Hypertension Research
https://doi.org/10.1038/s41440-024-01670-2

COMMENT

Mitochondrial fission: a new mechanism of hypertension and cardiovascular remodeling induced by Angiotensin II

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Keyword Vascular dysfunction · Mitochondria · Fission

Received: 1 March 2024 / Revised: 14 March 2024 / Accepted: 17 March 2024

Mitochondria are essential organelles that play a critical role in cellular energy production, apoptosis, and other vital functions. These dynamic organelles constantly undergo cycles of fission and fusion, which are critical for maintaining mitochondrial morphology and their function [1].

Mitochondrial fission is a process by which a single mitochondrion divides into two or more smaller mitochondria. This process is regulated by dynamin-related GTPase, Drp1, and its adapter proteins on mitochondrial outer membrane (OMM), Fis1, Mff, and MiD49/51 that mediate the constriction and scission of the OMM. Once Drp1 is activated by its post-transcriptional modification, such as phosphorylation of serine 616 and dephosphorylation of serine 637, for example, Drp1 moves onto the mitochondria and binds to the adapter proteins on the OMM. It aligns in a ring position, which is defined by the surrounding endoplasmic reticulum (ER), and subsequently generates tension by actin assembly through its GTPase activity, leading to constriction of the ring [1]. Drp1 is therefore accepted as a master regulator of mitochondrial fission.

Mitochondrial fusion is the process by which two or more mitochondria combine to form a single, larger mitochondrion. This process is regulated by a group of outer membrane GTPases (Mfn1/2) and inner membrane protein, Opa1, that mediate the fusion of the mitochondrial outer and inner membranes, respectively. Fusion enables the exchange of matrix components such as mtDNA, lipids, and proteins between the fused mitochondria, which can maintain the function of damaged mitochondria and can achieve the higher efficiency of ATP production in specific conditions such as cellular starvation [1] (Fig. 1).

The study by Preston et al. in this issue [2] analyzed the role of mitochondrial fission in the pathogenesis of hypertension and cardiovascular remodeling [2]. The importance of mitochondrial fission in the development of cardiovascular diseases has been suggested in previous studies [3]. During mitosis, fission is essential for mitochondrial biogenesis, ensuring the proper distribution of mitochondria to daughter cells [4]. In some pathological conditions of cells, fission allows for the segregation of damaged mitochondria, which can then be targeted for mitophagy, a selective form of autophagy that eliminates damaged mitochondria [5]. Fission can also promote apoptosis, a form of programmed cell death, by facilitating the release of cytochrome c from the mitochondria into the cytosol [6], although this point is still under discussion and seems to depend on its cellular context as stated below.

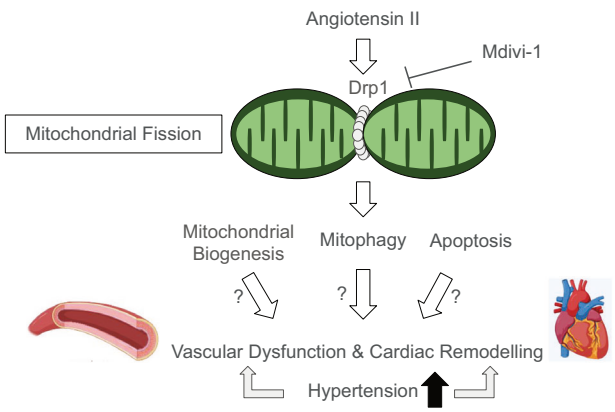

Fig. 1 Mitochondrial Fisson, Cardiovascular remodeling, and Hypertension. Mitochondrial fission is controlled by Drp1 which can be inhibited by a specific inhibitor Mdivi-1 and is suggested as a mechanism of cardiovascular remodeling and hypertension through the resultant cellular events [2]

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Published online: 10 April 2024

The diverse roles of fission could be understood by the relative position of the OMM where it is triggered and the type of adapter protein [5]. During biogenesis of mitochondria, the fission occurred in their midzone and the involvement of the Mff1-ER-Actin system was observed during the process. In contrast, fission involving Fis1 and lysosomes at the peripheral site was observed with decreased membrane potential of smaller daughter mitochondrion, showing its damaged state and the fate leading to mitophagy, which was suggested to save isoproterenol-treated cardiomyocytes from apoptosis [5]. Thus, the effect of mitochondrial fission on apoptosis seems bivalent depending on the cellular context, which makes it even more challenging to identify the role in disease models.

In rodent models of diabetes, hyperlipidemia and hyperglycemia have been reported to cause mitochondrial fission via S616 phosphorylation and/or S637 dephosphorylation, leading to myocardial insulin resistance, reduced contractile efficiency, and cardiomyocyte death [1]. Based on these results, the pathological role of mitochondrial fission was mainly studied by gene editing of Drp1, especially in Drp1 knockout mice, with the expectation of beneficial effects on the heart [1]. However, the deletion of the Drp1 gene, even cardiomyocyte-specific in the early postnatal period, caused embryonic lethality or dilated hearts with severe mortality. Even drug-inducible cardiac-specific Drp1 knockout mice at 15 weeks of age showed excessive cardiac remodeling reminiscent of hypertrophic cardiomyopathy [7]. Considering these results, the over-suppression of fission due to gene deletion might have led to poor outcomes. Therefore, the Drp1 inhibitor mdivi-1 needs to be tested not only for its potential clinical application but also in terms of its ability to "adequately" inhibit mitochondrial fission in disease states.

The authors of the paper in this issue [2] examined the possible beneficial effects of mdivi-1 on multiple organs of cardiovascular system in a mouse model of hypertension induced by chronic dosing of angiotensin II (AngII). Positive effects of mdivi-1 across the cardiovascular system were revealed: lowering blood pressure (BP); a decrease in the remodeling of aorta and coronary artery; mitigating contractile responses of mesenteric artery enhanced by AngII; improving left ventricular hypertrophy. Furthermore, the authors also showed that AngII-induced pro-inflammatory phenotype of cultured rat aortic endothelial cells was attenuated at secretome levels, which is a proteome analysis focusing on secretory proteins, and that the expression level of a fibrotic marker periostin was reduced in cultured rat adventitial fibroblasts stimulated with AngII.

Although BP lowering effect of mdivi-1 in AngII-induced hypertension was already demonstrated in a previous study [8], the study by Preston et al. is significant in that they provide comprehensive data on the cardiovascular system, including the secretome analysis. Moreover, the authors used a higher dose of AngII, which led to intriguing differences, compared to the previous one (1 μg/kg/min v.s. 400 ng/kg/min) and almost equivalent dose of mdivi-1 (25 mg/kg v.s. 20 mg/kg) in the mouse model. Probably because of the higher dose of AngII used in this study, the beneficial effect of mdivi-1 was partial or not evident in terms of the decrease in BP and the remodeling of renal artery, which were attenuated in the previous study. These results support an idea that the renal effect of AngII was not inhibited by the used dose of mdivi-1. In contrast, the cardiac remodeling induced by AngII was attenuated evidently by mdivi-1, as shown in the LV mass. These results indicate a specific beneficial effect of mdivi-1 on the heart, in addition to the effect of partial amelioration in BP on left ventricular hypertrophy.

Mdivi-1 reduced potassium- and phenylephrine-induced contraction of mesenteric arteries, indicating that it inhibits Ca^{2+}-dependent contraction of vascular smooth muscle in resistance vessels. This effect of mdivi-1 was significant not only in AngII-treated mesenteric arteries but also in the vehicle group, suggesting that mdivi-1 may act on factors independent of AngII. For example, the vasodilatory function of endothelial cells treated with AngII was improved by mdivi-1, as shown in the response to acetylcholine in the previous paper [8]. It would be important to clarify whether the impairment of endothelial function, as well as the pro-inflammatory phenotype of endothelial cells at secretome level, is attenuated by mdivi-1, even with the higher dose of AngII.

In conclusion, the beneficial effect of mdivi-1 on the cardiovascular system challenged with AngII was further well demonstrated in the paper of this issue [2]. It is still to be revealed in future study how mitochondrial fission, including its resultant cellular event (mitochondrial biogenesis, mitophagy, and/or apoptosis), in vascular tissue leads to its dysfunction and remodeling. Further studies using mdivi-1 in other animal models of hypertensive disorders are expected.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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