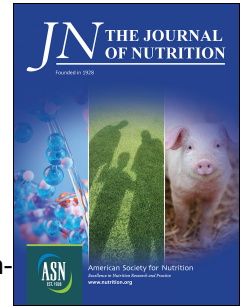


Journal Pre-proof

High-Salt Diet Disrupts Mitochondria-Associated Endoplasmic Reticulum Membrane:
A Unifying Mechanism Linking Nutrition to Systemic Pathologies

Hong-Li Han, Li-Min Zhang, Zi-Chen Wang, Hong Zhang, Jing Wang, Hui-Bo Du, Jun-
Ling Cui, Geng-Shen Zhang, Chun-Yu Niu, Zi-Gang Zhao



PII: S0022-3166(26)00238-5

DOI: <https://doi.org/10.1016/j.tjnut.2026.101589>

Reference: TJNUT 101589

To appear in: *The Journal of Nutrition*

Received Date: 5 February 2026

Revised Date: 13 April 2026

Accepted Date: 5 May 2026

Please cite this article as: H.-L. Han, L.-M. Zhang, Z.-C. Wang, H. Zhang, J. Wang, H.-B. Du, J.-L. Cui, G.-S. Zhang, C.-Y. Niu, Z.-G. Zhao, High-Salt Diet Disrupts Mitochondria-Associated Endoplasmic Reticulum Membrane: A Unifying Mechanism Linking Nutrition to Systemic Pathologies, *The Journal of Nutrition*, <https://doi.org/10.1016/j.tjnut.2026.101589>.

This is a PDF of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability. This version will undergo additional copyediting, typesetting and review before it is published in its final form. As such, this version is no longer the Accepted Manuscript, but it is not yet the definitive Version of Record; we are providing this early version to give early visibility of the article. Please note that Elsevier's sharing policy for the Published Journal Article applies to this version, see: <https://www.elsevier.com/about/policies-and-standards/sharing#4-published-journal-article>. Please also note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2026 American Society for Nutrition. Published by Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

High-Salt Diet Disrupts Mitochondria-Associated Endoplasmic Reticulum Membrane: A Unifying Mechanism Linking Nutrition to Systemic Pathologies

Hong-Li Han¹, Li-Min Zhang^{1,2,3}, Zi-Chen Wang^{1,2,3}, Hong Zhang^{1,2,3}, Jing Wang^{1,2,3}, Hui-Bo Du^{1,2,3}, Jun-Ling Cui⁴, Geng-Shen Zhang⁴, Chun-Yu Niu^{1,2,3*}, Zi-Gang Zhao^{1,2,3,5*}

¹ Institute of Microcirculation & Basic Medical College, Hebei North University, Zhangjiakou, Hebei, China.

² Hebei Key Laboratory of Critical Disease Mechanism and Intervention, Zhangjiakou & Shijiazhuang, Hebei, China.

³ Zhangjiakou Key Laboratory of Microcirculation and Shock, Zhangjiakou, Hebei, 075000, China.

⁴ Departments of Neurosurgery, The Second Hospital, Hebei Medical University, Shijiazhuang, Hebei, China.

⁵ Medical College, Zhangjiakou University, Zhangjiakou, Hebei, China.

Address correspondence to:

1. Zi-Gang Zhao, Institute of Microcirculation & Basic Medicine College, Hebei North University, Diamond South Road 11, Zhangjiakou, Hebei 075000, People's Republic of China. Tel: +86-313-4029223, +86-313-2116633; E-mail address: zzghyl@126.com, zhaozg@hebeinu.edu.cn.

2. Chun-Yu Niu, Institute of Microcirculation & Basic Medicine College, Hebei North University, Diamond South Road 11, Zhangjiakou, Hebei 075000, People's Republic of China. Tel: +86-313-4029118; E-mail address: ncylyxf@126.com, ncy@hebeinu.edu.cn.

The other authors details:

Hong-Li Han, Tel: +86-313-4029486; E-mail address: 18847468785@163.com

Li-Min Zhang, Tel: +86-313-4029486; E-mail address: zhangbmu@163.com

Zi-Chen Wang, Tel: +86-313-4029486; E-mail address: 2035244893@qq.com

Hong Zhang, Tel: +86-313-4029486; E-mail address: 2258190921@qq.com

Jing Wang, Tel: +86-313-4029486; E-mail address: wangjing1984@hebeinu.edu.cn

Hui-Bo Du, Tel: +86-313-4029486; E-mail address: dhb820424@126.com

Jun-Ling Cui, Tel: +86-311-83179550; E-mail address: cuijunling1@163.com

Geng-Shen Zhang, Tel: +86-311-83179550; E-mail address: horse90325@163.com

Running title: HSD and MAM during disease.

Journal Pre-proof

1 **Abstract:** The mitochondrial-associated endoplasmic reticulum membrane (MAM) is a
2 dynamic contact site formed through protein-mediated connections between the
3 endoplasmic reticulum (ER) and outer mitochondrial membrane. As a pivotal signaling and
4 metabolic hub, MAM regulates core cellular physiological processes, including calcium
5 homeostasis, lipid biosynthesis and trafficking, mitochondrial dynamics, autophagy,
6 apoptosis, and inflammasome formation and activation. Growing evidence indicates that
7 the disruption of MAM integrity and function is closely associated with various disorders
8 induced by excessive salt consumption. High salt intake perturbs ER-mitochondrial calcium
9 ion exchange, partly through elevated intracellular sodium concentrations, leading to the
10 structural and functional impairment of MAM. This disruption of calcium homeostasis
11 subsequently triggers the ER and oxidative stress responses, exacerbating cellular
12 damage. Concurrently, high-salt diets interfere with MAM-mediated lipid synthesis and
13 transport, contributing to mitochondrial dysfunction and accelerating disease development.
14 This review summarizes the involvement and underlying molecular mechanisms of MAM
15 in high-salt diet-related disorders including hypertension, cardiovascular disease, obesity,
16 and metabolic dysfunction-associated fatty liver disease. Furthermore, this review explores
17 the translational potential of targeting MAM as a therapeutic intervention, providing novel
18 insights for developing interventions that target inter-organelle communication to combat
19 salt-related systemic disorders.

20 **Keywords:** mitochondria-associated endoplasmic reticulum membrane, high-salt diet,
21 calcium homeostasis, lipid metabolism, metabolic disease

22 23 **Introduction**

24 In recent years, the mitochondria-associated endoplasmic reticulum membrane
25 (MAM), a specialized contact zone between the endoplasmic reticulum (ER) and
26 mitochondria, has been identified as a central macromolecular hub for cellular metabolic
27 regulation [1,2]. MAM coordinates critical signaling pathways that regulate diverse cellular
28 processes, precisely controlling calcium ion transport, lipid metabolism, energy balance,
29 and cell survival and death.

30 With ongoing changes in dietary patterns, excessive salt consumption has become a

31 major public health challenge worldwide. Substantial evidence indicates that excessive salt
32 consumption is a major risk factor for various metabolic disorders, including hypertension,
33 chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), and other cardiovascular
34 diseases [3]. These diseases exhibit interrelated pathophysiological characteristics that
35 collectively exacerbate a growing global disease burden. Beyond its well-characterized role
36 in increasing blood pressure, a high-salt diet exerts a wide-ranging influence on systemic
37 metabolic homeostasis by triggering inflammatory responses, promoting oxidative stress,
38 and disrupting lipid metabolism [4,5]. Despite the widespread recognition of the health
39 hazards posed by excessive salt consumption, the precise molecular mechanisms linking
40 dietary salt to disease pathogenesis remain unclear.

41 Emerging research indicates that an imbalance in intracellular homeostasis plays a
42 pivotal role in the pathological progression of high-salt-diet-related diseases. Under high-
43 salt exposure, MAM dysfunction and integrity compromises lipid metabolism and impairs
44 cellular function, thereby exacerbating the development of high-salt diet-related diseases.
45 Consequently, MAM is increasingly regarded as central metabolic regulators and promising
46 therapeutic targets for intervention in pathologies associated with high salt intake [6,7].

47 This review synthesizes the current evidence to propose that MAM dysfunction
48 serves as a central hub linking high-salt dietary stress to diverse pathologies through
49 disrupted cellular homeostasis. We elucidated the underlying molecular mechanisms
50 linking MAM impairment to disease pathogenesis and provided novel insights into the
51 pathophysiology of high-salt intake-related diseases. Furthermore, this study aims to
52 provide a theoretical foundation to guide future research and inform the development of
53 targeted clinical strategies to preserve or restore MAM integrity.

54 **1. Structure and Function of MAM**

55 MAM is a dynamic junctional structure formed between the outer mitochondrial and
56 ER membranes, and is primarily stabilized by the dynamic association of protein
57 complexes and lipid interactions [8]. These domains concentrate on diverse functional
58 molecules, including calcium channel complexes, bridging proteins, and
59 enzymes associated with lipid biosynthesis, collectively enabling MAM to serve as pivotal

60 regulatory hubs [8]. They coordinate essential cellular processes, such as lipid metabolism,
61 Ca^{2+} signaling, energy balance, and autophagy, which play crucial roles in both
62 physiological and pathological development [9,10]. In the following sections, we
63 systematically elucidate the structural and functional organization of MAM in terms of lipid
64 synthesis and transport, calcium signaling, energy metabolism, and cell survival [11].

65 **1.1 Lipid Synthesis and Transport**

66 Lipids are fundamental structural and functional components of MAM. Cardiolipin, the
67 primary phospholipid of the inner mitochondrial membrane, mitigates cardiomyocyte
68 damage caused by ischemia-reperfusion (I/R) injury by inhibiting cytochrome c release
69 from mitochondria. Furthermore, MAM regions are enriched in cholesterol and
70 sphingolipids, forming a localized platform for lipid synthesis and transport [12]. Cholesterol
71 transfer across the MAM is facilitated by caveolin-1, which forms cholesterol-enriched
72 signaling domains that regulate cholesterol transfer between the ER and mitochondria [13].
73 In addition, MAM harbors various enzymes involved in lipid metabolism, such as
74 phosphatidylserine synthase and long-chain fatty acid-CoA ligase 4, which regulate
75 phospholipid homeostasis by controlling the synthesis of phosphatidylserine,
76 phosphatidylcholine, and related species [14,15].

77 As a crucial platform for lipid synthesis and transport, MAM contributes to membrane
78 assembly, lipid metabolism regulation, vesicle formation, and transport. Contact between
79 the ER and mitochondria facilitates efficient lipid exchange and couples phospholipid
80 synthesis with cholesterol metabolism. Lipid transporters within the MAM, including
81 oxidase assembly protein 1 (OXA1) and ceramide transfer protein (CERT), synergistically
82 regulate the synthesis and transport of fatty acids, triglycerides, and other lipid species [16].
83 The coordinated activity of ER-derived fatty acid synthase and mitochondrial fatty acid β -
84 oxidase functions synergistically within the MAM to maintain lipid homeostasis, thereby
85 supporting the functional requirements of the cell membranes and organelles. Furthermore,
86 MAM influences the synthesis and degradation of lipid droplets by regulating fatty acid
87 uptake and release, thereby regulating cellular energy metabolism [17]. Thus, the lipid
88 transport mechanism mediated by MAM is closely associated with lipid metabolism
89 disorders, forming a pathological basis for lipid metabolism-related diseases associated

90 with high-salt diets [18].

91 **1.2 Calcium Channel Complexes and Calcium Ion Signaling**

92 The calcium channel complex located in MAM is a key regulator of intracellular calcium
93 signaling. This complex comprises ER calcium-releasing channels, mitochondrial calcium
94 channel proteins on both the inner and outer membranes, and ER calcium-uptake proteins.
95 Among these, inositol 1,4,5-trisphosphate receptors (IP3Rs) in the ER mediate calcium ion
96 release, the voltage-dependent anion channel (VDAC) in the mitochondrial outer
97 membrane facilitates calcium entry into the intermembrane space, and the mitochondrial
98 calcium uniporter (MCU) in the mitochondrial inner membrane transports calcium ions into
99 the mitochondrial matrix [19]. Thus, after release from the ER, calcium ions must cross
100 both the ER and outer mitochondrial membranes before being transported into the
101 mitochondrial matrix via the MCU. This transmembrane process is crucial for regulating
102 cellular energy metabolism, activating rate-limiting enzymes in glycolysis, and promoting
103 ATP synthesis [20,21].

104 As the primary intracellular calcium stores, the ER and mitochondria maintain close
105 physical contact and functional crosstalk through MAM, enabling the precise regulation of
106 calcium ion signaling and cellular calcium homeostasis. Within the MAM, IP3R interacts
107 with VDAC1 via the molecular chaperone glucose-regulated protein 75 (GRP75),
108 effectively facilitating calcium ion exchange from the ER to the mitochondria [22]. Once
109 inside the mitochondrial matrix, calcium ions activate calcium-sensitive metabolic enzymes,
110 thereby regulating cellular energy production and metabolism, which in turn influence
111 cellular function and fate. Notably, the precise dynamic regulation of calcium ions governs
112 cellular physiological processes and directly influences cell death; excessive calcium influx
113 into the mitochondria dissipates the mitochondrial membrane potential, disrupts function,
114 and triggers apoptotic pathways [23]. Therefore, MAM-mediated calcium ion signaling not
115 only participates in the control of normal cellular functions but also in stress responses and
116 disease progression.

117 MAM also functions as a key hub in energy metabolism. Mitochondria, acting as the
118 cellular "powerhouse," generate ATP via oxidative phosphorylation, whereas the ER
119 participates extensively in carbohydrate and lipid metabolism as well as protein synthesis.

120 By establishing physical membrane contact, MAM facilitates interactions between the two
121 organelles, thereby maintaining cellular energy homeostasis [24]. Signaling events within
122 the MAM regulate mitochondrial energy production, influencing oxidative phosphorylation,
123 ATP synthesis, and respiratory chain efficiency. Through the calcium signaling-mediated
124 activation of mitochondrial dehydrogenases and other metabolic enzymes, MAM
125 influences the rate of ATP synthesis. Additionally, MAM participates in the regulation of
126 glycolysis-related metabolic pathways, such as glycogenolysis and lactate production[25].
127 Collectively, MAM not only controls mitochondrial ATP production, but also exerts
128 pleiotropic effects on cellular and organismal energy metabolism.

129 **1.3 Bridging Proteins**

130 Beyond calcium channel complexes, MAM also contains specialized bridging proteins
131 that regulate calcium signaling by dynamically controlling the physical contact between the
132 ER and mitochondria. GRP75, a crucial bridging protein that connects ER-resident IP3Rs
133 with mitochondrial VDACs, forms a complete calcium channel complex for efficient calcium
134 transfer. Mitofusin (MFN), a mitochondrial fusion protein, promotes mitochondrial calcium
135 transport by regulating contact points between the ER and mitochondria [26]. In
136 cardiomyocytes, MFN2 mediates the connection between the ER and mitochondria and
137 regulates calcium signaling between these organelles. However, the regulatory role of
138 MFNs remains controversial. Some evidence suggests that MFN2 also acts as a negative
139 modulator, reducing ER-mitochondria contact to prevent excessive calcium accumulation
140 and cytotoxic overload [27]. This dual functionality highlights the complexity of MFN2 in
141 maintaining calcium homeostasis in the MAM.

142 **1.4 Other Functional Proteins**

143 Beyond the core structural and signaling proteins mentioned above, MAM also
144 enriched multiple regulatory proteins involved in autophagy, mitochondrial dynamics,
145 reactive oxygen species (ROS) generation, and inflammatory responses. For example,
146 AMP-activated protein kinase (AMPK) regulates autophagy by sensing the cellular energy
147 status and prevents mitochondrial calcium overload by inhibiting MAM formation [28].
148 Additionally, autophagy-related molecules, such as PTEN-induced kinase 1 (PINK1) and
149 Beclin-1 (BECN1), are enriched in MAM, where they participate in autophagy initiation and

150 activation. Under stress conditions, MAM recruits ROS-generating proteins, including
151 endoplasmic reticulum oxidoreductase 1 (ERO1) and p66Shc. These proteins directly
152 contribute to ROS generation, thereby influencing the cellular redox balance and
153 determining cell survival and death [29].

154 Autophagy is a key quality-control mechanism for degrading damaged cellular
155 components to maintain homeostasis, and is closely associated with MAM [30]. During
156 nutrient deprivation or other stresses, autophagy-related proteins localized to MAM (such
157 as ATG14L) activate the mechanistic target of rapamycin complex 2 (mTORC2), thereby
158 promoting the production and recruitment of autophagy-inducing factors and initiating
159 autophagosome formation [31]. PINK1, a key regulator of mitophagy, localizes to the MAM
160 and plays an essential role in mitochondrial regulation and cellular health. Following
161 autophagy stimulation, PINK1 and BECN1 co-re-localize to MAM, strengthening ER-
162 mitochondrial contacts and promoting the formation of autophagosome precursors
163 (omegasomes) [32]. Silencing *Pink1* impaired BECN1 enrichment in MAM, revealing a
164 novel role for PINK1 in autophagy regulation. Thus, MAM serves as a central platform that
165 integrates mitochondrial-ER communication with autophagy regulation by focusing on key
166 proteins such as PINK1. Dysfunction of the MAM-autophagy axis contributes to the
167 development of various diseases.

168 The dynamic equilibrium between mitochondrial fusion and fission is crucial for
169 preserving mitochondrial function and cellular metabolism. Abnormal mitochondrial
170 dynamics are involved in various pathologies, including aging and neurodegenerative
171 diseases. Within the MAM, MFN2 promotes the fusion of the outer mitochondrial
172 membrane by forming homodimers or heterodimers with MFN1 [33]. Additionally, MFN2
173 enhances the connection between the ER and mitochondria by interacting with ER, thereby
174 promoting mitochondrial fusion. Structural studies have indicated that the C-terminal α -
175 helical region of MFN2 forms homodimers or heterodimers, allowing adjacent mitochondria
176 to approach each other and ultimately fuse [34].

177 MAM also plays a decisive role in the modulation of cell survival and apoptosis. MAM
178 participates in the initiation and suppression of apoptotic signals by integrating calcium
179 signaling, lipid transport, and direct organelle crosstalk. In response to internal and external

180 stimuli, MAM modulates the activity of key apoptotic factors, such as Bcl-2 family proteins
181 and caspases, thereby initiating or inhibiting apoptosis and ultimately influencing cellular
182 survival and death [35]. For example, MAM induces apoptosis by regulating the calcium
183 ion and caspase pathways. Conversely, MAM may enhance cell survival by upregulating
184 the activity of the anti-apoptotic Bcl-2 family. The Bcl-2 family coordinates the balance
185 between autophagy and apoptosis by regulating mitochondrial outer membrane
186 permeability. Additionally, MAM participates in modulating stress response-related
187 pathways that aid cells in maintaining survival under adverse conditions [36].

188 In summary, as a critical junction linking the ER and mitochondria, MAM plays an
189 irreplaceable regulatory role in maintaining cellular homeostasis by precisely coordinating
190 core cellular processes, such as lipid metabolism, calcium signaling, energy balance,
191 autophagy, dynamics, and apoptosis (Figure 1). Their proper function is essential for
192 cellular health, and MAM dysfunction is increasingly recognized as a contributing factor in
193 a wide range of diseases.

194 **2. Effects of High-Salt Diets on MAM Function**

195 **2.1 Calcium Homeostasis Dysregulation and Mitochondrial Dysfunction**

196 High salt intake promotes mitochondrial calcium overload by increasing Ca^{2+} leakage
197 across the MAM, thereby stimulating excessive ROS production and impairing ATP
198 synthesis. Mitochondrial calcium overload not only directly stimulates ROS generation,
199 thereby damaging mitochondrial membrane integrity and function but also inhibits ATP
200 synthase activity, leading to impaired ATP production. Together, these disturbances disrupt
201 energy metabolism and damage cellular integrity and function [37]. This pathological
202 cascade is largely mediated by the IP3R-GRP75-VDAC pathway. Briefly, IP3R serves as
203 the primary calcium ions release channel in the ER, whereas the molecular chaperone
204 GRP75 stabilizes the interaction between IP3R and the outer mitochondrial membrane
205 VDAC1. They then form a ternary complex that facilitates the directional transfer of calcium
206 ions from the ER to mitochondria. In nephrotic syndrome models, elevated expression of
207 components along the IP3R-GRP75-VDAC1-MCU axis is closely correlated with the
208 development of proteinuria [38]. These studies indicate that the IP3R-GRP75-VDAC1

209 pathway plays a crucial role in the development of high-salt intake-induced diseases.

210 Despite the established role of the IP3R-GRP75-VDAC1 complex in high-salt-induced
211 pathology, the precise molecular mechanisms by which high-salt stress directly modulates
212 MAM-associated proteins remain incompletely understood. Existing evidence suggests
213 both direct and indirect pathways. Directly, elevated intracellular sodium ion concentrations
214 may influence the conformation or post-translational modifications of these proteins. For
215 instance, high-salt conditions have been shown to enhance IP3R expression, potentially
216 modulating calcium channel activity and inducing calcium overload [39], although the
217 upstream kinases involved remain to be fully characterized. Additionally, sodium-induced
218 changes in membrane lipid composition and fluidity may affect the spatial organization and
219 stability of MAM protein complexes. Indirectly, high-salt stress triggers ROS production [40],
220 which can secondarily impact MAM protein expression and function [41]. Oxidative stress,
221 for example, has been reported to promote the dissociation of the IP3R-GRP75-VDAC1
222 complex, thereby disrupting calcium homeostasis [42]. Furthermore, high-salt-induced
223 activation of stress-responsive signaling pathways, such as AMPK [43], which may
224 transcriptionally regulate the expression levels of MAM-associated proteins [31]. Direct
225 biophysical evidence, such as structural studies demonstrating sodium binding to these
226 proteins or high-resolution imaging of MAM complex dynamics under high-salt conditions,
227 is currently lacking. Nevertheless, the existing indirect evidence supports the concept that
228 high-salt stress disrupts MAM integrity through multifaceted mechanisms. Future studies
229 employing advanced techniques, including cryo-electron microscopy, proximity ligation
230 assays, and targeted proteomics, are warranted to elucidate the precise molecular events
231 linking high-salt exposure to MAM dysfunction.

232 **2.2 Endoplasmic Reticulum Stress**

233 The sigma-1 receptor (Sigma-1R) is an ER-localized membrane protein that is highly
234 enriched at MAM, where it physically interacts with IP3R to stabilize calcium signaling
235 between the ER and mitochondria [44]. Under physiological conditions, Sigma-1R acts as
236 a molecular chaperone at the MAM, modulating IP3R activity and preventing excessive
237 calcium transfer to mitochondria. A high-salt diet may dysregulate Sigma-1R expression or
238 function, thereby compromising its stabilizing role at the MAM. Specifically, high-salt-

239 induced Sigma-1R dysfunction leads to uncontrolled IP3R-mediated calcium
240 release, thereby exacerbating endoplasmic reticulum stress (ERS) and disturbing calcium
241 homeostasis [45]. Hence, high-salt diet triggers ERS and activates the unfolded protein
242 response (UPR) through the Sigma-1R. One major UPR branch involves protein kinase R-
243 like endoplasmic reticulum kinase (PERK), whose activation leads to phosphorylation of
244 eukaryotic initiation factor 2alpha (eIF2 α). Phosphorylated eIF2 α selectively activates
245 transcription factor 4 (ATF4), which in turn upregulates the pro-apoptotic protein
246 C/EBP-homologous protein (CHOP) [46]. CHOP promotes apoptosis through multiple
247 downstream mechanisms, including downregulation of anti-apoptotic factors, such as BCL-
248 2, BCL-XL, and MCL-1, and upregulation of pro-apoptotic proteins, such as BAX and BAK.
249 These alterations ultimately decrease mitochondrial membrane potential and initiate
250 apoptotic process [47]. Upregulation of CHOP not only promotes hepatocyte apoptosis and
251 impairs hepatic metabolism but also exacerbates insulin resistance [48]. Furthermore,
252 CHOP induces a high expression of ERO1 α , which enhances IP3R-mediated Ca²⁺ release,
253 leading to mitochondrial calcium overload and structural abnormalities, ultimately activating
254 the mitochondria-dependent apoptotic pathway [49]. Thus, Sigma-1R serves as a critical
255 link between high-salt stress, MAM dysfunction, ERS, and downstream apoptotic pathways
256 through the PERK-eIF2 α -ATF4-CHOP pathway.

257 **2.3 Abnormal Lipid Metabolism**

258 High salt consumption disrupts MAM function, partly through the activation of sterol
259 regulatory element-binding protein 1c (SREBP1c), a transcription factor that promotes
260 hepatic lipogenesis and insulin resistance, thereby exacerbating metabolic syndrome [50].
261 Activated SREBP1c upregulates key lipogenic enzymes such as fatty acid synthetase (FAS)
262 and acetyl-coenzyme A carboxylase (ACC), thereby enhancing fatty acid synthesis [51].
263 Concurrently, lipid transport proteins in MAM play a crucial role in maintaining lipid
264 metabolism. A high-salt diet disrupts these transport proteins, impairing normal lipid
265 transfer from the ER to the mitochondria and leading to the pathological accumulation of
266 lipid droplets in hepatocytes [52,53]. Specifically, CERT facilitates lipid exchange between
267 the ER and the mitochondria. A high-salt diet causes CERT dysfunction, which, in turn,
268 disrupts lipid transport and lipid droplet accumulation. Similarly, phosphofurin acid cluster

269 sorting protein 2 (PACS-2), a regulator of MAM integrity, participates in ER-mitochondrial
270 lipid exchange. PACS-2 is impaired by high salt intake, further contributing to aberrant lipid
271 deposition and hepatic steatosis [54]. Collectively, a high-salt diet promotes hepatic
272 lipogenesis, worsens insulin resistance, and aggravates metabolic syndrome by activating
273 SREBP1c and disrupting MAM-mediated lipid transport [55].

274 **2.4 Inflammasome Activation and Inflammation**

275 The activated NOD-like receptor family pyrin domain containing 3 (NLRP3)
276 inflammasome promotes the maturation and release of IL-1 β , triggering potent
277 inflammatory responses. This mechanism has been validated in various salt-sensitive
278 conditions, including obesity, T2DM, and cardiovascular diseases [56]. MAM functions as
279 a critical platform for NLRP3 inflammasome assembly and its structural and functional
280 integrity directly influence inflammatory activation. A high-salt diet perturbs calcium
281 channels (such as IP3R and VDAC) within the MAM, leading to the disruption of calcium
282 transport. The resulting calcium overload and excessive ROS production further promote
283 NLRP3 inflammasome activation [57]. Additionally, oxidative stress induced by a high-salt
284 diet activates thioredoxin-interacting protein (TXNIP), thereby initiating NLRP3
285 inflammasome formation and activation [58]. Therefore, high-salt diet promotes
286 inflammatory signaling via the TXNIP/NLRP3/IL-1 β axis. As a critical hub for NLRP3
287 assembly, MAM dysfunction not only disrupts calcium homeostasis and mitochondrial
288 performance but also amplifies inflammatory cascades, thereby exacerbating tissue injury
289 in salt-related diseases.

290 **3. The Role of MAM in the Progression of Diseases Associated with High-Salt Diets**

291 Long-term high salt consumption is a well-established risk factor for metabolic
292 disorders with multisystem pathophysiological interactions. By disrupting the structure and
293 function of MAM, excessive dietary salt interferes with key cellular processes, including
294 intracellular calcium homeostasis, mitochondrial dynamics, lipid metabolism, and
295 autophagy, which collectively promote the onset and progression of various high-salt diet-
296 related diseases, such as cardiovascular disease, obesity, fatty liver disease, and insulin
297 resistance [59]. Therefore, high-salt-diet-induced metabolic disorders are closely

298 associated with dysfunctional MAM.

299 Before discussing individual diseases, it is worth noting that the sensitivity of MAM to
300 high-salt stress may vary across different organs and cell types. Although the core MAM
301 machinery, such as the IP3R-GRP75-VDAC1 complex and MFN2, is ubiquitously
302 expressed, tissue-specific isoforms, differential expression levels of regulatory partners,
303 and distinct metabolic and calcium-handling demands may confer variable susceptibility to
304 high-salt-induced MAM disruption. For example, cardiomyocytes and hepatocytes, which
305 rely heavily on mitochondrial calcium homeostasis for energy production, may be
306 particularly vulnerable to MAM dysfunction, whereas other cell types with lower metabolic
307 demands may exhibit greater resilience. A comprehensive understanding of these tissue-
308 specific differences remains an important area for future investigation. Nonetheless, the
309 following sections summarize the current evidence linking MAM dysfunction to specific
310 high-salt diet-related diseases across multiple organ systems.

311 **3.1 Role of MAM in Cardiovascular Diseases Associated with High-Salt Diets**

312 MAM dysfunction plays a central role in the pathogenesis of high-salt-diet-induced
313 cardiovascular diseases. In cardiomyocytes, MAM disruption causes an imbalance in
314 calcium homeostasis, which impairs myocardial contraction and relaxation, ultimately
315 leading to heart failure [60]. Concurrently, a high-salt diet upregulates transient receptor
316 potential canonical 3 (TRPC3) expression, enhancing TRPC3-mediated calcium influx in
317 vascular smooth muscle cells (VSMCs) and promoting vasoconstriction [61]. Additionally,
318 high salt intake induces mitochondrial dysfunction and abnormal autophagy. MAM
319 dysregulation further exacerbates myocardial injury through intertwined mechanisms
320 involving oxidative stress, energy metabolism disorders, and apoptosis, thereby promoting
321 the development and progression of cardiovascular diseases [62].

322 **3.1.1 MAM and Hypertension Associated with High-Salt Diets**

323 Hypertension is one of the most common disorders associated with an excessive salt
324 intake. High salt intake disrupts the MAM function by elevating intracellular calcium ion
325 levels, leading to an imbalance in calcium homeostasis. This disturbance impairs the
326 contraction-relaxation equilibrium in VSMCs, ultimately resulting in hypertension [63]. Both
327 clinical observations and experimental studies have demonstrated that a high-salt diet

328 significantly increases TRPC3 expression, with TRPC3 expression positively correlated
329 with salt intake. In THP-1 monocytes, high-salt treatment elevates TRPC3 mRNA levels
330 and increases intracellular calcium ions [64]. Similarly, in salt-sensitive hypertensive rats,
331 TRPC3 expression was significantly increased in the aorta, carotid artery, and mesenteric
332 artery [65].

333 MAM participates in the pathogenesis of hypertension by regulating mitochondrial
334 function. A high salt intake disrupts mitochondrial dynamics in MAM, leading to impaired
335 cellular energy metabolism and increased oxidative stress, which collectively promotes
336 development [66,67]. Moreover, MAM-mediated lipid metabolism is disrupted in high-salt
337 environments, increasing oxidative stress and inflammatory responses, which collectively
338 promote the onset and progression of hypertension [68]. As MAM participates in regulating
339 vascular endothelial function, MAM dysfunction impairs endothelial-dependent
340 vasoregulation, further exacerbating hypertension [11]. Given the association between
341 hypertension and ERS, enhanced autophagy or ER-autophagy alleviates ERS and
342 reduces hypertensive tissue damage by clearing misfolded proteins and restoring ER
343 homeostasis [69].

344 **3.1.2 MAM and Myocardial Damage Associated with High-Salt Diets**

345 NLRP3 inflammasome recruitment and MAM composition play crucial roles in
346 myocardial I/R injury. Inhibition of caspase-1 activity significantly improves cardiac
347 contractility following I/R injury [70]. Likewise, ASC-deficient mice exhibit attenuated levels
348 of I/R-induced inflammatory cytokines IL-1 β and IL-18 along with reduced myocardial
349 infarction, fibrosis, and cardiac dysfunction [71]. Several proteins that maintain ER-
350 mitochondrial connections have been associated with I/R injury. For instance, loss of the
351 mitochondrial inner membrane motor-regulated protein optic atrophy 1 (OPA1) increases
352 myocardial sensitivity to I/R injury, whereas inhibition of mitochondrial fission protein 1
353 (FIS1) and dynamin-related protein 1 (DRP1) exerts cardioprotective effects [72].

354 Ca²⁺ signaling plays a pivotal role in the excitation-contraction coupling in
355 cardiomyocytes. I/R induces cytoplasmic Ca²⁺ accumulation, leading to mitochondrial
356 calcium overload. This activates the mitochondrial matrix chaperone cyclosporin D (CypD),
357 triggering the opening of the mitochondrial permeability transition pore and ultimately, cell

358 death [73]. Reducing ER-mitochondria contacts effectively prevents Ca^{2+} accumulation
359 and consequent cell death. Although abnormal calcium homeostasis is closely associated
360 with diabetic cardiomyopathy, the specific mechanisms linking MAM to diabetes-induced
361 calcium dysregulation remain to be fully elucidated [74-76]. High salt intake induces
362 mitochondrial calcium overload by enhancing calcium release from the ER, thereby
363 triggering mitochondrial dysfunction, apoptosis, and impaired myocardial metabolism,
364 which collectively increase the cardiac workload [77]. MAM plays a crucial role in
365 maintaining calcium homeostasis and mitigating high-salt-induced cardiomyocyte injury by
366 regulating the IP3R-GRP75-VDAC1 complex [78]. Additionally, a high-salt diet may alter
367 intracellular signaling and energy metabolism, creating permissive conditions for the
368 initiation and progression of myocardial I/R injury [79].

369 The mitophagy receptor FUN14 domain-containing 1 (Fundc1) is a highly conserved
370 mitochondrial protein containing three transmembrane α -helices. Its amino terminus (N-
371 terminus) faces the cytosol, whereas its carboxy terminus (C-terminus) is located in the
372 intermembrane space. Fundc1 contains a microtubule-associated protein 1A/1B light chain
373 3 (LC3)-binding motif, enabling interaction with LC3 to recruit mitochondria to
374 autophagosomes and promote mitochondrial fission by directly interacting with Drp1 at the
375 MAM [80,81]. Fundc1 is essential for MAM integrity and normal Ca^{2+} transport from the ER
376 to the mitochondria in cardiomyocytes. Cardiac-specific knockout of Fundc1 disrupts the
377 MAM architecture and results in cardiac dysfunction [16]. Under high salt conditions, AMPK
378 inactivation increases Fundc1 stability, inducing abnormal MAM formation, mitochondrial
379 calcium accumulation, and mitochondrial dysfunction, thereby contributing to cardiac
380 dysfunction. Conversely, AMPK activation reverses high-salt-induced myocardial injury by
381 inhibiting high-glucose-promoted MAM formation, mitochondrial Ca^{2+} overload, and
382 mitochondrial dysfunction [6]. Collectively, these findings suggest that pharmacological
383 strategies targeting AMPK activation, FUNDC1 modulation, or the IP3R-GRP75-VDAC1
384 complex may offer novel therapeutic approaches for high-salt-induced myocardial injury.

385 **3.1.3 MAM and Atherosclerosis-Related Diseases**

386 Mitochondrial and ER calcium signaling oscillations are fundamental for maintaining
387 the physiological properties of vascular cells. Precise Ca^{2+} transport from the ER to

388 mitochondria is largely governed by the composition and regulation of MAM [82].
389 Mitochondrial fusion proteins MFN1 and MFN2 are particularly important [83]. Combined
390 knockout of *Mfn1* and *Mfn2* in adult mouse cardiomyocytes impaired cardiac function,
391 increased left ventricular end-diastolic volume, and reduced cardiac contraction fraction. In
392 the *Mfn2*-knockout model, the ER-mitochondria contact area was significantly diminished,
393 Ca^{2+} transport was defective, and mitochondrial ROS levels were elevated [84].

394 Based on these observations, several lines of evidence suggest that MAM dysfunction
395 may contribute to atherosclerosis through multiple interconnected pathways. One
396 prominent mechanism involves the generation of ROS. Studies have indicated that reactive
397 chemicals such as ROS play a pivotal role in atherosclerosis. During atherosclerosis,
398 cholesterol crystals are deposited in the vessel wall, triggering inflammatory damage.
399 Excessive ROS production and consequent activation of the NLRP3 inflammasome are
400 particularly common in this process. Macrophages phagocytose cholesterol crystals to
401 trigger NLRP3 inflammasome activation, a process involving a series of molecular events
402 including lysosomal protease leakage into the cytoplasm, mitochondrial ROS
403 overproduction, and decreased intracellular potassium ion concentration [85].

404 Given the well-established correlation between excessive ROS and MAM structural
405 damage, it has been hypothesized that MAM injury contributes to atherosclerosis
406 progression, potentially through ROS-mediated pathways. However, it is important to
407 recognize that ROS directly damage vascular endothelial cells and promote
408 atherosclerosis through MAM-independent pathways, such as lipid peroxidation and
409 endothelial dysfunction. Furthermore, the relationship between MAM dysfunction and
410 atherosclerosis is complicated by the fact that multiple pathological drivers, including
411 dyslipidemia, inflammation, and oxidative stress, converge in this disease, making it difficult
412 to isolate the specific contribution of MAM disruption to atherosclerosis. Therefore, while
413 the hypothesis that MAM injury promotes atherosclerosis via ROS is mechanistically
414 plausible, it currently remains an inference based on associative evidence rather than a
415 validated causal pathway.

416 In addition to ROS-mediated mechanisms, MAM dysfunction may also promote
417 atherosclerosis by affecting lipid metabolism and apoptosis. A high-salt diet disrupts lipid

418 metabolism via SREBP activation, whereas MAM mitigates salt-induced dyslipidemia by
419 regulating phospholipid synthesis and cholesterol metabolism. Furthermore, a high-salt
420 diet activates caspase-dependent apoptosis via oxidative stress and ERS, and MAM
421 suppresses salt-induced cell death by modulating Bcl-2 family proteins and caspase
422 activity [86].

423 The inflammatory pathway, particularly the NLRP3 inflammasome, represents another
424 critical link between MAM to atherosclerosis. Notably, the NLRP3 inflammasome, which
425 can be assembled at the MAM, has been extensively implicated in atherosclerosis.
426 Apolipoprotein E (ApoE)-deficient mice spontaneously develop atherosclerotic plaques
427 under high salt stress. IL-1 β deficiency significantly reduces the atherosclerotic lesion area
428 in ApoE-null mice by up to 30% [87]. Similarly, IL-18 receptor (IL-18R) deficiency exerts
429 anti-atherosclerotic effects. Nevertheless, NLRP3 inflammasome may not be the sole
430 inflammatory activation in atherosclerosis [88]. Previous studies have indicated that in
431 ApoE-knockout mice, genetic ablation of key NLRP3 pathway components (such as
432 NLRP3, ASC, or Caspase-1) does not significantly alter atherosclerotic lesions compared
433 to ApoE-knockout control or wild-type mice [89]. These conflicting findings highlight the
434 need for further investigations to clarify the specific role of the NLRP3 inflammasome in
435 the pathogenesis of atherosclerosis.

436 Collectively, while existing evidence points to plausible connections between MAM
437 dysfunction and atherosclerosis through ROS, lipid metabolism, and inflammatory
438 pathways, direct experimental evidence linking MAM to the pathogenesis of human
439 atherosclerosis remains limited. The proposed role of MAM in atherosclerosis is primarily
440 inferred from associations involving ROS, NLRP3 inflammasome activation, and lipid
441 dysregulation rather than from direct mechanistic studies. Future research should prioritize
442 tissue-specific MAM-targeted interventions in preclinical atherosclerosis models to
443 establish causality, examine MAM integrity in human atherosclerotic lesions, and
444 investigate whether MAM dysfunction precedes or merely accompanies atherosclerotic
445 progression. Addressing these gaps is essential for determining whether MAM is a viable
446 therapeutic target in salt-related cardiovascular diseases.

447 **3.2 Role of MAM in Obesity Induced by High-Salt Diets**

448 A high-salt diet is an important contributor to obesity, and its mechanism is closely
449 linked to MAM dysfunction. Impaired MAM activity disrupts the lipid metabolism in
450 adipocytes, thereby affecting the balance between MAM synthesis and breakdown.
451 Specifically, MAM dysfunction reduces the activity of key lipolytic enzymes, such as
452 triglyceride lipase and hormone-sensitive lipase, thereby inhibiting triglyceride hydrolysis.
453 Concurrently, mitochondrial dysfunction caused by MAM impairment suppresses fatty acid
454 β -oxidation. Together, these defects diminish lipid clearance, promote fat accumulation,
455 and ultimately promote obesity [90]. In addition, MAM regulates autophagy in adipocytes.
456 Dysfunctional MAM impairs autophagy in fat cells, leading to insufficient degradation of
457 lipid droplets and aggravating abnormal intracellular lipid accumulation, which further
458 exacerbates obesity [91]. Although direct evidence in high-salt-induced obesity models is
459 limited, pharmacological activation of AMPK to restore MAM integrity represents a potential
460 therapeutic strategy that warrants further investigation.

461 **3.3 Role of MAM in Metabolic Dysfunction-Associated Steatotic Liver Disease**

462 Mitochondrial dysfunction plays a central role in the pathogenesis of metabolic
463 dysfunction-associated steatotic liver disease (MASLD). Under oxidative stress, inhibition
464 of mitochondrial electron transport chain activity increases ROS production and causes
465 mitochondrial dysfunction. Mitochondrial dysfunction impairs hepatic mitochondrial β -
466 oxidation, leading to fatty acid accumulation, lipotoxicity, and the activation of
467 proinflammatory pathways. Defective mitophagy hinders the clearance of damaged
468 mitochondria and exacerbates cellular injury. Additionally, mutations and damage to
469 mitochondrial DNA further compromise mitochondrial function and disrupt the energy
470 metabolism. ROS overproduction contributes to hepatocyte injury and fibrogenesis,
471 collectively driving MASLD progression [92]. High-salt diet is a major contributor to MASLD
472 development. Beyond increasing blood pressure, excessive salt intake disrupts hepatic
473 lipid metabolism through multiple mechanisms, leading to abnormal fat accumulation in the
474 liver, thereby promoting the onset and progression of MASLD [93-95].

475 Excessive dietary salt intake is widely recognized as a key factor in metabolic
476 disorders [96]. Within the ER, sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) is the
477 core protein responsible for maintaining calcium homeostasis by pumping calcium ions

478 from the cytoplasm into the ER lumen at the expense of ATP [97]. Research has indicated
479 that high-salt diets impair SERCA function, leading to the abnormal release of calcium ions
480 from the ER into the cytosol via alternative channels. This process depletes the ER calcium
481 pool and causes excessive calcium accumulation in the cytoplasm (and ultimately in
482 mitochondria), thereby triggering mitochondrial dysfunction and apoptosis. When ER
483 function is disrupted by calcium homeostasis imbalance or protein misfolding, ERS is
484 induced, activating the UPR, a complex signaling network aimed at restoring ER
485 homeostasis [98]. However, sustained or severe ERS may contribute to the onset and
486 progression of metabolic diseases by triggering apoptosis and related pathways [99].

487 Heat shock protein A9 (HSPA9), a molecular chaperone localized to MAM, plays a
488 crucial role in maintaining MAM structure and regulating calcium homeostasis, lipid
489 metabolism, and mitochondrial function [100]. A high-salt diet promotes fatty acid synthesis
490 and triglyceride accumulation by activating the SREBP1c pathway, a key transcription
491 factor involved in fatty acid synthesis. SREBP1c activation upregulates key lipogenic
492 enzymes, including fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), and
493 stearoyl-CoA desaturase (SCD). As it serves as a critical platform for SREBP1c activation,
494 MAM dysfunction leads to excessive SREBP1c activation. Furthermore, altered HSPA9
495 expression exacerbates SREBP1c activation by affecting MAM structure and function,
496 thereby contributing to MASLD pathogenesis [101]. Although these strategies remain
497 largely experimental, they provide a rationale for developing MAM-targeted interventions
498 for salt-aggravated MASLD.

499 Collectively, a high-salt diet promotes hepatic lipogenesis, worsens insulin resistance,
500 and aggravates MASLD by activating SREBP1c and disrupting MAM-mediated lipid
501 transport. Beyond high-salt stress, emerging evidence from toxicological models supports
502 the central role of MAM in regulating ferroptosis in metabolic liver diseases [102]. However,
503 whether MAM disruption-induced ferroptosis contributes to high-salt diet-related liver
504 diseases remains unclear.

505 **3.4 Role of MAM in High-Salt Diet-Induced Insulin Resistance**

506 MAM influences insulin sensitivity by coordinating calcium homeostasis, lipid
507 metabolism, mitochondrial function, and insulin signaling pathways, thereby contributing to

508 the development of insulin resistance. MAM regulate Ca^{2+} transfer between the ER and
509 mitochondria. Dysregulation of the IP3R-Grp75-VDAC1 complex disrupts Ca^{2+} transport,
510 thereby impairing insulin sensitivity. A high-salt diet disrupts calcium homeostasis in MAM,
511 leading to reduced Akt kinase activity and diminished Akt phosphorylation, thereby
512 impeding insulin signaling and promoting insulin resistance. On the other hand, MAM
513 dysfunction also causes lipid metabolism disorders, enhances oxidative stress and
514 inflammatory responses, and impairs pancreatic beta cell metabolic function, collectively
515 exacerbating insulin resistance [103-105].

516 **3.5 Role of MAM in CKD**

517 Recent studies have revealed that MAM plays a crucial role in the progression of CKD
518 driven by high-salt intake. Excessive dietary salt intake increases oxidative stress and
519 inflammatory responses in the kidneys, leading to tubulointerstitial injury and fibrosis.
520 These effects stem, in part, from the key regulators of MAM in the cellular metabolism and
521 signaling networks. A high-salt diet induces mitochondrial dysfunction and ER stress in the
522 kidney [106], processes closely linked to the disruption of MAM integrity and function [107].
523 In CKD, MAM impairment disrupts the release of calcium ions from the ER to mitochondria
524 via complexes such as IP3R-GRP75-VDAC1. Calcium dyshomeostasis causes renal cell
525 dysfunction and exacerbates kidney injury. A high-salt diet affects lipid synthesis and
526 transport in MAM, leading to intracellular lipid accumulation. This persistently activates
527 ERS and inflammatory responses, triggering the UPR and promoting apoptosis, thereby
528 accelerating CKD progression [107]. MAM-associated proteins also contribute significantly
529 to the pathogenesis of CKD. For instance, in CKD, abnormal expression of Drp1 leads to
530 excessive mitochondrial fission, whereas reduced expression of MFN2 results in
531 diminished mitochondrial fusion, collectively altering mitochondrial morphology and
532 function [108]. A deeper understanding of the structure, function, and specific roles of MAM
533 in CKD pathophysiology will provide a scientific foundation for novel therapeutic strategies.
534 Future research should further explore the detailed mechanisms of MAM involvement in
535 CKD and evaluate the feasibility and efficacy of therapeutic strategies targeting MAM
536 integrity and signaling pathway.

537 **3.6 Role of MAM in T2DM**

538 High salt intake increases the risk of developing T2DM through multiple mechanisms.
539 For instance, a high-salt diet induces insulin resistance by reducing insulin sensitivity,
540 inhibiting insulin mRNA expression, impairing insulin signaling, and increasing angiotensin
541 II production [109]. During the progression of T2DM, glucotoxicity-induced pancreatic β -
542 cell dysfunction is associated with alterations in the mitochondria and ER. Studies have
543 indicated that under high-glucose and high-fat conditions, pancreatic β -cells exhibit MAM
544 dysfunction, leading to increased mitochondrial calcium uptake, mitochondrial dysfunction,
545 and subsequent impairment of glucose-stimulated insulin secretion. MAM dysfunction
546 further triggers ERS and apoptosis, exacerbating β -cell injury [110].

547 Ca^{2+} signaling in MAM regulates mitochondrial bioenergetics [111], and mitochondrial
548 Ca^{2+} uptake is critical for the glucose-stimulated ATP increase in β -cells [112]. Studies have
549 revealed that β -cell dysfunction associated with glucotoxicity increases organelle
550 confinement in human islets and INS-1E cells, whereas the mitochondrial Ca^{2+} transfer
551 capacity progressively declines over time [113]. These findings suggest that MAM
552 represents a potential therapeutic target for restoring insulin sensitivity in the peripheral
553 tissues of T2DM patients.

554 **3.7 MAM and Alzheimer's Disease**

555 MAM are increasingly being recognized as pivotal players in the pathogenesis of
556 Alzheimer's disease (AD). Recent studies indicated that high-salt diets are associated with
557 an elevated overall risk of dementia, and high salt intake is significantly correlated with
558 cognitive impairment, a connection likely mediated by neuronal dysfunction and impaired
559 synaptic plasticity [114]. In animal models, a high-salt diet causes cognitive impairment,
560 neuronal loss, and immune activation, leading to tau protein accumulation [115]. For
561 example, a high-salt diet exacerbates anxiety-like behavior, cognitive decline, and neuronal
562 loss in the hippocampal CA1 region in AD mice. The influence of high salt intake on
563 cognitive function and dementia risk involves multiple mechanisms, including hypertension,
564 oxidative stress, and inflammatory responses, all of which are associated with AD
565 pathogenesis [116].

566 MAM dysfunction contributes to AD through several interconnected pathways,
567 including disruption of Ca^{2+} homeostasis, induction of ERS, defective mitophagy,

568 imbalance in mitochondrial fission and fusion, lipid metabolism disorders, and heightened
569 inflammation. These alterations collectively represent the key pathophysiological
570 mechanisms of AD. Altered MAM function-driven lipid metabolism disorders and calcium
571 imbalances emerge in the initial stages of AD progression and may contribute to early
572 cognitive decline [117]. Mitochondrial dysfunction, another key feature of AD, leads to
573 abnormal cellular energy metabolism and impaired neuronal function. MAM dysfunction
574 exacerbates mitochondrial damage, compromises neuronal viability, and accelerates the
575 progression of AD. For instance, abnormalities in MAM-resident proteins, such as VDAC
576 and IP3R cause mitochondrial calcium overload and disrupt energy synthesis [118].

577 Inflammation plays a pivotal role in AD by exacerbating excessive A β deposition and
578 tau hyperphosphorylation, ultimately resulting in neuronal injury. MAM dysfunction further
579 intensifies inflammatory responses, thereby aggravating AD pathology. Notably, the MAM
580 is a key site for A β generation. For instance, abnormal expression of inflammation-
581 associated proteins in the MAM, such as ACAT1, may promote A β generation. In addition,
582 amyloid precursor protein (APP), β -site APP-cleaving enzyme 1 (BACE1), and γ -secretase
583 are all localized in the MAM. BACE1 cleaves APP to produce sAPP β and the C-terminal
584 fragment C99. C99 is transported to MAM and cleaved by γ -secretase to yield A β and APP
585 intracellular domain (AICD). Furthermore, MAM is considered a key pathway for A β entry
586 into mitochondria, although alternative routes, such as direct translocation through
587 mitochondrial membrane channel proteins (e.g., transient receptor potential melastatin-2
588 (TRPM2) channel) or Presenilin-2 (PS2), have also been proposed in the literatures
589 [119,120]. Knockdown of *Mfn2*, which participates in MAM anchoring, reduces the proximity
590 between the mitochondria and ER, decreases γ -secretase activity, and reduces the intra-
591 and extracellular levels of A β 40 and A β 42 [121]. Pharmacological interventions targeting
592 MAM offer novel therapeutic strategies for AD. For instance, strategies aimed at
593 normalizing MAM protein expression or activity can potentially restore mitochondrial
594 function, reduce A β production, and slow the progression of AD. Furthermore, the
595 regulation of lipid metabolic pathways in MAM may also exert beneficial effects in the
596 treatment of AD [122].

597 In summary, MAM acts as a critical intracellular regulatory hub and plays a central role

598 in the pathogenesis of high-salt-diet-related diseases. Excessive salt intake disrupts the
599 structural integrity of MAM, leading to calcium dyshomeostasis, mitochondrial dynamics
600 disorders, lipid metabolism abnormalities, and autophagy dysfunction. This cascade of
601 cellular events subsequently triggers pathological alterations across multiple organ
602 systems including the cardiovascular, metabolic, and nervous systems. From hypertension
603 and myocardial injury to obesity and fatty liver disease, insulin resistance, T2DM, and AD,
604 MAM dysfunction constitutes a common molecular basis for these disorders (Figure 2).
605 This insight not only deepens our understanding of high-salt diet-induced diseases but also
606 provides new theoretical support for developing intervention strategies targeting MAM
607 homeostasis. Thus, maintaining or restoring MAM homeostasis may represent a novel
608 approach for preventing and treating pathologies associated with high-salt diets.

609 **4. Summary and Outlook**

610 A high-salt diet acts as a significant metabolic stressor and exerts a pathogenic impact
611 far beyond merely elevating the blood pressure. This review systematically assessed the
612 core role of high-salt diets contributing to the disruption of the structure and function of
613 MAM, which in turn triggers widespread cellular metabolic disorders. Specifically, high salt
614 intake interferes with key MAM complexes such as IP3R-GRP75-VDAC1, disrupting
615 calcium homeostasis between the ER and mitochondria. This induces mitochondrial
616 calcium overload, excessive ROS production, and impaired energy metabolism.
617 Furthermore, a high-salt diet induces ERS, activates UPR, and impairs mitochondrial
618 function via MAM, collectively leading to cellular dysfunction and injury.

619 High salt levels also increase hepatic lipid synthesis and impair lipid transport by
620 activating transcription factors, such as SREBP1c, and disrupting the function of lipid
621 transporters, such as CERT and PACS-2. These alterations promote abnormal lipid droplet
622 accumulation and cause systemic lipid metabolism disorders. Together, these changes
623 exacerbate mitochondrial structural and functional impairment, sustain ERS, amplify
624 oxidative stress, and activate NLRP3 inflammasome. Ultimately, they drive the onset and
625 progression of multiple diseases, including hypertension, cardiovascular disease, MASLD,
626 insulin resistance, CKD, and neurodegenerative disorders.

627 Research on the pathogenic mechanisms linking MAM to high-salt diets is evolving
628 and numerous critical questions await in-depth exploration. Future investigations should
629 focus on the following directions: elucidating the specific molecular mechanisms by which
630 high-salt diets regulate MAM composition and dynamic membrane contacts; clarifying
631 tissue-specific responses of MAM to high-salt stress in different organs, such as blood
632 vessels, liver, kidney, and nervous system, and defining their unique roles in organ-specific
633 damage; exploring intervention strategies that modulate the activity of key MAM proteins
634 (e.g., MFN2, GRP75, IP3R) to reverse high-salt-induced cellular damage and metabolic
635 disorders; and developing novel pharmacological or natural bioactive molecules that target
636 the integrity and function of MAM, thereby providing potential clinical approaches for the
637 prevention and treatment of high-salt diet-related diseases.

638 Several limitations in the current literature should be acknowledged, which also point
639 to key directions for future research. First, the vast majority of evidence linking high-salt
640 diets to MAM dysfunction is derived from animal models and cell-based systems. Clinical
641 data directly examining MAM integrity or MAM-associated molecular markers (e.g., plasma
642 or tissue levels of IP3R, GRP75, VDAC, or MFN2) in relation to dietary salt intake in human
643 populations remain scarce. Future translational studies, including case-control and cohort
644 studies, are urgently needed to validate whether MAM disruption occurs in humans under
645 high-salt conditions and whether it correlates with disease progression. Second, the dose-
646 response relationship between salt intake and MAM structural/functional impairment has
647 not been characterized systematically. It remains unclear whether MAM disruption follows
648 a threshold-dependent pattern or exhibits progressive deterioration with increasing salt
649 exposure. Well-controlled dose-escalation studies in both preclinical models and, where
650 feasible, human subjects are warranted to establish the quantitative relationship between
651 salt burden and MAM damage. Addressing these gaps is essential for translating MAM-
652 targeted strategies into clinical practice.

653 In summary, MAM represents not only a novel perspective for understanding the
654 pathogenic mechanisms of high-salt diet-induced diseases but also a crucial bridge linking
655 nutritional stress to cellular metabolic disorders. An in-depth investigation of MAM in high-
656 salt-diet-related diseases will provide a theoretical foundation for elucidating disease

657 pathogenesis and offer both theoretical frameworks and practical directions for developing
658 novel therapeutic strategies aimed at restoring inter-organelle communication and
659 metabolic homeostasis. Encouragingly, studies on other pathological conditions have
660 demonstrated the feasibility of MAM-targeted interventions. For instance, pharmacological
661 intervention with 2-aminoethyl diphenyl borate (an IP₃R1 inhibitor) or VBIT-12 (a VDAC1
662 oligomerization inhibitor) attenuated MAM ultrastructure injury and prolonged the survival
663 time in rats following hemorrhagic shock, revealing the systemic benefits of modulating key
664 MAM proteins [123]. However, whether these inhibitors can rescue high-salt diet-induced
665 MAM injury remains to be investigated, which is a critical step toward translating MAM-
666 targeted strategies for salt-related diseases into clinical practice.

667 **Declarations**

668 ***Competing interests***

669 The authors declare that they have no conflict of interest.

670 ***Funding***

671 This study was supported by the National Natural Science Foundation of China (No.
672 82570586) and the Natural Science Foundation of Hebei Province (H2022206449).

673 ***Author contributions***

674 Conception and Design: ZGZ and CYN; Investigation: HLH; Formal Analysis: HLH, ZGZ,
675 and CYN; Writing – Original Draft: HLH, LMZ, and HZ. Visualization: ZCW and HLH; Writing
676 – Review and Editing: ZGZ, CYN, JW, HBD, JLC, and GSZ.

677 **Authors statement**

678 All authors read and approved the final manuscript.

679 ***Acknowledgements***

680 Not applicable

681 ***Ethics approval and consent to participate***

682 Not applicable.

683 ***Consent for publication***

684 Not applicable.

685 ***Data Availability***

686 Data sharing is not applicable to this article as no data were created or analyzed in this
687 study.

688 ***Declaration of Generative AI and AI-assisted technologies in the writing process***

689 During the preparation of this manuscript, we have used DeePseek and Paperpal Preflight
690 to address common errors and omissions. Subsequently, the content was thoroughly
691 reviewed and edited as necessary, and the authors took full responsibility for the content
692 of the publication.

Journal Pre-proof

References

1. Gao P, Yan Z, Zhu Z. Mitochondria-Associated Endoplasmic Reticulum Membranes in Cardiovascular Diseases. *Front Cell Dev Biol.* 2020;8:604240. doi: 10.3389/fcell.2020.604240
2. Tubbs E, Chanon S, Robert M, et al. Disruption of Mitochondria-Associated Endoplasmic Reticulum Membrane (MAM) Integrity Contributes to Muscle Insulin Resistance in Mice and Humans. *Diabetes.* 2018;67(4):636-650. doi: 10.2337/db17-0316
3. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2019;393(10184):1958-1972. doi: 10.1016/s0140-6736(19)30041-8
4. Olié V, Grave C, Helft G, et al. Epidemiology of cardiovascular risk factors: Behavioural risk factors. *Arch Cardiovasc Dis.* 2024;117(12):770-784. doi: 10.1016/j.acvd.2024.10.328
5. Jiang X, Wang J, Deng X, et al. The role of microenvironment in tumor angiogenesis. *J Exp Clin Cancer Res.* 2020;39(1):204. doi: 10.1186/s13046-020-01709-5
6. Wu S, Lu Q, Ding Y, et al. Hyperglycemia-Driven Inhibition of AMP-Activated Protein Kinase $\alpha 2$ Induces Diabetic Cardiomyopathy by Promoting Mitochondria-Associated Endoplasmic Reticulum Membranes In Vivo. *Circulation.* 2019;139(16):1913-1936. doi: 10.1161/circulationaha.118.033552
7. Filipe A, Chernorudskiy A, Arbogast S, et al. Defective endoplasmic reticulum-mitochondria contacts and bioenergetics in SEPN1-related myopathy. *Cell Death Differ.* 2021;28(1):123-138. doi: 10.1038/s41418-020-0587-z
8. Li Z, Hu O, Xu S, et al. The SIRT3-ATAD3A axis regulates MAM dynamics and mitochondrial calcium homeostasis in cardiac hypertrophy. *Int J Biol Sci.* 2024;20(3):831-847. doi: 10.7150/ijbs.89253
9. Yang X, Zhuang J, Song W, et al. Mitochondria-associated endoplasmic reticulum membrane: Overview and inextricable link with cancer. *J Cell Mol Med.* 2023;27(7):906-919. doi: 10.1111/jcmm.17696
10. Choudhury D, Rong N, Ikhapoh I, et al. Inhibition of glutaminolysis restores mitochondrial function in senescent stem cells. *Cell Rep.* 2022;41(9):111744. doi: 10.1016/j.celrep.2022.111744
11. Luan Y, Luan Y, Yuan RX, Feng Q, Chen X, Yang Y. Structure and Function of Mitochondria-Associated Endoplasmic Reticulum Membranes (MAMs) and Their Role in Cardiovascular Diseases. *Oxid Med Cell Longev.* 2021;2021:4578809. doi: 10.1155/2021/4578809
12. Zhang H, Yu F, Tian Z, Jia D. Cardiolipin Remodeling in Cardiovascular Diseases: Implication for Mitochondrial Dysfunction. *Acta Physiol (Oxf).* 2025;241(7):e70073. doi: 10.1111/apha.70073
13. Grillo G, Falvo S, Latino D, et al. Polystyrene microplastics impair the functions of cultured mouse Leydig (TM3) and Sertoli (TM4) cells by inducing mitochondrial-endoplasmic reticulum damage. *Ecotoxicol Environ Saf.* 2024;274:116202. doi:

- 10.1016/j.ecoenv.2024.116202
14. Li Y, Fu W, Xiang J, et al. Long-chain acyl-CoA synthetase 4-mediated mitochondrial fatty acid metabolism and dendritic cell antigen presentation. *Inflamm Res*. 2024;73(5):819-839. doi: 10.1007/s00011-024-01868-7
 15. Barbuti PA, Guardia-Laguarta C, Yun T, et al. The role of alpha-synuclein in synucleinopathy: Impact on lipid regulation at mitochondria-ER membranes. *NPJ Parkinsons Dis*. 2025;11(1):103. doi: 10.1038/s41531-025-00960-x
 16. Pan M, Han Y, Basu A, et al. Overexpression of hexokinase 2 reduces mitochondrial calcium overload in coronary endothelial cells of type 2 diabetic mice. *Am J Physiol Cell Physiol*. 2018;314(6):C732-c740. doi: 10.1152/ajpcell.00350.2017
 17. Yue M, Hu B, Li J, et al. Coronaviral ORF6 protein mediates inter-organelle contacts and modulates host cell lipid flux for virus production. *Embo j*. 2023;42(13):e112542. doi: 10.15252/embj.2022112542
 18. Fernandes T, Domingues MR, Moreira PI, Pereira CF. A Perspective on the Link between Mitochondria-Associated Membranes (MAMs) and Lipid Droplets Metabolism in Neurodegenerative Diseases. *Biology (Basel)*. 2023;12(3):414. doi: 10.3390/biology12030414
 19. Cagalinec M, Mohd A, Borecka S, et al. Improving mitochondria-associated endoplasmic reticulum membranes integrity as converging therapeutic strategy for rare neurodegenerative diseases and cancer. *Biochim Biophys Acta Mol Cell Res*. 2025;1872(5):119954. doi: 10.1016/j.bbamcr.2025.119954
 20. Fan M, Zhang J, Tsai CW, et al. Structure and mechanism of the mitochondrial Ca(2+) uniporter holocomplex. *Nature*. 2020;582(7810):129-133. doi: 10.1038/s41586-020-2309-6
 21. Garbincius JF, Elrod JW. Mitochondrial calcium exchange in physiology and disease. *Physiol Rev*. 2022;102(2):893-992. doi: 10.1152/physrev.00041.2020
 22. Rowland AA, Voeltz GK. Endoplasmic reticulum-mitochondria contacts: function of the junction. *Nat Rev Mol Cell Biol*. 2012;13(10):607-625. doi: 10.1038/nrm3440
 23. Belosludtsev KN, Belosludtseva NV, Dubinin MV. Diabetes Mellitus, Mitochondrial Dysfunction and Ca(2+)-Dependent Permeability Transition Pore. *Int J Mol Sci*. 2020;21(18). doi: 10.3390/ijms21186559
 24. Guo R, Si R, Scott BT, Makino A. Mitochondrial connexin40 regulates mitochondrial calcium uptake in coronary endothelial cells. *Am J Physiol Cell Physiol*. 2017;312(4):C398-c406. doi: 10.1152/ajpcell.00283.2016
 25. Pralea IE, Petrache AM, Tigu AB, et al. Phytochemicals as Regulators of Tumor Glycolysis and Hypoxia Signaling Pathways: Evidence from In Vitro Studies. *Pharmaceuticals (Basel)*. 2022;15(7). doi: 10.3390/ph15070808
 26. Patergnani S, Suski JM, Agnoletto C, et al. Calcium signaling around Mitochondria Associated Membranes (MAMs). *Cell Commun Signal*. 2011;9:19. doi: 10.1186/1478-811x-9-19
 27. Franchino CA, Motori E, Bergami M. Janus-faced Mitofusin 2 (MFN2): mitochondria-endoplasmic reticulum shaping and tethering functions unveiled. *Signal Transduct Target Ther*. 2024;9(1):4. doi: 10.1038/s41392-023-01730-y

28. Tamargo-Gómez I, Mariño G. AMPK: Regulation of Metabolic Dynamics in the Context of Autophagy. *Int J Mol Sci.* 2018;19(12). doi: 10.3390/ijms19123812
29. An G, Park J, Song J, Hong T, Song G, Lim W. Relevance of the endoplasmic reticulum-mitochondria axis in cancer diagnosis and therapy. *Exp Mol Med.* 2024;56(1):40-50. doi: 10.1038/s12276-023-01137-3
30. Chen Y, Xin Y, Cheng Y, Liu X. Mitochondria-Endoplasmic Reticulum Contacts: The Promising Regulators in Diabetic Cardiomyopathy. *Oxid Med Cell Longev.* 2022;2022:2531458. doi: 10.1155/2022/2531458
31. Hu Y, Chen H, Zhang L, et al. The AMPK-MFN2 axis regulates MAM dynamics and autophagy induced by energy stresses. *Autophagy.* 2021;17(5):1142-1156. doi: 10.1080/15548627.2020.1749490
32. Cai C, Guo Z, Chang X, et al. Empagliflozin attenuates cardiac microvascular ischemia/reperfusion through activating the AMPK α 1/ULK1/FUNDC1/mitophagy pathway. *Redox Biol.* 2022;52:102288. doi: 10.1016/j.redox.2022.102288
33. Tilokani L, Nagashima S, Paupe V, Prudent J. Mitochondrial dynamics: overview of molecular mechanisms. *Essays Biochem.* 2018;62(3):341-360. doi: 10.1042/ebc20170104
34. Zanfardino P, Amati A, Perrone M, Petruzzella V. The Balance of MFN2 and OPA1 in Mitochondrial Dynamics, Cellular Homeostasis, and Disease. *Biomolecules.* 2025;15(3). doi: 10.3390/biom15030433
35. Dho SH, Cho M, Woo W, Jeong S, Kim LK. Caspases as master regulators of programmed cell death: apoptosis, pyroptosis and beyond. *Exp Mol Med.* 2025;57(6):1121-1132. doi: 10.1038/s12276-025-01470-9
36. Chen C, Dai G, Fan M, Wang X, Niu K, Gao W. Mitochondria-associated endoplasmic reticulum membranes and myocardial ischemia: from molecular mechanisms to therapeutic strategies. *J Transl Med.* 2025;23(1):277. doi: 10.1186/s12967-025-06262-3
37. Wu Q, Burley G, Li LC, Lin S, Shi YC. The role of dietary salt in metabolism and energy balance: Insights beyond cardiovascular disease. *Diabetes Obes Metab.* 2023;25(5):1147-1161. doi: 10.1111/dom.14980
38. Xu H, Guan N, Ren YL, et al. IP(3)R-Grp75-VDAC1-MCU calcium regulation axis antagonists protect podocytes from apoptosis and decrease proteinuria in an Adriamycin nephropathy rat model. *BMC Nephrol.* 2018;19(1):140. doi: 10.1186/s12882-018-0940-3
39. Lam LK, Xu PL, Xie PC, et al. Taohong Siwu Decoction alleviates high salt-induced calcium overload and ferroptosis in vascular endothelial cells in hypertension by regulating ATF4. *Front Nutr.* 2025;12:1647017. doi: 10.3389/fnut.2025.1647017
40. Drenjančević I, Stupin A, Jukić I, et al. Oral Carnosine Supplementation Preserves Vascular Function of Sprague Dawley Rats on a High-Salt Diet via Restored Antioxidative Defence. *Nutrients.* 2024;17(1). doi: 10.3390/nu17010036
41. Huang S, Zeng Z, Chu Y, et al. Mitigation of lipopolysaccharide-induced intestinal injury in rats by *Chimonanthus nitens* Oliv. essential oil via suppression of mitochondrial fusion protein mitofusin 2 (MFN2)-mediated mitochondrial-associated endoplasmic reticulum membranes (MAMs) formation. *J*

- Ethnopharmacol. 2025;337(Pt 2):118856. doi: 10.1016/j.jep.2024.118856
42. Huo Q, Zhang Y, Guo J, Jiang YA, Zhao J. Dexmedetomidine protects against postoperative neurocognitive disorder by mitigating mitochondrial dysfunction through regulating the IP3R-GRP75-VDAC1 complex-mediated calcium transport. *Immunol Res.* 2025;73(1):156. doi: 10.1007/s12026-025-09705-7
 43. Li Y, Xu R, Zhang Y, Jiang K, Zhong T. TRPV4-dependent signaling pathways play essential regulatory roles in high salt-induced cardiac hypertrophy via autophagic alterations. *J Cardiovasc Pharmacol.* 2025. doi: 10.1097/fjc.0000000000001711
 44. Bui V, Santerre M, Shcherbik N, Sawaya BE. Mitochondria-associated membranes (MAMs): molecular organization, cellular functions, and their role in health and disease. *FEBS Open Bio.* 2026;16(1):11-24. doi: 10.1002/2211-5463.70121
 45. Prasanth MI, Verma K, Brimson S, Tencomnao T, Brimson JM. Simple ammonium salt and sigma-1 receptor ligand dipentylammonium provides neuroprotective effects in cell culture and *Caenorhabditis elegans* models of Alzheimer's disease. *Biomed Pharmacother.* 2024;173:116455. doi: 10.1016/j.biopha.2024.116455
 46. Park SJ, Kim TS, Park CK, et al. hCG-induced endoplasmic reticulum stress triggers apoptosis and reduces steroidogenic enzyme expression through activating transcription factor 6 in Leydig cells of the testis. *J Mol Endocrinol.* 2013;50(2):151-166. doi: 10.1530/jme-12-0195
 47. Chen W, Sun M, Sun Y, et al. Proteasome inhibition induces apoptosis through simultaneous inactivation of MCL-1/BCL-XL by NOXA independent of CHOP and JNK pathways. *Toxicology.* 2024;508:153906. doi: 10.1016/j.tox.2024.153906
 48. Jo HJ, Yang JW, Park JH, et al. Endoplasmic Reticulum Stress Increases DUSP5 Expression via PERK-CHOP Pathway, Leading to Hepatocyte Death. *Int J Mol Sci.* 2019;20(18). doi: 10.3390/ijms20184369
 49. Ma FF, Ma RH, Thakur K, et al. miRNA omics reveal neferine induces apoptosis through Ca(2+)mediated endoplasmic reticulum stress pathway in human endometrial cancer. *Phytomedicine.* 2024;134:155988. doi: 10.1016/j.phymed.2024.155988
 50. Meng S, Xia F, Xu J, et al. Hepatocyte growth factor protects pulmonary endothelial barrier against oxidative stress and mitochondria-dependent apoptosis. *Chin Med J (Engl).* 2022;135(7):837-848. doi: 10.1097/cm9.0000000000001916
 51. DeBose-Boyd RA, Ye J. SREBPs in Lipid Metabolism, Insulin Signaling, and Beyond. *Trends Biochem Sci.* 2018;43(5):358-368. doi: 10.1016/j.tibs.2018.01.005
 52. Fernandes T, Domingues MR, Moreira PI, Pereira CF. A Perspective on the Link between Mitochondria-Associated Membranes (MAMs) and Lipid Droplets Metabolism in Neurodegenerative Diseases. *Biology (Basel).* 2023;12(3). doi: 10.3390/biology12030414
 53. Kumagai K, Hanada K. Structure, functions and regulation of CERT, a lipid-transfer protein for the delivery of ceramide at the ER-Golgi membrane contact sites. *FEBS Lett.* 2019;593(17):2366-2377. doi: 10.1002/1873-3468.13511
 54. Li C, Li L, Yang M, Zeng L, Sun L. PACS-2: A key regulator of mitochondria-associated membranes (MAMs). *Pharmacol Res.* 2020;160:105080. doi: 10.1016/j.phrs.2020.105080

55. Lee M, Sorn SR, Lee Y, Kang I. Salt Induces Adipogenesis/Lipogenesis and Inflammatory Adipocytokines Secretion in Adipocytes. *Int J Mol Sci.* 2019;20(1). doi: 10.3390/ijms20010160
56. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature.* 2011;469(7329):221-225. doi: 10.1038/nature09663
57. Zhao J, Li J, Li G, Chen M. The role of mitochondria-associated membranes mediated ROS on NLRP3 inflammasome in cardiovascular diseases. *Front Cardiovasc Med.* 2022;9:1059576. doi: 10.3389/fcvm.2022.1059576
58. Wan Z, Wen W, Ren K, et al. Involvement of NLRP3 inflammasome in the impacts of sodium and potassium on insulin resistance in normotensive Asians. *Br J Nutr.* 2018;119(2):228-237. doi: 10.1017/s0007114517002926
59. Liu Y, Yang C, Feng X, et al. Prenatal High-Salt Diet-Induced Metabolic Disorders via Decreasing Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 α in Adult Male Rat Offspring. *Mol Nutr Food Res.* 2020;64(14):e2000196. doi: 10.1002/mnfr.202000196
60. He P, Chang H, Qiu Y, Wang Z. Mitochondria associated membranes in dilated cardiomyopathy: connecting pathogenesis and cellular dysfunction. *Front Cardiovasc Med.* 2025;12:1571998. doi: 10.3389/fcvm.2025.1571998
61. Xia W, Wang Q, Lin S, et al. A high-salt diet promotes hypertrophic scarring through TRPC3-mediated mitochondrial Ca^{2+} homeostasis dysfunction. *Heliyon.* 2023;9(8):e18629. doi: 10.1016/j.heliyon.2023.e18629
62. Cai S, Zhao M, Zhou B, et al. Mitochondrial dysfunction in macrophages promotes inflammation and suppresses repair after myocardial infarction. *J Clin Invest.* 2023;133(4). doi: 10.1172/jci159498
63. Stocher DP, Klein CP, Saccomori AB, et al. Maternal high-salt diet alters redox state and mitochondrial function in newborn rat offspring's brain. *Br J Nutr.* 2018;119(9):1003-1011. doi: 10.1017/s0007114518000235
64. Hu Y, Xia W, Li Y, et al. High-salt intake increases TRPC3 expression and enhances TRPC3-mediated calcium influx and systolic blood pressure in hypertensive patients. *Hypertens Res.* 2020;43(7):679-687. doi: 10.1038/s41440-020-0409-1
65. Zhao Y, Li L, Lu Z, et al. Sodium-Glucose Cotransporter 2 Inhibitor Canagliflozin Antagonizes Salt-Sensitive Hypertension Through Modifying Transient Receptor Potential Channels 3 Mediated Vascular Calcium Handling. *J Am Heart Assoc.* 2022;11(15):e025328. doi: 10.1161/jaha.121.025328
66. Afsar B, Afsar RE. Mitochondrial Damage and Hypertension: Another Dark Side of Sodium Excess. *Curr Nutr Rep.* 2023;12(3):495-507. doi: 10.1007/s13668-023-00486-9
67. Li Z, Wang W, Sun Q, et al. Postconditioning of stellate ganglion block improves intestinal barrier function by inhibiting autophagy in conscious rats following hemorrhagic shock and resuscitation. *Chin Med J (Engl).* 2022;135(8):1003-1005. doi: 10.1097/cm9.0000000000001968
68. Cherezova A, Sudarikova A, Vasileva V, et al. The effects of the atrial natriuretic peptide deficiency on renal cortical mitochondrial bioenergetics in the Dahl SS rat.

- Faseb j. 2024;38(16):e23891. doi: 10.1096/fj.202400672RR
69. Camargo LL, Wang Y, Rios FJ, McBride M, Montezano AC, Touyz RM. Oxidative Stress and Endoplasmic Reticular Stress Interplay in the Vasculopathy of Hypertension. *Can J Cardiol.* 2023;39(12):1874-1887. doi: 10.1016/j.cjca.2023.10.012
 70. Pomerantz BJ, Reznikov LL, Harken AH, Dinarello CA. Inhibition of caspase 1 reduces human myocardial ischemic dysfunction via inhibition of IL-18 and IL-1beta. *Proc Natl Acad Sci U S A.* 2001;98(5):2871-2876. doi: 10.1073/pnas.041611398
 71. Zhou W, Yang Y, Feng Z, et al. Inhibition of Caspase-1-dependent pyroptosis alleviates myocardial ischemia/reperfusion injury during cardiopulmonary bypass (CPB) in type 2 diabetic rats. *Sci Rep.* 2024;14(1):19420. doi: 10.1038/s41598-024-70477-5
 72. Kawaguchi M, Takahashi M, Hata T, et al. Inflammasome activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury. *Circulation.* 2011;123(6):594-604. doi: 10.1161/circulationaha.110.982777
 73. Titus AS, Sung EA, Zablocki D, Sadoshima J. Mitophagy for cardioprotection. *Basic Res Cardiol.* 2023;118(1):42. doi: 10.1007/s00395-023-01009-x
 74. Paillard M, Tubbs E, Thiebaut PA, et al. Depressing mitochondria-reticulum interactions protects cardiomyocytes from lethal hypoxia-reoxygenation injury. *Circulation.* 2013;128(14):1555-1565. doi: 10.1161/circulationaha.113.001225
 75. Choi KM, Zhong Y, Hoit BD, et al. Defective intracellular Ca(2+) signaling contributes to cardiomyopathy in Type 1 diabetic rats. *Am J Physiol Heart Circ Physiol.* 2002;283(4):H1398-1408. doi: 10.1152/ajpheart.00313.2002
 76. Pierce GN, Russell JC. Regulation of intracellular Ca²⁺ in the heart during diabetes. *Cardiovasc Res.* 1997;34(1):41-47. doi: 10.1016/s0008-6363(97)00010-2
 77. Tiyasatkulkovit W, Aksornthong S, Adulyaritthikul P, et al. Excessive salt consumption causes systemic calcium mishandling and worsens microarchitecture and strength of long bones in rats. *Sci Rep.* 2021;11(1):1850. doi: 10.1038/s41598-021-81413-2
 78. Zhang C, Liu B, Sheng J, et al. Potential targets for the treatment of MI: GRP75-mediated Ca(2+) transfer in MAM. *Eur J Pharmacol.* 2024;971:176530. doi: 10.1016/j.ejphar.2024.176530
 79. Liu BY, Dai ZH, Mao L, Guo LZ, Yang ZB. CaM promotes cardiomyocyte mitophagy in myocardial ischemia-reperfusion injury involving in the regulation of the IP3R3-GRP75-VDAC1 complex. *Sci Rep.* 2025;15(1):22379. doi: 10.1038/s41598-025-07977-5
 80. Liu L, Feng D, Chen G, et al. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. *Nat Cell Biol.* 2012;14(2):177-185. doi: 10.1038/ncb2422
 81. Chen G, Han Z, Feng D, et al. A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy. *Mol Cell.* 2014;54(3):362-377. doi: 10.1016/j.molcel.2014.02.034
 82. Missiroli S, Patergnani S, Carocchia N, et al. Mitochondria-associated membranes

- (MAMs) and inflammation. *Cell Death Dis.* 2018;9(3):329. doi: 10.1038/s41419-017-0027-2
83. Dorn GW, 2nd, Song M, Walsh K. Functional implications of mitofusin 2-mediated mitochondrial-SR tethering. *J Mol Cell Cardiol.* 2015;78:123-128. doi: 10.1016/j.yjmcc.2014.09.015
84. Papanicolaou KN, Khairallah RJ, Ngoh GA, et al. Mitofusin-2 maintains mitochondrial structure and contributes to stress-induced permeability transition in cardiac myocytes. *Mol Cell Biol.* 2011;31(6):1309-1328. doi: 10.1128/mcb.00911-10
85. Duewell P, Kono H, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature.* 2010;464(7293):1357-1361. doi: 10.1038/nature08938
86. Le Page S, Niro M, Fauconnier J, et al. Increase in Cardiac Ischemia-Reperfusion Injuries in Opa1+/- Mouse Model. *PLoS One.* 2016;11(10):e0164066. doi: 10.1371/journal.pone.0164066
87. Kirii H, Niwa T, Yamada Y, et al. Lack of interleukin-1beta decreases the severity of atherosclerosis in ApoE-deficient mice. *Arterioscler Thromb Vasc Biol.* 2003;23(4):656-660. doi: 10.1161/01.Atv.0000064374.15232.C3
88. Mallat Z, Corbaz A, Scoazec A, et al. Interleukin-18/interleukin-18 binding protein signaling modulates atherosclerotic lesion development and stability. *Circ Res.* 2001;89(7):E41-45. doi: 10.1161/hh1901.098735
89. Menu P, Pellegrin M, Aubert JF, et al. Atherosclerosis in ApoE-deficient mice progresses independently of the NLRP3 inflammasome. *Cell Death Dis.* 2011;2(3):e137. doi: 10.1038/cddis.2011.18
90. Bernal AF, Mota N, Pamplona R, Area-Gomez E, Portero-Otin M. Hakuna MAM-Tata: Investigating the role of mitochondrial-associated membranes in ALS. *Biochim Biophys Acta Mol Basis Dis.* 2023;1869(6):166716. doi: 10.1016/j.bbadis.2023.166716
91. Zhang Y, Li T, Pan M, et al. SIRT1 prevents cigarette smoking-induced lung fibroblasts activation by regulating mitochondrial oxidative stress and lipid metabolism. *J Transl Med.* 2022;20(1):222. doi: 10.1186/s12967-022-03408-5
92. Xie X, Liao Y, Lin Z, et al. Patchouli alcohol alleviates metabolic dysfunction-associated steatohepatitis via inhibiting mitochondria-associated endoplasmic reticulum membrane disruption-induced hepatic steatosis and inflammation in rats. *Int Immunopharmacol.* 2024;138:112634. doi: 10.1016/j.intimp.2024.112634
93. Zhou L, Yang Y, Feng Y, et al. Association between dietary sodium intake and non-alcoholic fatty liver disease in the US population. *Public Health Nutr.* 2021;24(5):993-1000. doi: 10.1017/s136898001900483x
94. Chen H, Zhang X, Lin S, Wu Q. Adding salt to foods increases the risk of metabolic dysfunction-associated steatotic liver disease. *Commun Med (Lond).* 2025;5(1):342. doi: 10.1038/s43856-025-01074-4
95. Lee J, Lee JY, Yang YJ. Sex-Specific Association between Sodium Intake Estimated by 24-Hour Urinary Sodium Excretion and Nonalcoholic Fatty Liver Disease: The Community-Based Prospective Cohort Study. *Nutrients.* 2024;16(4).

- doi: 10.3390/nu16040548
96. Lanaspa MA, Kuwabara M, Andres-Hernando A, et al. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. *Proc Natl Acad Sci U S A*. 2018;115(12):3138-3143. doi: 10.1073/pnas.1713837115
 97. Toyoshima C. Structural aspects of ion pumping by Ca²⁺-ATPase of sarcoplasmic reticulum. *Arch Biochem Biophys*. 2008;476(1):3-11. doi: 10.1016/j.abb.2008.04.017
 98. Díaz-Hung ML, Martínez G, Hetz C. Emerging roles of the unfolded protein response (UPR) in the nervous system: A link with adaptive behavior to environmental stress? *Int Rev Cell Mol Biol*. 2020;350:29-61. doi: 10.1016/bs.ircmb.2020.01.004
 99. Solarz-Andrzejewska A, Majcher-Maślanka I, Kryst J, Chocyk A. Modulation of the endoplasmic reticulum stress and unfolded protein response mitigates the behavioral effects of early-life stress. *Pharmacol Rep*. 2023;75(2):293-319. doi: 10.1007/s43440-023-00456-6
 100. Ruzza A, Zaltron E, Vianello F, et al. HSPA8 and HSPA9: Two prognostic and therapeutic targets in breast, colon, and kidney cancers? *Biochim Biophys Acta Mol Basis Dis*. 2025;1871(6):167827. doi: 10.1016/j.bbadis.2025.167827
 101. Bhattacharya D, Kaushal S, Chakraborty B, et al. Zebrafish model of palmitic acid induced MAFLD recapitulates pathways conserved in mice and humans. *Sci Rep*. 2025;15(1):33343. doi: 10.1038/s41598-025-13154-5
 102. Chen H, Dai X, Xiong Z, et al. Dual-pathway mechanism of vanadium-induced hepatotoxicity in ducks: Synergistic crosstalk between glucose homeostasis disruption and NADH/FSP1/COQ10 axis-driven ferroptosis. *Int J Biol Sci*. 2026;22(1):43-59. doi: 10.7150/ijbs.123482
 103. Sergi D, Naumovski N, Heilbronn LK, et al. Mitochondrial (Dys)function and Insulin Resistance: From Pathophysiological Molecular Mechanisms to the Impact of Diet. *Front Physiol*. 2019;10:532. doi: 10.3389/fphys.2019.00532
 104. Cheng H, Gang X, He G, et al. The Molecular Mechanisms Underlying Mitochondria-Associated Endoplasmic Reticulum Membrane-Induced Insulin Resistance. *Front Endocrinol (Lausanne)*. 2020;11:592129. doi: 10.3389/fendo.2020.592129
 105. Li X, Yang Y, Shi X, Zhang Z, Ding S. Mitochondria-Associated Membranes as Key Regulators in Cellular Homeostasis and the Potential Impact of Exercise on Insulin Resistance. *Int J Mol Sci*. 2024;25(6). doi: 10.3390/ijms25063196
 106. Parveen H, Boder P, Mullen W, et al. Early renal response to long-term salt loading: mitochondrial dysfunction, ER stress, and uromodulin accumulation in the kidney medulla. *Am J Physiol Renal Physiol*. 2025;329(1):F112-f127. doi: 10.1152/ajprenal.00348.2024
 107. Gao P, Yang W, Sun L. Mitochondria-Associated Endoplasmic Reticulum Membranes (MAMs) and Their Prospective Roles in Kidney Disease. *Oxid Med Cell Longev*. 2020;2020:3120539. doi: 10.1155/2020/3120539
 108. Liu Y, Qiao Y, Pan S, et al. Broadening horizons: the contribution of mitochondria-

- associated endoplasmic reticulum membrane (MAM) dysfunction in diabetic kidney disease. *Int J Biol Sci.* 2023;19(14):4427-4441. doi: 10.7150/ijbs.86608
109. Haimoto H, Murase T, Watanabe S, Maeda K, Wakai K. Associations of Dietary Salt and Its Sources with Hemoglobin A1c in Patients with Type 2 Diabetes Not Taking Anti-Diabetic Medications: Analysis Based on 6-Month Intervention with a Moderate Low-Carbohydrate Diet. *Diabetes Metab Syndr Obes.* 2021;14:4569-4578. doi: 10.2147/dmso.S337032
110. Madec AM, Perrier J, Panthu B, Dingreville F. Role of mitochondria-associated endoplasmic reticulum membrane (MAMs) interactions and calcium exchange in the development of type 2 diabetes. *Int Rev Cell Mol Biol.* 2021;363:169-202. doi: 10.1016/bs.ircmb.2021.06.001
111. Sharma N, Arora S, Saurav S, Motiani RK. Pathophysiological significance of calcium signaling at Mitochondria-Associated Endoplasmic Reticulum Membranes (MAMs). *Current Opinion in Physiology.* 2020;17:234-242. doi: <https://doi.org/10.1016/j.cophys.2020.08.012>
112. Tarasov AI, Semplici F, Li D, et al. Frequency-dependent mitochondrial Ca(2+) accumulation regulates ATP synthesis in pancreatic β cells. *Pflugers Arch.* 2013;465(4):543-554. doi: 10.1007/s00424-012-1177-9
113. Dingreville F, Panthu B, Thivolet C, et al. Differential Effect of Glucose on ER-Mitochondria Ca(2+) Exchange Participates in Insulin Secretion and Glucotoxicity-Mediated Dysfunction of β -Cells. *Diabetes.* 2019;68(9):1778-1794. doi: 10.2337/db18-1112
114. Wang S, Deng K, Zhao H, et al. Analysis of the association between dietary sodium intake and cognitive function: a NHANES-based machine learning study and animal experimental validation. *Front Nutr.* 2025;12:1626651. doi: 10.3389/fnut.2025.1626651
115. Faraco G, Hochrainer K, Segarra SG, et al. Dietary salt promotes cognitive impairment through tau phosphorylation. *Nature.* 2019;574(7780):686-690. doi: 10.1038/s41586-019-1688-z
116. Xia C, Dai W, Carreno J, et al. Higher sodium in older individuals or after stroke/reperfusion, but not in migraine or Alzheimer's disease - a study in different preclinical models. *Sci Rep.* 2024;14(1):21636. doi: 10.1038/s41598-024-72280-8
117. Zhao Y, Hu D, Wang R, et al. ATAD3A oligomerization promotes neuropathology and cognitive deficits in Alzheimer's disease models. *Nat Commun.* 2022;13(1):1121. doi: 10.1038/s41467-022-28769-9
118. Eysert F, Kinoshita PF, Mary A, Vaillant-Beuchot L, Checler F, Chami M. Molecular Dysfunctions of Mitochondria-Associated Membranes (MAMs) in Alzheimer's Disease. *Int J Mol Sci.* 2020;21(24):9521. doi: 10.3390/ijms21249521
119. Çınar R, Nazıroğlu M. TRPM2 Channel Inhibition Attenuates Amyloid β 42-Induced Apoptosis and Oxidative Stress in the Hippocampus of Mice. *Cell Mol Neurobiol.* 2023;43(3):1335-1353. doi: 10.1007/s10571-022-01253-0
120. Pizzo P, Basso E, Filadi R, et al. Presenilin-2 and Calcium Handling: Molecules, Organelles, Cells and Brain Networks. *Cells.* 2020;9(10):2166. doi: 10.3390/cells9102166

121. Li Z, Cao Y, Pei H, Ma L, Yang Y, Li H. The contribution of mitochondria-associated endoplasmic reticulum membranes (MAMs) dysfunction in Alzheimer's disease and the potential countermeasure. *Front Neurosci.* 2023;17:1158204. doi: 10.3389/fnins.2023.1158204
122. Yu W, Jin H, Huang Y. Mitochondria-associated membranes (MAMs): a potential therapeutic target for treating Alzheimer's disease. *Clin Sci (Lond).* 2021;135(1):109-126. doi: 10.1042/cs20200844
123. Zheng HN, Zhang H, Wang J, Jia GY, Zhao ZG, Niu CY. Exercise preconditioning improves mesenteric lymphatic contractility through mam in rats following hemorrhagic shock. *Shock.* 2024;62(5):698-706. doi: 10.1097/shk.0000000000002424

Figure legends

Figure 1 Schematic diagram of mitochondria-associated endoplasmic reticulum membrane (MAM) and key molecular components.

MAM is a dynamic membrane contact site between the endoplasmic reticulum (ER) and the mitochondria. The diagram highlights major functional modules: 1) lipid synthesis and transport, involving Caveolin-1 and cholesterol (Chol); 2) Ca²⁺ channel complex, centered on the IP3R-GRP75-VDAC1 complex and MCU, regulating calcium flux; 3) adaptor proteins, such as MFN2, which tether the two organelles; and 4) cellular regulation, including autophagy (BECN1 and PINK1), energy sensing (AMPK), and apoptosis (caspase). The release of cytochrome c indicates the role of MAM in cell death signaling pathway. This figure was created using SciDraw based on the molecular mechanisms described in this review. The key molecular components and pathways are derived from representative references [11,19,22,26,29,31,35].

Figure 2. Mitochondria-associated endoplasmic reticulum membrane (MAM) dysfunction serves as a convergent mechanism in the pathogenesis of multiple diseases.

This schematic illustrates that the disruption of molecular networks in MAM contributes to metabolic, cardiovascular, and neurodegenerative disorders. Key pathological mechanisms include: 1) calcium dysregulation, in which disrupted IP3R-GRP75-VDAC1-mediated calcium signaling is implicated in myocardial injury, insulin resistance, and neurodegenerative processes; 2) metabolic dysfunction, in which altered lipid metabolism through FAS/SCD/ACC pathways at MAM promotes obesity, fatty liver disease, and atherosclerosis; 3) mitochondrial impairment, in which abnormal mitochondrial dynamics (DRP1/MFN/OPA1), and energy production (ETC) contribute to pancreatic β -cell failure, cardiac injury, and neurological degeneration; and 4) cellular stress activation, in which MAM-localized stress sensors (HSPA9, Caspase-1, TRPC3), and amyloidogenic processing (BACE1) drive inflammatory and degenerative processes in chronic kidney disease, Alzheimer's disease, and cardiovascular disorders. This figure was created using SciDraw and integrates pathological mechanisms supported by representative references [6,7,16,38,50,54,61,64,80,81,84,92,101,107,110,115,117,118,121].

