

动脉粥样硬化中自噬与凋亡相互作用的研究进展

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【摘要】 动脉粥样硬化是心血管疾病的病理基础, 以血管内脂质沉积和斑块形成为特点。凋亡和自噬作为细胞生存的调控者, 在动脉粥样硬化中发挥重要作用。近期研究发现凋亡与自噬之间存在复杂的相互作用, 通过二者的相互作用可反馈调节自噬或凋亡, 进而调节动脉粥样硬化, 可能为心血管疾病提供治疗方案。

【关键词】 凋亡; 自噬; 相互作用; 动脉粥样硬化

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Crosstalk Between Autophagy and Apoptosis in Atherosclerosis

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【Abstract】 Atherosclerosis is the pathological basis of cardiovascular diseases and is characterized by intravascular lipid deposition and plaque formation. As regulators of cell survival, apoptosis and autophagy play an important role in atherosclerosis. Recent studies have found a complex crosstalk between apoptosis and autophagy which can feedback regulate autophagy or apoptosis, and then regulate atherosclerosis, further may provide treatment options for cardiovascular diseases.

【Key words】 Apoptosis; Autophagy; Crosstalk; Atherosclerosis

心血管疾病已被公认是导致老年人死亡的主要原因^[1]。动脉粥样硬化(atherosclerosis, AS)是造成心血管疾病不断增加的病理基础。AS的病理过程包括内皮细胞受损、脂质沉积、泡沫细胞形成、内膜纤维化以及斑块形成,不稳定的斑块破裂或侵蚀,最终导致不良心血管事件发生,危及生命。因此,寻找导致斑块加速进展和不稳定的因素至关重要。研究发现破裂斑块的特征是体积较大且富含脂质的核心和薄的纤维帽,大量巨噬细胞和血管内皮细胞(vascular endothelial cell, VEC)死亡并伴随血管的生成与动脉外膜炎,其中自噬与凋亡扮演重要角色^[2]。自噬与凋亡并非独立作用,它们相互影响彼此交叉调节,通过平衡这两种反应可维持AS斑块的稳定性,从而为心血管疾病的预防和治疗提供方案。

1 凋亡概述

凋亡是一个平衡人体内环境稳态的自我杀灭过程,通常由缺血和缺氧等刺激因素激活。当凋亡被激活时,多种分解代谢酶被激活,特别是胱天蛋白酶(caspase)家族,导致细胞器和细胞结构的快速降解,核染色质浓缩、核碎裂和细胞萎缩,随后质膜融合,

凋亡小体形成,巨噬细胞吞噬凋亡小体完成凋亡^[3]。经典的凋亡途径有三种:(1)死亡受体介导的外源性途径;(2)线粒体介导的内源性途径;(3)内质网(endoplasmic reticulum, ER)介导的应激途径。

2 自噬概述

自噬是存在于真核细胞内,进化上高度保守的一种自我保护的分解代谢过程,它可被饥饿、缺氧和活性氧蓄积等多种细胞应激所激活,消除多余或受损的细胞器。自噬的完成需多种保守的自噬相关基因(autophagy related gene, Atg),涉及哺乳动物雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1, mTORC1)、AMP活化蛋白激酶(AMP-activated protein kinase, AMPK)、ER应激和p53基因介导的多条通路^[4]。

3 凋亡和自噬的相互作用

凋亡和自噬是消除多余、受损或老化的细胞或细胞器的两个过程,表1^[5-16]显示凋亡和自噬之间存在多种交叉的关键蛋白,通过它们可在凋亡和自噬间建立相互作用的桥梁。

3.2.2 哺乳动物雷帕霉素靶蛋白介导的相互作用

哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 是细胞营养状态传感器, 激活标志细胞进入“生长”状态。为满足细胞生长代谢需求, 激活的 mTORC1 通过磷酸化 unc-51 样自噬激活激酶 1 (unc-51 like autophagy activating kinase 1, ULK1) 和 Atg13, 阻止早期自噬体的形成, 抑制分解代谢和自噬。相反, 当营养物质不足时, 细胞从生物合成转变为自噬^[20]。此外, mTOR 还对细胞凋亡产生影响, 如雷帕霉素可调节慢性梗死后 mTORC1 与 ER 应激的平衡, 有效阻止心肌细胞凋亡, 促进心肌细胞自噬, 改善心脏功能^[7]; 通过 Akt/mTOR 通路抑制 mTOR 激活自噬, 可下调 Atg3 保护细胞免于凋亡^[21]; 另有激活 AMPK/mTOR/Atg5 或抑制 ULK1 的磷酸化恢复自噬同样可挽救细胞凋亡^[22-23]。以上结果可看出, 靶向抑制 mTOR 可通过上调自噬抑制细胞凋亡, 发挥保护作用。故推测被抑制的自噬和 mTOR 引起的凋亡的增加参与 AS 的病理过程, 以此为靶点可预防晚期 AS 斑块的进展。

3.2.3 p53 介导的相互作用

p53 是目前研究最广泛的肿瘤抑制因子, 研究关注最多的是 p53 调控细胞凋亡的能力。作为促凋亡因子的 p53 还可与多种自噬基因结合, 依赖反激活的方式诱导自噬。例如, 有研究^[16]发现缺乏 p53 基因的果蝇表现出自噬通量受损。另有研究^[24]报道, 细胞质 p53 通过失活 AMPK 并激活 mTOR 信号传导来抑制自噬。产生该差异的部分原因是自噬与凋亡受到 p53A 和 p53B 亚型的差异调节: p53A 通过激活 caspase Dronc、Drice 和 Dep-1 抑制自噬促进凋亡; 而 p53B 诱导细胞自噬, 防止细胞凋亡^[25]。这种亚型的差异调节可确保 p53 产生适当的生物学反应, 维持机体稳态。此外, 突变体 ATXN7 通过 p53 破坏自噬关键蛋白黏着斑激酶家族相互作用蛋白 200 和 ULK1 来抑制自噬活性, 而用 p53 抑制剂可恢复自噬抑制细胞凋亡^[5]。由此看出, p53 基因介导的细胞凋亡与自噬之间的相互作用已经建立, 促进 p53B 亚型或抑制 p53A 亚型可使凋亡向自噬转变, 能为缓解 AS 晚期斑块的进展提供可能的治疗方案。

3.2.4 细胞因子肿瘤坏死因子相关凋亡诱导配体介导的相互作用

细胞因子肿瘤坏死因子相关凋亡诱导配体 (tumor necrosis factor-related apoptosis-inducing ligand, TRAIL) 可诱导多种癌细胞凋亡^[26]。近期发现, TRAIL 不仅具有杀伤作用, 还可调节一系列细胞内反应, 如细胞增殖、迁移以及自噬等^[27]。有研究^[28]发现, 在 TRAIL 介

导的结肠癌耐药细胞中, Beclin-1 显著增加, 自噬增强, Beclin-1 通过与 caspase-8 结合导致其降解而抑制细胞凋亡, 说明 Beclin-1 诱导的自噬增强是 TRAIL 导致的凋亡受抑制的原因。类似地, TRAIL 还可通过 JNK 途径调节 Atg 表达, 从而促进肺癌细胞自噬, 抑制凋亡^[29]。此外, 受体相互作用蛋白激酶 1 (receptor interacting protein kinase 1, RIP1) 通过调节 TRAIL 诱导的自噬和细胞凋亡中核因子 κ B 的活性, 增强自噬, 减少细胞凋亡, 表明 RIP1 对于自噬向凋亡转化至关重要^[26]。以上结果可看出, TRAIL 连通了细胞凋亡与自噬之间的转化, 所以推测靶向 TRAIL 可促进自噬, 抑制细胞凋亡。

3.3 凋亡与自噬在 AS 的作用

巨噬细胞、VEC 和血管平滑肌细胞 (vascular smooth muscle cell, VSMC) 的异常凋亡是 AS 的共同特征, 它导致 AS 斑块的形成与进展, 且在不同细胞中激活细胞凋亡对 AS 具有不同作用。有研究^[30]发现由 CHOP-Bax 介导的 ER 应激促进巨噬细胞凋亡, 是 AS 斑块破裂的原因, 增加了患急性冠状动脉综合征的风险。在 8-氯腺苷诱导的 AS 病变中, 8-氯腺苷诱导持续的 ER 应激, 导致钙释放到细胞质, 引起 VEC 凋亡, 加速内皮损伤, 加速 AS 进展^[31]。不同于 ER 应激引起的细胞凋亡, 炎症引起的 VSMC 凋亡对 AS 的作用则相反。有研究^[32]表明在 AS 中, 白介素-10 通过 JAK2-STAT3 途径增加 Bcl-2 表达, 抑制 VSMC 凋亡。以上结果表明, 巨噬细胞和 VEC 的过度凋亡促进了 AS, 而 VSMC 诱导的 AS 归因于其凋亡不足。

自噬在 AS 中发挥的作用具有争议。在巨噬细胞中, 氧化低密度脂蛋白通过诱导 ER 应激激活自噬, 自噬促进受损蛋白质和细胞器的清除而促进巨噬细胞存活。此外, 自噬还通过调节脂滴向溶酶体降解来促进巨噬细胞源泡沫细胞释放出游离胆固醇, 延缓 AS 的发展。与之相似, VSMC 自噬也可被氧化的脂质激活并促进细胞存活, 氧化低密度脂蛋白 (oxidized low density lipoprotein, ox-LDL) 处理 VSMC 可触发线粒体自噬, 从而对抗 VSMC 凋亡^[32]。此外, 血小板衍生生长因子通过 AMPK 和 mTOR 诱导 VSMC 自噬, 保护 VSMC 免于死亡^[33]。然而, 另有研究^[5]发现肿瘤坏死因子- α 通过激活 JNK 上调 Beclin-1 和微管相关蛋白 1 轻链 3 (microtubule associated protein 1 light chain 3, LC3) 的表达, 促进 VSMC 自噬, 导致 AS 斑块不稳定。虽然通常认为自噬是对抗 AS 应激的保护过程, 但过度激活的自噬能诱导 VSMC 自噬性死亡, 导致胶原蛋白合成减少以及斑块不稳定^[34]。目前普遍认为成功的自噬促进 VSMC 存活, 有缺陷的 VSMC 自噬加速应

激从而促进 AS。在 VEC 中,摄取 ox-LDL 后脂质被转运至自噬体中降解,ox-LDL 同样激活自噬以保护内皮细胞^[33]。此外,用棕榈酸处理 VEC 也会触发线粒体自噬,抑制凋亡,防止 VEC 损伤^[35]。但有研究^[5]发现与之相反的结果,即抑制内皮祖细胞自噬时,在冠心病中观察到细胞活力增加和凋亡水平降低,表明自噬

对 VEC 的调控可能与其成熟度有关。从以上结果可看出,适度激活自噬在大部分情况下有利于 AS,自噬介导的抗 AS 作用主要得益于巨噬细胞和 VEC 的脂质调节。目前,已有许多抗 AS 药物靶向细胞凋亡和自噬,见表 2^[5,36-39],它们为 AS 提供了有希望的治疗方向。

表 2 靶向凋亡与自噬的潜在治疗 AS 药物

| 药物 | 作用 | 机制 | 参考文献 |
|-----------------|---------------------------------------|--|------|
| olmesartan | 改善心肌梗死后左心室重塑 | 抑制 Fas 介导的细胞凋亡,降低 Fas、Bax、caspase-3 和 c-Jun 水平 | [5] |
| simvastatin | 减少心肌细胞凋亡,改善心肌梗死后心功能 | 抑制 Bax,促进 caspase-3 和 Bcl-2 | [36] |
| 17-AAG | 减少心肌细胞凋亡 | 抑制 p53 | [5] |
| sulfaphenazole | 增强心功能,减少梗死面积 | 抑制细胞色素 P450,激活蛋白激酶 C 依赖性自噬 | [5] |
| chloramphenicol | 保护心肌免受缺血再灌注损伤 | 抑制细胞色素 P450,增加 LC3 和 Beclin-1 表达水平 | [5] |
| metformin | 减轻缺血再灌注损伤,改善心功能 | 诱导心肌自噬 | [37] |
| Tongxinluo | 稳定 AS 斑块 | 破坏 Beclin-1-Bcl-2 复合物,增强巨噬细胞自噬并减少细胞凋亡 | [38] |
| curcumin | 改善心功能 | 破坏 Beclin-1-Bcl-2 复合物,恢复心肌细胞自噬,减少细胞凋亡 | [39] |
| rapamycin | 预防 AS 和冠状动脉狭窄,减少梗死后不良重塑,改善左心室肥厚和心功能不全 | 促进自噬,改善细胞凋亡和 ER 应激 | [5] |
| AMPK activator | 对冠状动脉搭桥术后缺血再灌注损伤和冠心病患者有益 | 激活自噬 | [5] |

注:17-AAG 表示 17-烯丙氨基-17-脱甲基格尔德霉素。

4 总结与展望

凋亡和自噬作为细胞生存的调控者参与 AS 的发生和发展过程。已有研究^[31,40]证实,晚期 AS 斑块的不稳定性与内皮细胞和巨噬细胞的过度凋亡以及巨噬细胞自噬阻隔高度相关,恢复巨噬细胞自噬可促进细胞存活。因此,靶向凋亡向自噬转变对 AS 具有重要的治疗意义。在 AS 中细胞凋亡和自噬的相互作用发挥重要的调控作用,细胞凋亡和自噬相互作用相当复杂且涉及多条通路,在大多数情况下,自噬与凋亡互相拮抗,激活自噬能抑制细胞凋亡,对机体起到保护作用。但关于自噬和凋亡途径之间分子交叉目前的认识依旧零散和不完整,关于分解代谢之间的交叉调控机制仍有待进一步发掘。现以此为切入点,在晚期 AS 斑块中寻找平衡细胞内的自噬与凋亡的方法,从而实现自噬向凋亡转化,可有效地预防 AS 斑块破裂导致的急性心血管事件的发生,为 AS 的治疗提供新思路。

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