Shuttling of calcium between endoplasmic reticulum and mitochondria in the renal vasculature

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MITOCHONDRIA AND ENDOPLASMIC RETICULUM (ER) are endowed with diverse functionalities, and among them is a recently emerged concept of a direct line of communication between the ER and mitochondria to regulate intracellular calcium ([Ca\(^{2+}\)]\(_{\text{c}}\)) homeostasis, and thereby to influence various fundamental biological processes, including cell survival and programmed cell death, apoptosis (2, 3). Under basal conditions, Ca\(^{2+}\) is pumped into the ER by sarcoplasmic-ER calcium adenosine triphosphatase (SERCA) and is released by inositol 1,4,5-triphosphate (IP\(_3\)) or ryanodine receptor (RyR), collectively termed as (IP\(_3\)R). On the other hand, Ca\(^{2+}\) entry and release from the mitochondria are modulated by mitochondrial calcium uniporter (mCU) and Na\(^+\)/Ca\(^{2+}\) exchanger (mNCE), respectively (Fig. 1). Expectedly, a rise in the cytosolic calcium ([Ca\(^{2+}\)]\(_{\text{c}}\)) upon release from the intracellular stores would be channeled by IP\(_3\)R and mCU into the mitochondrion resulting in an increase in the mitochondrial calcium ([Ca\(^{2+}\)]\(_{\text{m}}\)) following various stimuli, a prototype being an oxidant stress (2, 3). The role for Ca\(^{2+}\) entry into mitochondria did not receive much attention until it was recognized that a marked rise in [Ca\(^{2+}\)]\(_{\text{m}}\) contributes to apoptosis (8). A precipitous accumulation of Ca\(^{2+}\) in mitochondria may lead to the opening of the "transition pore" and accelerate ion exchanges across the inner mitochondrial membrane. As a result, there is a loss of negative membrane potential (\(\Delta\psi\)) that contributes to the release of apoptotic factors, such as cytochrome c (2, 4). This has been demonstrated in cardiac, skeletal muscle and neural tissues (1, 6, 10); however, no studies have been performed in cells of the kidney. In the present issue of the journal, the elegant studies by Pacher et al. (7) demonstrated that a similar ER-mitochondrial Ca\(^{2+}\) communication is operative in a crucial cell type of the kidney, i.e., the afferent arteriolar vascular smooth muscle cell that regulates the glomerular blood flow and thereby its pathophysiology. Furthermore, they identified a novel relationship between ER-mitochondrial Ca\(^{2+}\) communication and transforming growth factor-\(\beta\) (TGF-\(\beta\)), the latter being pivotal to the extracellular matrix pathobiology relevant to the pathogenesis of diabetic nephropathy (12).

Thus far, studies have focused on positive regulators of apoptosis and how accentuated Ca\(^{2+}\) release enters mitochondria. The alternate view has not received as much attention; that is, what factors inhibit the uptake of mitochondrial [Ca\(^{2+}\)]\(_{\text{m}}\), uptake and therefore may block apoptosis? Since normally the [Ca\(^{2+}\)]\(_{\text{c}}\) is shuttled into the mitochondria, thus a relevant question arises as to what is the physiologic role of Ca\(^{2+}\) entry into mitochondria [Ca\(^{2+}\)]\(_{\text{m}}\)? There are several biological processes that have been linked to requiring the presence of Ca\(^{2+}\) in the mitochondria, the primary being [Ca\(^{2+}\)]\(_{\text{m}}\) role in the regulation of mammalian intramitochondrial metabolism pertinent to the generation of ATP (4). Other beneficial roles may be cell specific, such as, contraction and relaxation of myocytes in cardiac and skeletal muscleature and neuronal transmission at the synaptic junctions (1, 6, 10). Another interesting role of [Ca\(^{2+}\)]\(_{\text{m}}\) is to stimulate insulin secretion selectively from the apical domains of beta cells of pancreas, while dampening the secretagogue response in its acinar cells (9, 11). The latter perhaps is related to the unique

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The organelle structure-function relationship whereby the positioning of mitochondria in a ring-like format prevents the diffusion of calcium and subsequent activation of trypsin, which otherwise could lead to pancreatitis (11). Besides the above described functions, there may be other roles of \( [Ca^{2+}]_{im} \) that are cell specific and need to be explored.

In the present study, Pacher et al. (7) elucidated a cell-specific role whereby \( IP_3 \)-mediated \( Ca^{2+} \) release via the \( IP_3 \) receptor enters the mitochondria of preglomerular arteriolar smooth muscle cells by employing specific dyes for localization of \( [Ca^{2+}]_{im} \). Following ANG II administration, a rise in \( [Ca^{2+}]_{im} \) was noted, which peaked 2–3 s after the \( [Ca^{2+}]_{ic} \) peak, whereas in permeabilized cells the \( [Ca^{2+}]_{im} \) rise occurred almost immediately following the rise of \( [Ca^{2+}]_{ic} \) upon direct stimulation with high dosages of \( IP_3 \). Thus, their studies demonstrated that the \( [Ca^{2+}]_{ic} \) increase of \( IP_3 \)-induced \( Ca^{2+} \) release is followed closely by \( [Ca^{2+}]_{im} \) uptake. Although the functional role of the \( [Ca^{2+}]_{im} \) rise was not assessed in this article, nevertheless, it most likely contributes to the effective contraction and relaxation of the preglomerular smooth muscle cell. Whether a marked increase in \( [Ca^{2+}]_{im} \) over and above the normal range is a prelude to apoptosis is an important question that remains unanswered.

The other pertinent question the authors addressed in this article relates to the factors/molecules that perturb the ER-mitochondria \( Ca^{2+} \) communication. Previously, McGown and Sharma (5) demonstrated that the TGF-\( \beta \) interferes with the normal functioning of \( IP_3 \) receptors in vascular smooth muscle and mesangial cells. To gain insights into the mechanisms involved, the authors attempted to tease out events relevant to ER-mitochondria \( [Ca^{2+}]_{im} \) shuttle under the influence of TGF-\( \beta \). As expected from their prior work and the effect of TGF-\( \beta \) to downregulate \( IP_3 \) receptors, there was a remarkable inhibition of \( [Ca^{2+}]_{im} \) uptake when cells were pretreated with TGF-\( \beta \). This was noted with the challenge of ANG II in intact cells as well as to \( IP_3 \) exposure in permeabilized cells. It is likely that the interruption in ER-mitochondrial communication is due to direct effects on the \( IP_3 \) receptors as there was no structural difference of mitochondrial-ER spatial distribution, and \( [Ca^{2+}]_{im} \) uptake was not affected following \( Ca^{2+} \) loading of cells. This dramatic effect of TGF-\( \beta \) to disrupt ER-mitochondrial \( Ca^{2+} \) communication may well underlie the coordinated functioning of the glomerular vasculature in states associated with TGF-\( \beta \) overexpression, such as diabetic nephropathy (13). This inhibition of ER-mitochondrial communication may also play a role in protecting the cells from apoptosis which may be beneficial or potentially deleterious, depending on the participation of other anti- or proapoptotic signaling molecules that can tip the balance in either direction (Fig. 1).

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