 represents a negative prognostic marker in human gastric cancer and its inhibition exerts anti-cancer effects. *J Cancer* 8: 1153-1161.
- Zhang GE, Jin HL, Lin XK, Chen C, Liu XS, et al. (2013) Anti-tumor effects of mfn2 in gastric cancer. *Int J Mol Sci* 14: 13005-13021.
- Ong SB, Kalkhoran SB, Hernández-Reséndiz S, Samangouei P, Ong SG, et al. (2017) Mitochondrial-Shaping Proteins in Cardiac Health and Disease - the Long and the Short of It! *Cardiovasc Drugs Ther* 31: 87-107.