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Review

A detailed review of pharmacology of MFN1 (mitofusion-1)-mediated mitochondrial dynamics: Implications for cellular health and diseases

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ABSTRACT

The mitochondria are responsible for the production of cellular ATP, the regulation of cytosolic calcium levels, and the organization of numerous apoptotic proteins through the release of cofactors necessary for the activation of caspases. This level of functional adaptability can only be attained by sophisticated structural alignment. The morphology of the mitochondria does not remain unchanged throughout time; rather, it undergoes change as a result of processes known as fusion and fission. Fzo in flies, Fzo1 in yeast, and mitofusins in mammals are responsible for managing the outer mitochondrial membrane fusion process, whereas Mgm1 in yeast and optic atrophy 1 in mammals are responsible for managing the inner mitochondrial membrane fusion process. The fusion process is composed of two phases. MFN1, a GTPase that is located on the outer membrane of the mitochondria, is involved in the process of linking nearby mitochondria, maintaining the potential of the mitochondrial membrane, and apoptosis. This article offers specific information regarding the functions of MFN1 in a variety of cells and organs found in living creatures. According to the findings of the literature review, MFN1 plays an important part in a number of diseases and organ systems; nevertheless, the protein's function in other disease models and cell types has to be investigated in the near future so that it can be chosen as a promising marker for the therapeutic and diagnostic potentials it possesses. Overall, the major findings of this review highlight the pivotal role of mitofusin (MFN1) in regulating mitochondrial dynamics and its implications across various diseases, including neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes. Our review identifies novel therapeutic targets within the MFN1 signaling pathways and underscores the potential of MFN1 modulation as a promising strategy for treating mitochondrial-related diseases. Additionally, the review calls for further research into MFN1′s molecular mechanisms to unlock new avenues for clinical interventions, emphasizing the need for targeted therapies that address MFN1 dysfunction.

1. Introduction to mitochondrial fusion

Mitochondria are subcellular dynamic organelles that experience migration and morphological fluctuations as observed by the Time-lapse microscopic examination of living cells {Bereiter-Hahn, 1994 #263}{Bereiter-Hahn, 1994 #262}{Bereiter-Hahn, 1994 #261}{Bereiter-Hahn, 1994 #261}(Bereiter-Hahn and Vöth, 1994, Nunnari et al., 1997, Rizzuto et al., 1998). The variations in mitochondrial shape occur due to the developmental stages, metabolic conditions, and environmental stimuli (Shaw and Nunnari, 2002, Karbowski and Youle, 2003, Youle and Van Der Bliek, 2012, Mishra and Chan, 2016). Defective mitochondria can cause various degenerative diseases in humans. Encephalomyopathies, neuropathies myopathies, and many other disorders are linked with the mutated mitochondrial DNA. In most cases, clinical symptoms appear very late, as the proportion of mutant to wild-type mitochondrial DNA reaches a critical threshold depending on the energy requirements of that tissue (Graff et al., 1999). Studies on the influence of mutated mitochondrial DNA on different diseases in transgenic murine model depicts the protective effect against the outset of symptoms (Inoue et al., 2000, Nakada et al., 2001a). Electron microscopic analysis of individual cells having mutant and wild-type mitochondria shows that most of the mitochondria have the activity of cytochrome *C*. oxidase (Nakada et al., 2001a). These mutations in mice mitochondrial DNA (mtDNA) signify that the fusion process between mitochondria of different genotypes may give the protective mechanism to the cells from displaying disease phenotypes occurring due to the mtDNA mutation-induced mitochondrial dysfunction (Santel et al., 2003).

Mitochondria display a variety of morphologies in various cell types and also in the same cell with different conditions (Bereiter-Hahn and

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Vöth, 1994). Even the cells having a seemingly stable organization of mitochondrial tubules face continuous and frequent phases of mitochondrial fission and fusion, the processes that are opposite but in equilibrium and maintain the overall structure of mitochondria (Bereiter-Hahn and Vöth, 1994, Nunnari et al., 1997). In flies and yeast, the fusion event is regulated by transmembrane GTPase, Fzo, which is encoded by the nucleus (Chen et al., 2003). In *Drosophila*, fuzzy onions (Fzo) are particularly and transiently present in spermatids. Disturbance in Fzo expression blocks developmentally mediated fusion in post-meiotic spermatids and causes male sterility (Hales and Fuller, 1997). The absence of Fzo in budding yeast perturbs the highly organized and branched mitochondrial tubules of normal cells and leads to the formation of small spherical mitochondrial tubules. *Fzo*1Δ yeast make "petite" colonies that do not have a mitochondrial DNA (Hermann et al., 1998, Rapaport et al., 1998). Moreover, mating-related mitochondrial fusion is also disrupted. In humans, there are two Fzo homologues, mitofusin 1 and mitofusin 2, that have the capacity to change the structure of the mitochondria when they are overexpressed in cells (Santel and Fuller, 2001a, Rojo et al., 2002). In humans, DNA has two functional genes, with different expression pattern, encode MFN1 and MFN2. Surprisingly drosophila also possess two different genes encrypting fzo-GTPase proteins *fzo* and *dmfn*. *Fzo* protein is only expressed in male early spermatids, where it is involved in the excessive mitochondrial fusion for the differentiation of germ cells (Hales and Fuller, 1997). Contrary to *Fzo*, *dmfn* is widely present in different stages of development and in many tissues maintaining the equilibrium between fusion and fission processes in various cells (Hwa et al., 2002).

Human MFN1 protein is controlling the mitochondrial fusion in many human cells in the same way as Fzo protein in drosophila and Fzo1p protein in yeast is mediating fusion process. Highly expressed MFN1 in cultured cells causes the development of perinuclear grape-like array of mitochondria with large mitochondria present around the outward edge. In overexpressed MFN1 cells, large mitochondria with deformed internal structure appear when MFN1 causes the fusion of outer mitochondrial membrane (OMM) (Rapaport et al., 1998, Fritz et al., 2001) in adjacent mitochondria without affecting the inner mitochondrial membrane (Santel et al., 2003). Furthermore, mitofusin proteins exhibit two transmembrane regions passing over the OMM twice, with both C-terminal coiled-coil and N-terminal G domain facing the cytoplasm, where they interact with MFN family proteins or other proteins present on the exterior of neighboring mitochondria (Fritz et al., 2001). Mixing of matrix contents through inner mitochondrial membrane fusion is carried out by other proteins and factors. The highly expressed human MFN1-mediated fusion event in mammalian cells relies on the GTPase domain similar to yeast Fzo1p and Drosophila Fzo. Mutation at K88 residue to T in the G1 G domain of mitofusin 1 diminishes the activity of $MFN1^{K88T}$ to construct the mitochondrial tubular network and grape-like array of elongated mitochondrial tubules. The G1 is the conserved part of P-loop of Ras (rat sarcoma virus) (Bourne et al., 1991) and other GTPase family members that makes the crucial portion of nucleotide binding pocket communicating with α/β phosphates of GDP/GTP. This K residue is well conserved in GTPase superfamily and ATPase motor proteins like kinesins and myosin. The ε-amino group of lysine, K16, with positive charges in Ras sustains GTP phosphates by making ionic bonding with γ- and β-phosphates of nucleotide (Maegley et al., 1996). The deficiency of complementary K residue in the mutant $MFN1^{K88T}$ may alter the binding of guanine nucleotide leading to the decreased hydrolysis of GTPase activity. Thus, mutation of K88 to T in human mitofusin 1 inhibits the capability of highly expressed MFN1 for constructing the enlarged mitochondria and suggests that MFN1-induced mitochondrial fusion relies on the GTPase cycle with the possibility that fusion event is controlled by other proteins, much as guanine nucleotide exchange factor and GTPase activating protein, that maintain the activity cycles of various GTPases. On the other side, high expression of mutated MFN1 protein on different G subdomain ($MFN1^{T109A}$) shows different mitochondrial morphology. Residue T109 is present in the G2 motif of MFN1. It is found that mutation of human MFN1 at G2 motif threonine, $MFN1^{T109A}$, acts as dominant negative upon its overexpression in cultured cells (Santel, Frank et al. 2003). Cells having this mutant form of MFN1 express small mitochondria sharing the same picture as is observed in the deficiency of yeast Fzo1p (Hermann and Shaw, 1998). The mechanism through which $MFN1^{T109A}$ intervene in the activity of endogenous mitofusin in transfected cells is based on the action cycle of GTPase group members.

Many GTPase family members depend on the communication with guanine exchange factor to liberate the bound GDP which permit GTP to get into the binding pocket after every action cycle. Observation of GTPase EF-Tu suggests that the protein faces an empty transient phase, not having nucleotide, but still attached to its guanine exchange factor EF-Ts (Romero et al., 1985). Attachment of GTP then permits the liberation of EF-Ts, probably because of the striking change in GTPase conformation upon the binding of GTP. If a matching GTPase cycle having guanine exchange factor functions as a crucial part of mitofusin in the fusion process, then high expressions of $MFN1^{T109A}$ may work as a dominant negative by titrating out guanine exchange factor. However, in the absence of crucial G2 threonine residue, mutated $MFN1^{T109A}$ may not go through the GTP binding-mediated conformational change for the release and use of guanine exchange factor by endogenous mitofusin protein. This causes the failure of the fusion process with unbalanced fission operation leading to the aggregation of small mitochondria as seen in yeast having a deficiency of Fzo1p (Santel et al., 2003). Thus, the normal structure of mitochondria in mammalian cells is handled by a critical balance between DRP-induced mitochondrial fission and mitofusin-induced mitochondrial fusion. As co-expression of $DRP1^{K38A}$, an interfering dominant type of DRP1 (Smirnova et al., 2001), with MFN1 causes the generation of interconnected mitochondrial tubules of OMM. Moreover, co-expression of mutated $MFN1^{T109A}$ with dominant negative $DRP1^{K38A}$ blocks the mitochondrial fission and leads to the formation of mitochondria with modified morphology as investigated in cells having $DRP1^{K38A}$ alone or with WT MFN1 and MFN2 (Santel and Fuller, 2001b). These results are similar to the condition of dnm1Δ/fzo1-1 double mutation in yeast, where mitochondrial structure resembles to that analyzed in dnm1 Δ cells (Bleazard et al., 1999). Modified mitochondrial morphology is also observed in mitofusin-mutant mouse embryonic fibroblasts having $DRP1^{K38A}$ in comparison with repaired morphology in mitofusin-deleted cells protected by epitope-tagged MFN (Chen et al., 2003).

The human mitofusin proteins, MFN1 and MFN2, have different behaviors relating to their actions on mitochondrial morphology following high expression in the cell line. High expression of MFN1 is sufficient for GTPase-dependent mitochondrial fusion leading to the development of large mitochondria along the outward perinuclear tubular clusters. Contrary to that, the GTPase-dependent action of high expression of MFN2 is best studied in cells also having the high expression of $DRP1^{K38A}$. In contrast, a higher level of MFN2 makes the mitochondrial clusters rely on the C-terminal coiled-coil region of MFN2 (Smirnova et al., 2001). OPA1 also controls the shape of mitochondrial tubule but genetic analysis shows that OPA1-induced fusion process is dependent on mitofusin 1 not mitofusin 2. In MFN1-deleted cells, OPA1 is unable to stimulate mitochondrial fusion. This deficiency is recovered by reintroducing MFN1 not MFN2, implying that outer mitochondrial membrane MFN1 is crucial partner of OPA1. Furthermore, MFN1 cannot stimulate mitochondrial elongation in the ablation of OPA1. Thus, MFN1 and OPA1 are functionally dependent on each other (Cipolat et al., 2004). Mahogunin Ring Finger-1, MGRN1, is an ubiquitin ligase that interacts with and ubiquitinates MFN1 through K63 linkages. The mitochondrial tethering in forming MFN1 complex is not dependent on MGRN1-induced ubiquitination. Nevertheless, successful fusion process needs development of higher oligomers of mitofusin-1 which is dependent on intact HR regions of MFN1, GTPase activity and MGRN1-induced ubiquitination. After ubiquitination, proteasomal activities of MFN1 finishes the fusion process (Mukherjee and Chakrabarti, 2016).

Transmembrane domain (TM), consists of two helices named TM1 and TM2, plays a critical role in the tubular localization of mitofusin 1, the same as of mitofusin 2, and anchoring of the outer mitochondrial membrane (Sinha and Aradhyam, 2019). In hypoxic condition, mitochondrial elongation is controlled through SIRT1-induced mitofusin-1 deacetylation and accumulation, as nicotinamde, a blocker of SIRT deacetylases, causes degradation of MFN1 whose acetylation is necessary for protein stability. It is the TIP60 that reduces the level of mitofusin 1. SIRT1 deacetylase knockdown reduces the level of MFN1 while overexpression increases its level (Oanh et al. 2017). MFN1 stimulates apposing lipid vesicle-membrane adhesion. GDP-bound state of mitofusin 1 maintains adhesion forces following GTP hydrolysis. On the other hand, GDP:AlF_4^-, imitates GTP transition state, does not mediate membrane adhesion. The adhesion strength, however, depends on the MFN1 concentration via interactive binding mechanism because of the flexibility of lipid membranes (Tolosa-Díaz et al., 2020).

2. Search strategy

Our comprehensive literature search strategy was designed to capture the broad spectrum of research on mitofusin (MFN1) and its implications in various diseases. We systematically searched databases including PubMed, Web of Science, and Google Scholar using a combination of keywords such as 'MFN1′, 'mitofusin', 'mitochondrial dynamics', 'mitochondrial dysfunction', and disease-specific terms (e.g., 'neurodegenerative diseases', 'cardiovascular diseases', 'metabolic disorders'). The search was limited to articles published in English from January 2000 to December 2023 to ensure the inclusion of the most recent and relevant findings. Studies were selected based on their relevance to MFN1′s role in health and disease, with a focus on original research articles, reviews, and meta-analyses. Exclusion criteria included studies not directly related to MFN1, articles without full text available, and duplicate publications. The initial search results were screened by titles and abstracts, followed by a full-text review to determine their inclusion in our analysis. Discrepancies in study selection were resolved through discussion among the research team, ensuring a thorough and unbiased review of the literature on MFN1.

3. Structure of Mfn1

Mitochondrial fusion is an important subcellular process for the physiological activities of mitochondrial tubules including the regulation of tubular membrane potential and complementation of distorted mitochondrial DNAs (Nakada et al., 2001b, Chan, 2012, Friedman and Nunnari, 2014). Mitofusins are dynamin-associated GTPases that have an important part in tubular fusion (Santel and Fuller, 2001b, Praefcke and McMahon, 2004). They are attached to the OMM and fuse with the adjacent mitochondria through GTP hydrolysis and combined oligomerization (Rojo et al., 2002, Chen et al., 2003, Koshiba et al., 2004). The mechanism behind this process is still unknown. The crystal structure (Fig. 1) of human mitofusin 1 has the helical domain and the GTPase domain in various stages of GTP hydrolysis. Its helical domain consists of different elements from widely scattered sequence areas of engineered mitofusin 1 and is similar to the neck of a bacterial dynamin-like protein. The structures disclose peculiar characteristics of the catalytic body and tell the mechanism through which the binding of GTP produces conformational changes to assist the dimerization of the GTPase domain in the transition state. Disorganization of this dimerization diminishes the role of MFN1 in mitochondrial fusion. It is also observed that the conserved aspartate fraction trigger influences the elongation of mitochondria in MFN1, possibly through the rearrangement of the GTP-loading-associated domain. $MFN1_{IM}$, a human internally modified MFN1, consists of a G (GTPase) domain with residues from 75 to 336 and a four-helix-bundle. (Cao et al., 2017). HR1 (Heptad repeat region 1) is the region that affects the docking ability and oligomerization of MFN1 along with its mutation, showing the possibility that it plays a critical role in MFN1-mediated tubular tethering. T562 and T564 are the regions that lie in the HR1 domain, presenting the sites where MFN1 is phosphorylated (Pyakurel et al., 2015). HR2 (Heptad repeat region 2) domain from 660 to 735 is also essential for fusogenic activity as disrupted HR2 structure abrogates MFN1-controlled mitochondrial fusion. It induces MFN oligomerization by bringing together antiparallel dimeric coiled-coil (Koshiba et al., 2004).

4. MFN1 and apoptosis

MFN1 phosphorylated by Mitogen-activated protein, MAP, cascade component extracellular-signal-regulated kinase, ERK, modulates its role in mitochondrial fusion and cellular apoptosis. Phosphorylation of MFN1 takes place at the atypical site of ERK in its HR1 domain. This site is necessary for mitofusin 1-mediated tubular elongation and control of cell death by MEK/ERK. A mutant imitating constitutive phosphorylation of MFN1 shows less effectiveness in mitochondrial tethering and oligomerization but binds to the pro-apoptotic protein Bak, *Bcl-2* homologous antagonist/killer, to stimulate its activation and apoptosis. Also, neuronal cell death after the activation of MEK/ERK activation and oxygen-glucose destitution requires intact MFN1 phosphorylated at T562 (Pyakurel et al., 2015). Mitochondrial damage caused by the permeabilization of OMM with the release of apoptotic factors leads to cell death. Mitochondrial fragmentation is decreased in Bak-deleted murine embryonic fibroblasts, primary neurons form the cortical region of Bak-deleted mouse and baby mouse renal cells. Reconstitution of Bak, although less effective, into Bak/Bax knockout cells reestablishes mitochondrial fragmentation. Bak communicates with both mitofusin 1 and mitofusin 2, but during cell death, it disconnects from mitofusin 2 and increases its connection with mitofusin 1 (Brooks et al., 2007). Endonuclease G takes an active part in controlling reactive oxygen species-induced apoptotic DNA fragmentation. Its release from mitochondria is inhibited by MFN1 and stimulated by DRP1 (Li et al., 2010). Mitofusins take part in the translocation to mitochondria and conformational activation of Bax for apoptosis-linked mitochondrial changes. MFN1, not MFN2, blocks mitochondrial N-terminal activation of Bax during apoptosis. During cell death, the knockdown of mitofusin 1 promotes oligomerization of Bax-activated form on mitochondrial tubules. Surprisingly, mitochondrial translocation of Bax is not blocked by MFN1 in apoptosis, it is N-terminal activation that is inhibited by MFN1 (Ryu et al., 2012).

5. MFN1 and the circulatory system

Investigation on cardiac cell-specific mitofusin1 knockout (MFN1 KO) reveals that deletion of MFN1 results in a profound shift in the fission and fusion balance, indicated by the detection of small and round-shaped mitochondria in MFN1 KO cardio-myocytes (Papanicolaou et al., 2012). However, mice have normal left-ventricular output and isolated cardiac mitochondria express normal respiratory reserves. MFN1 knockout hearts are working well detected by ECG and no cardiac hypertrophy is observed, whereas MFN2 knockout hearts are slightly hypertrophied, depicting that MFN2 KO hearts have enlarged mitochondria. This hypertrophy occurs due to the intracellular load on the

Fig. 1. Structure of MFN1, G domain means GTPase domain; T means transmembrane region; HR1 and HR2 mean (Heptad repeat region1 and 2).

myocytes in the presence of exceptionally enlarged mitochondria, as elongated mitochondria change the mechanical characteristics of cardiac muscle cells (Kaasik et al., 2010). These cardiac cells are secured from depolarization of mitochondria and have a good survival rate when exposed to hydrogen peroxide-induced reactive oxygen species production, expressing that MFN1 depletion protects myocytes from ROS-mediated mitochondrial dysfunction. In vitro experiments show the weak response of MFN1 KO tubules to experience peroxide-mediated opening of mitochondrial permeability transition pores. These observations assume that mitochondrial fragmentation is not enough to bring about myocardial dysfunction or initiate cardiac cell death (Papanicolaou et al., 2012). MFN1-deleted muscle cells have smaller mitochondria compared to enlarged mitochondria in MFN2-deficient cells due to the possibility of dependence of tubular size on the relative GTPase activity of mitofusin in the cells. An initial study on finding out the difference between mitofusins shows remarkable variations in the case of binding and hydrolyzing GTP with MFN1 expresses eight times more GTPase activity compared to MFN2 (Ishihara et al., 2004). MFN1 communicates with mutant MFN2 for the formation of a fusion-competent network, however, endogenous MFN2 does not have this ability, exhibiting that MFN1 is more active in the process of mitochondrial fusion than MFN2 (Detmer and Chan, 2007). Because heterotypic communication between mitofusin homologs is suitable for fusion event than homotypic communication (Hoppins et al., 2011). NFATc3 (also called as NFAT4) the homolog of NFAT, nuclear factor of activated T cells, is produced by NFATc3 gene (Ho et al., 1995) and is expressed in large amounts in heart muscles (van Rooij et al., 2002). In heart muscle cells, it activates mitochondrial fission, changes mitochondrial shape and structure, and cell death in myocardial infarction (Wang et al., 2015). Its signaling is also important in the progress of cardiac hypertrophy (Zhang et al., 2018a, Chao et al., 2019). miR-153-3p is a pro-hypertrophic element in regulating cardiac muscle cell mitochondrial dynamics whose transcription level is upregulated by NFATc3. Its level is upregulated in response to hypertrophy and it stimulates mitochondrial fission which is accompanied by the downregulation and post-transcriptional depression of MFN1. Inhibiting either NFATc3 or miR-153-3p increases the level of mitofusin 1 which reduces the myocardial dysfunction in the hypertrophy (Wang et al., 2020). The transcription and translation of MFN1 in the heart are higher than that of the MFN2 (Santel et al., 2003). MFN1 level is decreased in apoptotic response while micro-RNA, miR-140 suppresses its level by controlling endonuclease G, presenting that knockdown of miR-140 can decrease the size of myocardial infarct in animals. The blockade of MFN1 by apoptosis-inducing agents causes mitochondrial membrane permeabilization with the subsequent release of mitochondrial apoptotic proteins into cytosol. Endonuclease G is a mitochondrial protein in cellular physiology, but it can be translocated to the nucleus after releasing from mitochondria and degrades the DNA (Li et al., 2014a). Phosphorylation of MFN1 by βIIPKC causes the partial loss of GTPase activity leading to the abundance of dysfunctional and fragmented mitochondria in cardiac failure (Ferreira et al., 2019a). In the repairmen of cardiac microcirculation after myocardial infarction, long non-coding RNA Malat1 functions as endogenous RNA for miR-26b-5p and makes a connection with MFN1 to streamline endothelial functions and mitochondrial dynamics. In hypoxic conditions, Silencing of MFN1 reduces the cardiac microvascular endothelial cell viability, migration ability, proliferation ability, NO synthesis, and tube formation activity. However, overexpression of MFN1 reverses the endothelial malfunction and reduces the reactive oxygen species, GSSG and MDA, and increases the level of glutathione and activities of Mn-SOD and t-SOD, indicating the role of mitofusin 1 in reducing cellular ROS (Chen et al., 2021). “Non-responders” are the heart failure patients who show no response to established treatment. It is investigated that MFN1 expression and size of mitochondria in cardio-myocytes are significantly decreased in these patients. A study on cardiac-specific MFN1-deleted mice uncovers that systolic function is reduced in these mice while mitochondrial alteration is increased. In vitro analysis reveals the negative control of MFN1 expression by βAR-cAMP-PKA-miR-140-5p signaling, causing the remarkable decrease in tubular respiration of neonatal rat ventricular myocytes. The level of miR-140-5p is also enhanced in non-responders and mitofusin 1 is the biomarker of cardiac failure (Hsiao et al., 2021). MnTBAP, manganese-III-tetrakis (4-benzoic acid) porphyrin, expresses a significant angiogenic effect in endothelial cells by stimulating P13K/Akt/eNOS pathway that is dependent on MFN1 (Zhou et al., 2015). Nitrite prevents growth factor-activated proliferation of RASMC, rat aortic smooth muscle cell, which is dependent on MARCH 5 and causes upregulation of MFN1 and cell cycle arrest. Orally administered nitrite attenuates neointimal hyperplasia in mitofusin-1 knock-out mice, as MFN1 knockout mice have a significant increase in neointimal hyperplasia in restenosis (Reyes, 2020). Pregestational diabetes can cause congenital heart defects in the newborn. Maternal diabetes increases the level of miR-140 and downregulates its target protein MFN1 in cardio-myocytes. miRNA-140 is attached to the 3’ untranslated area of mitofusin-1 mRNA, causing its degradation, mitochondrial fragmentation and cardiac cell apoptosis. Moreover, deletion of JNK2 diminishes the increase in the level of miR-140, and restores MFN1 and mitochondrial fusion, indicating that JNK2/miRNA-140/MFN1 signaling takes an active part in maternal diabetes-mediated fusion impairment and congenital heart defect (Chen et al., 2018). The molecular effects of MFN1 on the cardiovascular system are shown in Fig. 2.

6. MFN1 and cancer

Mitochondrial fragmentation induced by the inhibition of MFN1 influences tumorigenesis of hepatocellular carcinoma (HCC). FUN14 domain containing 2, FUNDC2, is a mitochondrial protein that is elevated in primary murine hepatic tumors and 40 % of human HCC. Its increased level is inversely associated with patient survival as its inhibition blocks mouse hepatic tumorigenesis. Its amino-terminal domain interrelates with the G domain of MFN1, leading to the inhibition of MFN1-induced fusogenic activity of Outer Mitochondrial Membrane (OMM), as mitofusin 1 and mitofusin 2 *trans* interact for the fusion of OMM in GTPase-associated manner (Gao and Hu, 2021). Loss of FUNDC2 does not affect the activity of MFN1, leading to the elongation of mitochondria, reduced mitochondrial respiration, and reorganized cellular metabolism (Li et al., 2022a). The effects of MFN1 on cancer cells are summarized in Table 1.

Cellular proteins that participate in mitochondrial dynamics show their metastatic role in HCC and among them, MFN1 is the main downregulated gene closely linked with metastatic HCC. MFN1 functions as a tumor suppressor gene, activating the fusion process to depress the metastasis and invasion in vitro and in vivo. The clinical evidence supports that both cell line and xenograft models express the association of poor prognosis of hepatocellular carcinoma patients with the decreased level of MFN1. HCC cells having MFN1 deficiency express downregulation of E-cadherin and elevated mesenchymal indicators, critical modulators of the epithelial to mesenchymal transition, EMT. Mitofusin 1 regulates the metastasis of HCC through shifting the metabolic pathway from glycolysis to OXPHOS, attributed only to the fusion event (Cheng et al., 2020). In osteocarcinoma cells, MFN1 prevents cellular proliferation and metastasis leading to cell cycle arrest and apoptosis. Its transcription level was downregulated by miR-19b, a component of the miR-17–92 cluster, whose level was significantly upregulated in osteocarcinoma cells, as MFN1 is the target gene of miR-19b. miR-19b controls the MFN1 gene through its 3′UTR sequences, blocks the protein level of MFN1, and enhances the tumor cell growth. Thus, blocking the miR-19b or activating the MFN1 contributes to the anticancer effect (Li et al., 2014b). Decreasing the protein expression of MFN1 makes the prostate cancer cells susceptible to apoptotic inducers like CGP37157 (CGP), a blocker of mitochondrial calcium efflux. It is observed that prostate cancer cells having higher levels of MFN1 express higher levels of DRP1, indicating the balance between fusion and fission

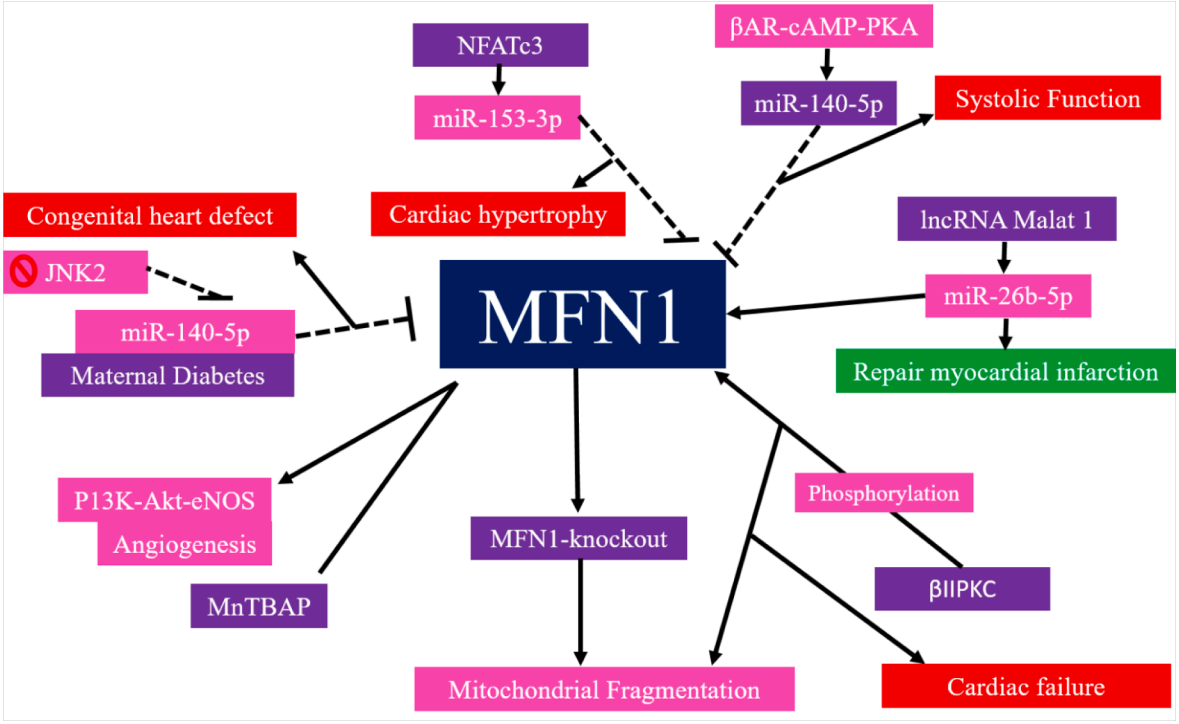

Fig. 2. Effect of MFN1 on the cardiovascular system.

proteins for their survival. CGP37157 caused the ubiquitination of MFN1, through March 5 ubiquitin ligase, leading to its destruction by proteasomes (Choudhary et al., 2014). March 5, membrane-associated ring-Ch, is an E3 ubiquitin ligase of mitochondria. It binds with fission proteins like hFis1, and DRP1 and fusion proteins like MFN2. However, shRNA-induced MARCH 5 knockdown produces the aggregates of elongated and highly interconnected mitochondria. It is the MFN1 whose level is significantly increased in MARCH5-deficient cells, not the MFN2 or fission proteins, depicting that mitofusin 1 is a main ubiquitylation substrate. Use of $MFN1^{T109A}$, a mutant of mitofusin 1 with deficient GTPase, into MARCH5-depleted cells interrupts mitochondrial elongation and diminishes the increase in the activity of SA-β-Gal that is associated with cellular senescence (Park et al., 2010). The role of MFN1 is also very crucial in selenium-based nanoparticle-targeted mitochondria of cancer cells in inducing cancer cell apoptosis and inhibiting inflammatory cytokines in malignant ascites. Nanoparticles use TLR4, TRAF3, and MFN1pathway for targeting tumor cell mitochondria. Although TLR4 (Toll-like receptor 4) is not located in mitochondria, TRAF3 (Tumor Necrosis Factor receptor-associated factor) functions as a bridge between MFN1 and TLR4 to initiate the fusion of endocytic vesicle to the mitochondrial tubule (Liu et al., 2020a). Protodioscin is a steroidal saponin that has disrupted mitochondrial membrane potential, ER expansion, and apoptosis of HCC cells by increasing the levels of MFN1 and Bak, which is reversed by the downregulation of Bak or MFN1. Furthermore, Bak and MFN1 make the complex with IP3R, the main calcium-releasing channels in the endoplasmic reticulum, to promote the shifting of calcium form the endoplasmic reticulum, ER, to mitochondria and cell death (Yu et al., 2022). Release of calcium from ER to mitochondrial tubule causes the endoplasmic reticulum-induced cell death (Marchi et al., 2018). MFN1/MFN2 complex functions as a bridge that monitors the development of mitochondrial-associated membrane between mitochondria and endoplasmic reticulum and calcium uptake (Yang et al., 2020a). The interaction between MFN1 and Bak causes the oligomerization of Bak followed by the enhanced OMM permeabilization of mitochondria, liberation of cytochrome *C* and ultimately cell death. (Yu et al., 2022). Excessive mitochondrial fusion is observed in *in vitro* grown tumor organoids of cholangiocarcinoma (CCA) and tumor tissues of HCC patients. Knockdown of either mitofusin 1 or optic atrophy 1 inhibits the fusion in tissue organoids of CCA and HCC cell lines, leading to the prevention of cell growth in vitro and in vivo. This inhibitory action is linked with the apoptosis, not with the cell cycle arrest (Li, Wang et al., 2020). Melittin, a honeybee venom ingredient, shows anticancer activity against breast cancer cells by increasing the mRNA levels of MFN1 and DRP1 (Moghaddam et al., 2020). In acute myeloid leukemia, interleukin 6 upregulates MFN1-induced mitochondrial fusion, activates oxidative phosphorylation, and causes chemoresistance in acute myeloid leukemia (AML) cells. Knockdown of MFN1 disrupts the action of IL-6 on mitochondria and chemo-resistance in cells. Contrary to that, an antibody against IL-6 downregulates MFN1, suppresses oxidative phosphorylation and mitochondrial fusion, and increases the overall survival (Hou et al., 2023). Progression of glioblastoma uses aerobic glycolysis for energy expenditures. MFN1, highly expressed in glioblastoma than MFN2, regulates the fusion of outer mitochondrial membrane in glycolysis. Silencing of MFN1 decreases the level of hypoxia inducible factor 1-alpha and phosphoinositide-dependent kinase 1 with significant reduction in the expression of c-myc. Thus, MFN1 can be a possible therapeutic target for treating glioblastoma (Guda et al., 2018). MFN1, in lung adenocarcinoma cells, causes the high glucose-mediated EMT which is inhibited by silencing MFN1. MFN1 does this by regulating the role of Pink, PTEN-induced kinase, in autophagy. This activation of autophagy promotes cellular migration, infiltration and EMT progression (Liu et al., 2020b). Epithelial mesenchymal transition stimulates mitochondrial fusion by upregulating MFN1 that is needed for PKCα-induced NUMB phosphorylation for cell division. MFN1-PKCα signaling tethers fused mitochondria into daughter stem cells. This fusion process increases the synthesis of glutathione to stimulate stem cell self-renewal (Wu et al., 2019). Plant-derived miR5338 has therapeutic effect for benign prostate hyperplasia (BPH) by inhibiting the expression of MFN1 in prostate. In rat BPH, Mitochondria in prostate cells have different shape compared to the control group (Hu et al., 2010). Posterior part of prostate gland in rat BPH has significant higher level of MFN1 compared to the control group that changes the mitochondrial morphology, enhances mitochondrial fusion, inhibits apoptosis and plays a role in the pathogenesis of BPH.

Table 1
Effect of MFN1 on cancer and nervous system.

MFN1 expression	Condition	Effect	Reference
Cancer			
Low	HCC	High FUNDC2 level is inversely associated with patient survival.	(Gao and Hu, 2021)
		Downregulation of E-cadherin and poor prognosis of patients	(Cheng et al., 2020)
Low	Osteocarcinoma	High miR-19b level increases tumor cell growth	(Li et al., 2014b)
High	Cholangiocarcinoma (tumor organoids)	Excessive mitochondrial fusion along with OPA1 and increase in cell growth	(Li et al. (2020))
High	acute myeloid leukemia	Interleukin-6 upregulates MFN1-induced mitochondrial fusion, activates OXPHOS, and causes chemo-resistance	(Hou et al., 2023)
High	Glioblastoma	Progression of glioblastoma and regulation of the fusion of outer mitochondrial membrane in glycolysis.	(Guda et al., 2018)
High	Lung adenocarcinoma	Regulation of the role of Pink-linked autophagy and promotion of migration, infiltration and EMT progression	(Liu et al., 2020b)
High	BPH	enhanced mitochondrial fusion, inhibition of apoptosis and progression of BPH	(Chen et al., 2018)
Nervous system			
Low	POMC neurons	an elevation in ROS, weak glucose metabolism and discloses the association between insulin release and POMC neurons through the sympathetic nervous system	(Ramírez et al., 2017)
Phosphorylation at serine 86	subarachnoid hemorrhage	Phosphorylation by βIIPKC with impairment of fusion and neuronal damage in subarachnoid hemorrhage	(Chen et al., 2022)
Low	Atrophied gastrocnemius	Mitochondrial fragmentation by miR-142a-5p with inhibition of oxidative phosphorylation and activation of PINK1/Parkin pathway	(Yang et al., 2020b)
Transgenic expression	CMT2A	Improvement of vision and retinal morphology through restoring the ration between MFN/MFN2 and PINK 1-dependent and Parkin-independent mitochondrial autophagy	(Shahin et al., 2023)
Normal physiological	iPSCs	Induction of mitochondrial fusion in the neural differentiation	(Yamada et al., 2018)

Application of miR5338 decreases the level of MFN1, inhibits fusion, reverses tubular morphology, enhances apoptosis and improves BPH (Chen et al., 2018). The effect of MFN1 on cancer and nervous system is summarized in Table 1.

7. MFN1 and neurons

Proopiomelanocortin neurons (POMC) are located in the hypothalamic arcuate nucleus and are organizers of glucose metabolism, energy expenditure, and food intake (Schneeberger et al., 2014). Metabolic challenges create the disturbance in maintaining tubular fusion and fission in POMC neurons resulting in the fluctuations in glucose sensing and hypothalamic gene expression schedule. This change in mitochondrial dynamics is related to the loss of MFN1 which causes an elevation in reactive oxygen species generation, mitochondrial respiration, and neuronal activity. Impaired MFN1-associated mitochondrial fusion weakens glucose metabolism and discloses the association between insulin release and POMC neurons through the sympathetic nervous system. Glucose challenge-mediated insulin secretion is diluted in POMC MFN1 knockout mice. However, this response has a neural basis, because antagonizing sympathetic activity reverses the insulin secretion. In addition, POMC MFN1 knockout mice do not have distorted islet anatomy, indicating mild sympathetic deregulation. Modified glucose-induced insulin secretion in POMC MFN1 knockout mice is connected with enhanced reactive oxygen species production and mitochondrial respiration while dealing with glucose. Importantly, increased reactive oxygen species level in POMC MFN1 knockout mice has no link with body weight fluctuations or appetite (Ramírez et al., 2017). This observation is consistent with a previous study where a deficiency of MFN1 is enough to increase the respiratory capacity in a variety of cells in a cell-autonomous style (Kulkarni et al., 2016). Role of MFN1 in nervous system is presented in Table 1.

Neuronal damage by Subarachnoid hemorrhage is associated with mitochondrial dysfunction and oxidative stress. βIIPKC belongs to the class of protein kinase C, aggregates on OMM, and causes the phosphorylation (Ferreira et al., 2019b) of MFN1 at serine 86 for the impairment of mitochondrial fusion and neuronal damage in subarachnoid hemorrhage. Inhibition of the βIIPKC-MFN1 pathway reverses mitochondrial dysfunction and neuronal damage along with the activation of Sirt3 and antioxidant enzymes, resulting in the alleviation of brain damage in subarachnoid hemorrhage (Chen et al., 2022). Mitochondria play a substantial role in dendritic branching (Sheng and Cai, 2012), whereas mitochondria are preferentially directed to the proximal end of dendrites during the period of development. Depletion of mitochondria from dendrites during development either by the over-activity of TRAK2-MBD (Trafficking kinesin-binding protein 2-methyl-CpG-binding domain) or MFN1 is linked with the enhanced dendritic branching and it is more obvious in the proximal end of dendrites. This dendritic pathogenesis is unlikely to be associated with changes in the distribution of membrane-surrounded organelles, as distributions of endosomes, endoplasmic reticulum, and Golgi apparatus are not affected by the over-activity of MFN1. This effect is not linked with the modified mitochondrial function or neurodegeneration, as neither mitochondrial potential nor cell viability is changed by the over-activity of TRAK2-MBD or MFN1 (Kimura and Murakami, 2014). The sharp increase in the length of mitochondria in DRP1-inhibited axons is due to the blockade of mitochondrial fission coupled with continuous fusion.

Overexpression of MFN1 through EGFP-MFN1 plasmid (Santel et al., 2003) in DRG (dorsal root ganglion) neurons tremendously increases the length of axonal mitochondria that are examined from the proximal region to the distal region of transfected neurons. The formation of extremely lengthy mitochondria by the overexpression of MFN1 in the entire axon shows the happening of local mitochondrial fusion in the DRG neurons. A balance between tubular fission and fusion in non-neuronal cells that maintain the mitochondrial morphology suggests that the above-mentioned events occur specifically in the axonal region (Amiri and Hollenbeck, 2008). Loss of nerve supply to the skeletal muscles brings about a programmed and rapid decrease in muscle size and activity, called muscle atrophy. Mitochondrial malfunctioning plays a key role in muscle atrophy showing changes in mitochondrial respiration, biogenesis, fusion, and fission after muscular tissue unloading. MFN1 expression was decreased by miR-142a-5p in atrophied gastrocnemius, causing mitochondrial fragmentation. This miR-142a-5p/MFN1 signaling also depressed the mitochondrial function by disturbing mitochondrial depolarization and inhibition of oxidative phosphorylation. Moreover, mitochondria-associated apoptosis and mitophagy is also activated by this pathway in atrophied gastrocnemius. PINK1/Parkin is the leading pathway of mitochondrial autophagy that is controlled by the miR-142a-5p/mitofusin 1 axis leading to the decrease in tubular number (Yang et al., 2020b). Mitochondrial damage related to MFN1 takes part in the progression of cerebral ischemia–reperfusion injury. MFN1-induced mitochondrial protection attenuates reperfusion-caused mitochondrial stress and this protective mechanism is associated with AMPK signaling (Gao et al., 2019). Charcot-Marie-Tooth type 2A, CMT2A, is an inherited peripheral axonal neurological disorder with progressive loss of motor and sensory activity and visual acuity along with defective color vision. Mechanistic analysis shows that the abnormal MFN1/MFN2 ratio causes the degeneration of the retina through P62/LC3B-regulated autophagy/mitophagy in CMT2A mouse model. However, transgenic MFN1 improves the vision and retinal morphology through restoring the ration between MFN/MFN2, PINK 1-dependent and Parkin-independent mitochondrial autophagy (Shahin et al., 2023). Another study on how CMT2A-mediated mutations accommodate MFN1-induced fusion, informs that minimal GTPase domain (MGD) of MFN1 has a complex with GDP-BeF_3^-. The MGD with four helix structure, HB1, makes a dimer. The HB1 goes through conformational changes and has the ability to pull tethered mitochondrial membrane for fusion. Enzymatic analysis explains that potassium is necessary for MFN1-mediated GTP hydrolysis (Yan et al., 2018). Chlorpyrifos, an organophosphate, is used as an insecticide causing neurodevelopmental toxicity. In induced pluripotent stem cells of human, chlorpyrifos at micro-molar concentration decreases ATP level, energy production by mitochondria, and promotes mitochondrial fragmentation through reducing the level of MFN1. MFN1 knockdown in these cells downregulates the level of PAX6, a factor for neurogenesis, indicating that mitofusin 1 stimulates neural induction in these cells (Yamada et al., 2017). MFN1-induced mitochondrial fusion plays a role in the neural differentiation of iPSCs, human induced pluripotent stem cells, as its knockdown creates fragmented mitochondria, reduces ATP content and mitochondrial membrane potential along with the inhibition of differentiation markers like FOXG1, NCAM and PAX6 in iPSCs (Yamada et al., 2018).

8. MFN1 and diabetes

Disruption of mitochondrial morphology and fusion-associated genes are investigated in obesity and type 2 diabetes, producing highly fragmented mitochondrial tubules. Mice with liver-specific knockout of mitofusin 1 gene express highly fissioned tubular network with increased mitochondrial respiration and utilize lipids as the preferred source of energy. An increase in lipid droplet size and reduced aggregation of acylcarnitine elements give the clue that MFN1-deleted livers have better lipid management and fatty acid oxidation. This leads to the blockade of aggregation of secondary lipid bodies involved in the interference with the insulin effect and the production of multilocular fat droplets, a key feature of steatohepatitis and liver mitochondrial dysfunction. These mice are secured against high-fat-diet-mediated glucose tolerance and insulin resistance. Depletion of MFN1 enhances the abundance of complex I and increases the sensitivity to the hypoglycemic impact of metformin in high-fat-diet-fed mice, which is reflected by a sharp reduction in the respiratory control and state-3 respiration using malate and glutamate in the presence of low millimolar concentrations of metformin. Metformin may stimulate high energy imbalance in MFN1-deleted mitochondria. MFN1 deficiency aggravates metformin-mediated glucose-lowering effects (Fig. 3) and liver AMPK, Adenosine monophosphate-activated protein kinase, activation (Kulkarni et al., 2016). Depletion of MFN1 increases the production of reactive oxygen species, ROS, as complex I is related to the production of superoxide by mitochondria (Brand et al., 2004). In contrast to this, MFN1 deletion in myocytes protects the cells from ROS-mediated cell death (Papanicolaou et al., 2012). Respiratory control in MFN1-depleted liver mitochondria is increased only by malate-glutamate activity, not by succinate activity that can be related to the capability of complex I to modulate its association with complex III and complex IV to make respiratory super-complexes (Lapuente-Brun et al., 2013). Gestational diabetes has the characteristic of glucose tolerance with vascular damage and enhanced pro-inflammatory cytokines leading to adverse outcomes like neonatal hypoglycemia, cesarean section, and macrosomia (Yuen et al., 2019). In gestational diabetes, expression of miR-17-5p is increased in plasma and placental tissue. Furthermore, the levels of mitofusin proteins are reduced in the placenta of gestational diabetes patients, suggesting that these proteins are targets of miR-17-5p. Clinical data indicates that miR-17-5p/Mitofusin/NF-κB is therapeutic targets for treating gestational diabetes (Li et al., 2022b). Another study on diabetes-induced cognitive impairment shows that genipin, an active ingredient extracted from gardenia fruit, reduces cognitive damage by blocking lipid accumulation, and inflammation and increasing mitochondrial fusion through the FABP4/MFN1 pathway (Liu et al., 2023a).

9. MFN1 and reproduction

MFN1, not MFN2, is needed for the development of oocytes, and deletion of only MFN1 blocks the growth of oocytes and ovulation because of the inhibition of folliculogenesis. Female mice having a deficiency of MFN1 are infertile, whereas deletion of both mitofusin 1 and mitofusin 2 surprisingly recovers the failure of ovulation. Deletion of MFN1 causes the blockade of pre-antral to antral follicular transition (Fig. 3). This defective folliculogenesis is linked with mitochondrial dysfunction including the aberrant levels of ATP, FAD, mtDNA, and oxidative phosphorylation subunits. MFN1 KO disturbs the P13K-AKT pathway and interaction with other somatic cells, thus blocking folliculogenesis and oocyte growth (Carvalho et al., 2020). A study on the role of MFN1 in oocyte development shows that oocyte-specific knockout of mitofusin 1 causes female mice infertility related to abnormal folliculogenesis and oocyte quality. This causes the decreased proliferation of granulosa cells and follicular arrest at the secondary stage along with the severed mitochondrial activity (Hou et al., 2019). Deletion of MFN1 in oocytes brings on impairment of oocyte-granulosa cell interaction with the downregulation of connexins and cadherins leading to the arrest of follicle development at the secondary follicle stage. Deficiency of MFN1 results in the accumulation of ceramide which leads to an increase in apoptosis. Therefore, a deficiency of MFN1 with apoptotic cell loss depletes ovarian follicular reserve and accelerates reproductive aging (Zhang et al., 2019). Another study on the effect of MFN1 on oocyte-granulosa cell interaction shows that oocyte-specific knockout of mitofusin 1 completely blocks oocyte growth as a result of the inhibition of folliculogenesis at the pre-antral to antral transition. Furthermore, mitofusin 1-null oocytes do not have the capacity to produce somatic cell factor GDF9. Surprisingly, deficiency of both mitofusin

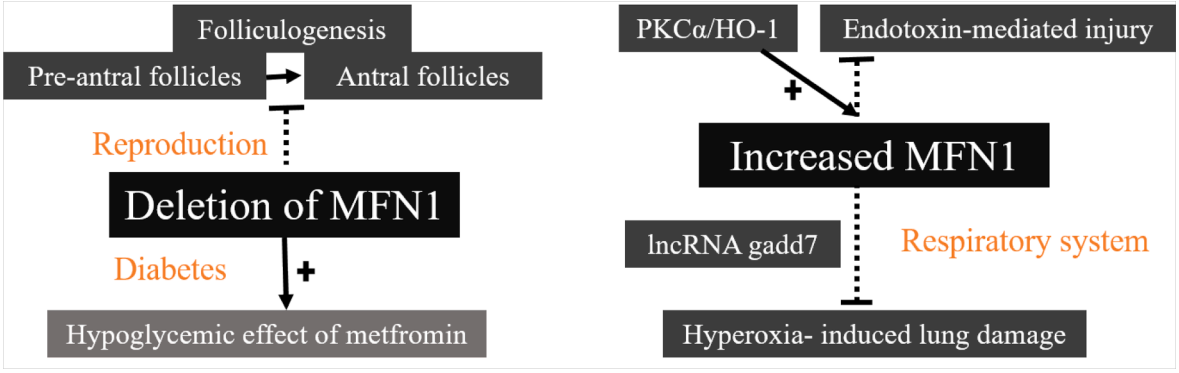

Fig. 3. Effect of MFN1 on diabetes, reproduction and respiratory system.

1 and mitofusin 2 alleviates the actions on oocyte growth and ovulation, indicated by partial recovery of folliculogenesis and oocyte-to-somatic cell interaction (Machado et al., 2018). MFN1 knockout female mice are infertile and do not generate any pups and ovaries have primordial, primary, and secondary follicles same as wild-type but do not have antral follicles in the presence or absence of pregnant mare serum gonadotropin (PMSG) stimulation. This is because of defective mitochondrial dynamics (Zhang et al., 2018b).

10. MFN1 and the respiratory system

Pulmonary arterial smooth muscle cell (PASMC) proliferation is involved in hypoxic pulmonary hypertension. MFN1 level is enhanced in hypoxia leading to hypoxia-mediated mitochondrial malfunction and cell cycle shifting from the G_o or G_1 phase to the S phase along with proliferation of smooth muscle cells. Inhibition of MFN1 causes a decrease in PASMC-disordered growth in hypoxia (Ma et al., 2017). In another study on pulmonary arterial hypertension, the level of miR-140 is elevated in the hypertrophic right ventricle. This increased level of miR-140 is reducing the expression of its target protein MFN1 in the right ventricle relative to the left ventricle and septum of rats. It shows that upregulated miR-140 and downregulated mitofusin 1 are correlated with enhanced right ventricular hypertrophy and systolic pressure (Joshi et al., 2016). In hyperoxia-mediated acute lung damage, levels of LncRNA gadd7 and MFN1 (Fig. 3) are increased in alveolar type 2 epithelial cells. LncRNA gadd7 positively controls MFN1 and MFN1 overexpression cancels out the blocking effects of gadd7 knockout on a decrease in tubular membrane potential and cell death, mentioning that gadd7 promotes a decrease in tubular membrane potential and cell death by positively controlling the level of MFN1 (Liu et al., 2023b). PKCα/HO-1 pathway-stimulated MFN1 has the endogenous protective role in endotoxin-mediated injury (Fig. 3) to alveolar macrophages (LI et al., 2017). Carbon monoxide-mediated upregulation of MFN1 in endotoxin-affected alveolar macrophages of rats is linked with the P13k/Akt signaling (LI et al., 2017).

11. Miscellaneous

Elimination of both mitofusin proteins (MFN1 and MFN2) causes the death of the embryo several days earlier. However, MFN1-depleted mice placentas possess normal enlarged cells but have deformities in other cells, because wild-type placenta saves MFN1-depleted mice from embryonic lethality (Chen and Chan, 2010). Low levels of MFN1 cause mitochondrial malfunction and apoptosis in porcine SCNT, somatic cell nuclear transfer, embryos. The speed of the formation of the blastocyst is significantly reduced compared to parthenogenetic activation embryos. SCNT embryos have significantly low levels of mitochondrial membrane potential and MFN1, while have enhanced reactive oxygen species and cell death (Park et al., 2020). Miscellaneous effects of MFN1 are illustrated in Fig. 4.

Fasting or a decreased level of glucose stimulates a metabolic shift of increased energy production to mitochondrial tubules. This adaptation although competes with the energy deficit challenge, also leads to oxidative damage to mitochondria. These metabolically disturbed mitochondria activate the fusion process to repress oxidative stress. In fasting condition, MFN1 communicates with deacetylase HDAC6 (Histone deacetylase 6), causing deacetylation and activation of MFN1 for mitochondrial fusion. Deletion of either HDAC6 or MFN1 blocks fusion caused by fasting state and this failure of fusion process does not affect the adaptive energy generation response instead there is oxidative damage and excessive generation of reactive oxygen species in mitochondrial tubules (Lee et al., 2014). In viral infection, MFN1 takes part in the redistribution of interferon-β promoter stimulator 1, IPS-1, and virus-mediated interferon production. Interferon production is initiated by cytoplasmic retinoic acid-inducible gene I-like receptor, RLR, which senses viral RNA. Upon activation of RLR, its interaction with IPS-1, present on the OMM, leads to its redistribution and formation of speckle-like arrangement on mitochondria for the antiviral action (Onoguchi et al., 2010). Human cytomegalovirus infection (HCMV) causes fusion through MFN1 that is related to mitochondrial antiviral protein (MVAS) and also positively controls interferon-1 response. Knockdown of either MVAS or MFN1 inhibits the production of interferon-1. In contrast, an agonist of MFN1, leflunomide, promotes interferon-1 production, attributing that MFN1 can be a potential target for HCMV infection (Huang et al., 2023). Downregulation of MFN1 is also involved in cisplatin-mediated acute kidney injury. It is the miR-125b whose expression is increased in cisplatin-mediated nephrotoxicity and causes mitochondrial fragmentation by alleviating the level of MFN1. By inhibiting the level of miR-125b, the MFN1 level is upregulated along with the recovery of mitochondrial injury (Zhao et al., 2021). Organotin compound tributyltin, an endocrine disrupter, inhibits cell viability and ATP level of induced pluripotent stem cells. Tributyltin reduces the level of MFN1 through MARCH5-induced degradation of MFN1, as knockdown of MARCH 5 diminishes the tributyltin-mediated downregulation of MFN1 (Yamada et al., 2016). Mitochondrial dynamics plays an active part in the ATP production by mitochondria which is associated with host defense in *Mycobacterium tuberculosis* infection. *M. tuberculosis* infection mediates fusion process by elevating the mitofusin 1 expression leading to enhanced ATP generation. Deletion of MFN1 blocks the mitochondrial fusion and decreases ATP generation which impairs mycobactericidal activity of macrophages by blocking autophagy and suggesting that MFN1-regulated metabolic pathway can be a promising target for the host direct therapy (Ning et al., 2021). An investigation to find out the relation between myopia and polymorphisms in the MFN1 gene in the Chinese population reveals that the C allele of rs13098637 in MFN1 has a link with low to moderate level of myopia (Zou et al., 2015). In line with this, some rough changes in the expression of MFN1 in LIM, lens-induced animal myopia, eyes of

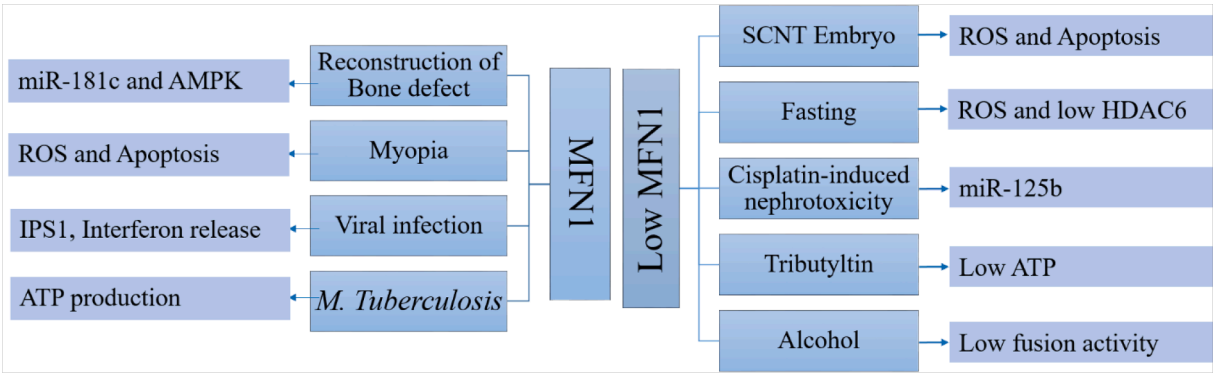

Fig. 4. Miscellaneous effects of MFN1.

guinea pig have been observed, suggesting that MFN1 genetic variations may promote the development of myopia (Cai et al., 2016). MFN1 is a molecular marker for cattle breeding as there is a relation between mitofusin-1 gene CNV and rump length and chest width of Yunling cattle, huckle bone width of Qinchuan cattle, height at the sacrum and hip width of Jiaxian red cattle (Yao et al., 2022). Regenerative therapy based on bone mesenchymal stem cells is crucial for the reconstruction of craniofacial defect. It has been explored that miR-181c promotes reconstruction of craniofacial defect through stimulating AMPK-MFN1 pathway in bone mesenchymal stem cells. Silencing of MFN1 perturbs the protective effects of miR-181c on the proliferation and migration of stem cells in oxidative stress condition (Fan et al., 2019). Chronic alcohol consumption causes the depletion of MFN1 leading to the suppression of fusion in muscles. Chronic depletion of MFN1 in mouse embryonic fibroblasts exhibits the calcium phenotype of ethanolic muscle tissue. Also, chronic exposure of EtOH and MFN1 knockout reduces the tubular membrane potential in repetitive stimulations by calcium. Short-term re-expression of MFN1 can rescue the fusion process in both MFN1 knockout and prolonged EtOH but unable to restore full mitochondrial biogenesis (Eisner et al., 2014).

12. Future recommendations and limitations

The potential limitations and challenges associated with the research on mitofusins, like MFN1, include the complexity of mitochondrial dynamics, the difficulty in specifically targeting mitochondrial proteins without affecting other cellular functions, and the limited understanding of the precise mechanisms through which mitofusins affect disease pathology. Additionally, translating findings from cell models and animal studies to human clinical applications poses significant challenges, including variability in patient responses and potential side effects. These factors make it crucial to conduct further studies to fully elucidate the roles of mitofusins in health and disease and to develop safe and effective therapeutic strategies. For future research in the area of mitofusins, especially MFN1, recommendations include focusing on elucidating the detailed molecular mechanisms of MFN1 in various diseases, exploring the therapeutic potential of modulating MFN1 activity, and conducting clinical trials to assess the efficacy and safety of MFN1-targeted therapies. Additionally, research should aim to identify biomarkers for MFN1 activity to facilitate the diagnosis and monitoring of diseases linked to mitochondrial dysfunction. Investigating the interaction between MFN1 and other mitochondrial dynamics proteins could also provide insights into novel therapeutic strategies. Overall, the novelty of this study lies in its comprehensive analysis and synthesis of the most recent findings regarding MFN1′s pharmacological properties across various diseases. This review uniquely integrates current research to offer new insights into MFN1′s therapeutic potential and molecular mechanisms, filling gaps in the existing literature by highlighting underexplored areas. This approach not only updates the scientific community on the latest developments but also proposes new frameworks for understanding MFN1′s role in disease pathology and treatment, setting the stage for future research directions.

13. Conclusion

Significant scientific struggle has explored the structure and functions of MFN1 in living cells, but still many questions need clarification. MFN1 controls mitochondrial dynamics, metabolism, and apoptosis, but which functional domains of MFN1 take part in carrying out these functions? Defining the role of other molecules that communicate with MFN1 for maintaining the shape, size, and overall behavior of mitochondria. How is MFN1 present in active/inactive state, how these confirmations are regulated, and the impact of this regulation on human diseases? MFN1 expresses its significant role in various diseases and organ systems, but its role in other disease models and cell types needs to be evaluated in the future, as it can be selected as a promising marker for the therapeutic and diagnostic potentials.

In conclusion, this review elucidates the multifaceted roles of mitofusin (MFN1) in mitochondrial dynamics and its implications for human health and disease. We've underscored the significance of MFN1 in regulating mitochondrial function and its potential as a therapeutic target in mitigating diseases characterized by mitochondrial dysfunction, such as neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes. The review highlights the necessity for advanced research to fully understand MFN1′s mechanisms and to develop targeted therapies. Future studies should aim to explore MFN1′s therapeutic efficacy, with a focus on designing drugs that modulate its activity for disease treatment and prevention, thus opening new pathways for clinical applications.

CRediT authorship contribution statement

Adel Alghamdi: Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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