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Commentary

Endoplasmic reticulum mitochondria contacts modulate apoptosis of renal cells and its implications in diabetic neuropathy

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In diabetic neuropathy (DN), the kidney injury occurs as the renal cells undergo apoptotic-mediate d cell death [1]. Current therapeutics can barely reverse course of the disease progression, and this necessitates the better understanding of mechanisms underlying disease pathogenesis in order to design effective strategies. Cells induce apoptosis in scenarios such as endoplasmic reticulum (ER) stress and presence of irreparably damaged mitochondria [2]. Recently emerging concept that ER and mitochondria communicate at a specific interface called MAM (mitochondria associated ER membranes) is important for cellular as well as organismal homeostasis [3]. Although the evidences suggesting existence of membrane contact sites can be traced back to 1980's literature, the field was really re-born after a seminal study published in 2009, that deciphered the tethering factors at MAM [3]. MAM is vital for carrying out various essential cellular pathways such as autophagy, lipid synthesis, calcium exchange and mitochondrial DNA replication [4–6]. MAM interface spans around 10 nm area of the juxtaposed ER and mitochondrial membranes. This interface not only helps in attaining and maintaining homeostasis but also altering the signaling events during stress conditions [3]. Perturbation in MAM integrity elevates oxidative stress, compromises autophagy as well as reduces mitochondrial respiration [6]. As shown by Marc claret and colleagues, in diet-induced obesity mice, the mitofusin-mediated altercations (MAM defect) in proopiomelanocortin (POMC) neurons affect POMC processing, increases ER stress and leptin resistance [7]. This previous study documented the role of malfunctioning MAM in POMC neurons towards regulating the pathology of diet-induced obesity. However, the role of MAM dysfunction in driving the apoptotic death of renal cells has not been explored yet.

The article by Yang *et al.*, in *EBioMedicine* demonstrated the clinically relevant and previously undocumented role of Disulfide-bond A oxidoreductase-like protein (DsbA-L) in regulating MAM that alter apoptotic signaling events of renal cells during progression of diabetes [8]. DsbA-L is a cellular detoxifying enzyme that is involved in catalyzing the formation of disulphide bonds during adiponectin multimerization in adipocytes [9]. Previous studies have showed a protective role for DsbA-L against diet-induced obesity and insulin resistance [10]. Earlier studies have highlighted a role of dysregulated mitofusin-2 (MFN-2) as a key mitochondrial fusion protein implicated in MAM of POMC neurons [7]. In the present study, during pathology, MAM was reduced due to the following consequences namely, a) downregulated DsbA-L and MFN-2 levels, b) elevated ER stress. These events led to increased apoptotic-mediated death of renal cells. The authors proposed that DsbA-L might regulate MAM *via* MFN2 and the exact mechanism is yet to decipher. So how DsbA-L regulates MFN-2? Is the chaperoning ability of DsbA-L necessary to regulate MFN-2? These questions need to be addressed to gain further mechanistic insights. *In cellulo* high glucose treatment elevated ER stress along with increased apoptotic markers and this phenotype could be reversed upon overexpression of DsbA-L with concomitant rescue in MAM defects. Such beneficial effects achieved upon overexpressing DsbA-L could be nullified by expressing FATE-1 protein (a molecule involves in detaching the ER-mitochondria contacts). This is in concordance with the previous observation that DsbA-L was shown to be protective in other metabolic disorders [9]. Interestingly, the authors note that although MAM architecture was intact in DsbA-L knock out mice, the pathologies were manifested and eventually progressed aggressively [8]. The authors also confirmed the observations of compromised MAM, reduced DsbA-L protein level and elevated apoptotic cells in the diabetic patient's renal biopsies. These data may suggest that although DsbA-L may not necessarily be involved in maintaining MAM architecture at steady state, during metabolic stress, it may be one of the drivers in regulating disease pathogenesis.

The findings in this study has opened up following questions in the field, 1) deciphering the mechanism of DsbA-L mediated regulation of MFN2 in steady and diseased state of renal cells, 2) precise mechanism of MAM regulation by DsbA-L protein during the progression of diabetic pathogenesis, 3) understanding the kinetics and dynamics of DsbA-L mediated MAM disruption to exactly decipher the cell biological event using live cell microscopy probably by utilizing diabetic patient derived primary renal cells, 4) pharmacological agents either new chemical entities (NCE) or FDA (food and drug administration) approved drugs can be identified that can ameliorate MAM disruption mediated apoptosis.

This study is one of the few investigations that highlight the importance of MAM in contributing to disease pathogenesis adding significance to basic as well as translational research aspects. Take home message from this study is that the antioxidant protein DsbA-L regulates MAM probably *via* MFN2 to induce apoptosis in driving the pathogenesis of renal injury in diabetic condition. Targeting the DsbA-L/MFN2 axis

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using genetic or pharmacological ways to improve the MAM architecture as well as activity to negate apoptosis in renal cells could be a new avenue in therapeutics of diabetes.

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