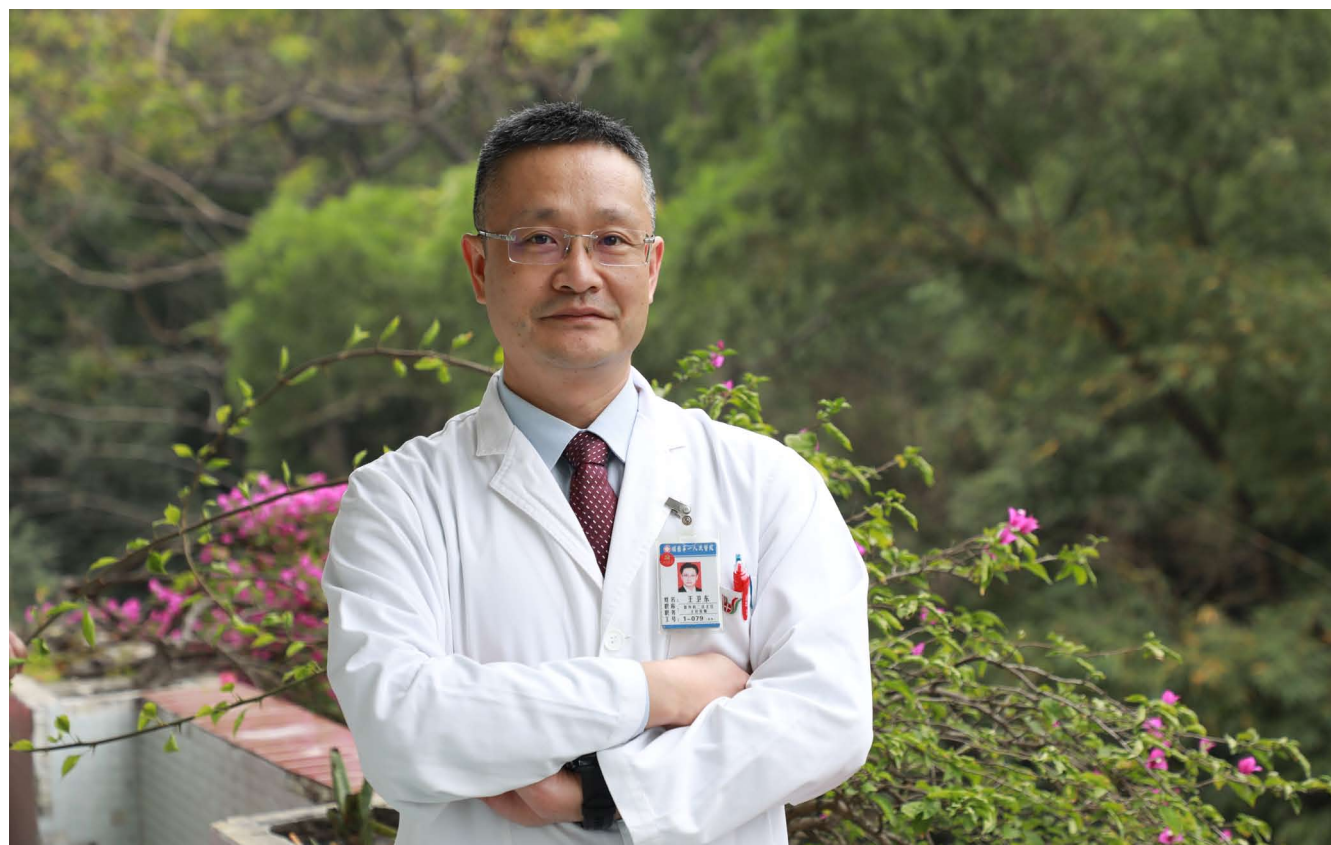


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主编

程英升, 教授, 200233, 上海市, 上海交通大学附属第六人民医院放射科

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## 腺泡细胞死亡方式对急性胰腺炎病情影响的研究现状

张美凤, 金相任

张美凤, 哈尔滨医科大学附属第一医院干部病房 黑龙江省哈尔滨市 150001

金相任, 哈尔滨医科大学附属第一医院胰胆外科 黑龙江省哈尔滨市 150001

张美凤, 住院医师, 主要从事消化系统疾病的研究.

作者贡献分布: 本文由张美凤写作; 金相任审校.

通讯作者: 金相任, 助理研究员, 150001, 黑龙江省哈尔滨市南岗区邮政街 33号, 哈尔滨医科大学附属第一医院胰胆外科. [jinxiangren78@163.com](mailto:jinxiangren78@163.com)

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### Effect of mode of acinar cell death on acute pancreatitis

Mei-Feng Zhang, Xiang-Ren Jin

Mei-Feng Zhang, Department of Cadre Ward, First Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang Province, China

Xiang-Ren Jin, Department of Pancreatic and Biliary Surgery, First Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang Province, China

Correspondence to: Xiang-Ren Jin, Assistant Researcher, Department of Pancreatic and Biliary Surgery, First Affiliated Hospital of Harbin Medical University, 33 Youzheng Street, Nangang District, Harbin 150001, Heilongjiang Province, China. [jinxiangren78@163.com](mailto:jinxiangren78@163.com)

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### Abstract

Acinar cell death is the most important pathophysiological change in the early stage of acute pancreatitis, and it has

been the emphasis of the research. The mode of acinar cell death includes apoptosis, necrosis, necroptosis, autophagy, and pyroptosis. Some scholars have shown that acinar cell death affects the outcome of acute pancreatitis. Therefore, studying the mode of acinar cell death has great value in the assessment of the severity of acute pancreatitis. Apoptosis can reduce inflammatory response, and necrosis aggravates inflammatory response. In recent years, research on the effect of necroptosis and pyroptosis on acute pancreatitis has been carried out. This article will review the effect of apoptosis, necrosis, necroptosis, and pyroptosis on acute pancreatitis.

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Key Words: Acinar cell; Death modality; Acute pancreatitis

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### 摘要

腺泡细胞死亡方式是急性胰腺炎(acute pancreatitis, AP)病程早期最主要的病理生理学变化, 也一直是AP的研究重点, 主要包括凋亡、坏死、程序性凋亡、自噬和焦亡等. 部分学者已经证明腺泡细胞死亡方式影响AP病情转归, 因此研究腺泡细胞死亡方式对AP病情具有重要价值. 凋亡能减轻炎症反应, 而坏死加重炎症反应, 近年对于坏死性凋亡和焦亡对于AP影响的相关研究也逐渐开展. 本文将对凋亡、坏死、坏死性凋亡和焦亡对AP病情的影响作一综述.

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关键词: 腺泡细胞; 死亡方式; 急性胰腺炎

**核心提要:** 腺泡细胞死亡方式是急性胰腺炎(acute pancreatitis, AP)研究的重点, 凋亡能减轻炎症反应, 坏死会加重炎症反应, 而坏死性凋亡和焦亡对于AP的研究较少. 本篇综述概括了凋亡、坏死、坏死性凋亡和焦亡对AP的影响, 并对AP死亡方式的研究提出了个人见解.

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## 0 引言

20世纪末, 众多学者对细胞死亡的认识仅限于形态学变化, 认为细胞死亡只有两种方式, 即坏死和凋亡. 随着生物分子技术的发展, 细胞死亡的分子机制逐渐被发现, 对于细胞死亡方式的理解由两种方式变为两种形式: 程序性死亡和非程序性死亡. 坏死被认为是非程序性死亡, 凋亡、自噬、坏死性凋亡和焦亡为程序性死亡<sup>[1-9]</sup>. 随着生活水平不断提高, 急性胰腺炎(acute pancreatitis, AP)发病率持续增长<sup>[10-13]</sup>. AP发病急、病情进展快, 可进展为死亡率极高的重症胰腺炎(severe acute pancreatitis, SAP). 众所周知, 胰腺腺泡细胞具有分泌多种消化酶的能力, 如胰蛋白酶、胰脂肪酶等. 在胰腺受损伤后会引发胰酶异常激活等病理生理学改变. AP发病初期, 激活的胰酶、过量的氧自由基和促炎细胞因子使腺泡细胞发生损伤, 部分损伤的腺泡细胞的胞膜在炎症介质及促炎细胞的作用下发生破裂, 胞内容物及炎症因子释放, 导致腺泡细胞坏死; 部分细胞经线粒体途径或死亡受体途径发生凋亡. 腺泡细胞的死亡方式一直是AP研究的重点. AP病程早期腺泡细胞死亡方式大致决定了AP的转归情况. 研究<sup>[14-16]</sup>证明AP患者的病情与腺泡细胞凋亡比例呈负相关, 而与坏死比例呈正相关. 轻型AP腺泡细胞死亡方式主要以凋亡为主, 而SAP则常伴大量腺泡细胞坏死, 导致局部及全身一系列炎症反应, 甚至发生全身炎症反应综合征(systemic inflammatory response syndrome, SIRS)和多器官功能障碍综合征(multiple organ dysfunction syndrome, MODS). 坏死性凋亡具有坏死和凋亡的共同特征, 部分学者<sup>[17]</sup>针对其与AP的关系进行了初步研究, 但其对于AP功能学改变和作用机制仍需探讨. 焦亡与凋亡都具有核固缩、TUNEL染色阳性的特点, 但目前关于焦亡的研究发现焦亡有促进炎症反应的作用, 这就与凋亡有着本质的区别. 近年关于焦亡与AP的研究较少, 需进一步的实验探究. 本文将从凋亡、坏死、坏死性凋亡以及焦亡对AP的影响进行综述.

## 1 腺泡细胞死亡方式对AP的影响

AP病程中存在胰酶异常激活、钙离子超载、腺泡细胞能量供应减少等现象. 腺泡细胞早期受损导致胰酶异常激活以及释放, 引起胰腺局部炎症, 部分病例会引起一系列全身炎症反应, 导致胰腺腺泡细胞大量坏死, 即SAP. AP是涉及到局部及全身各系统的炎症反应性疾病, 如何从源头上控制AP的炎症反应的启动和扩散是控制AP病情的关键因素. 腺泡细胞死亡和胰酶异常激活是各型胰腺炎共同特征. 但三者病情程度和转归截然不同. 因此腺泡细胞的死亡方式在很大程度上决定了AP炎症轻重. 凋亡是内源性基因调控下的一种主动的细胞程序性死亡方式, 不会引起强烈的炎症反应, 对周围组织损伤极小. 坏死是腺泡细胞被动的死亡方式, 信号传导通路不确定, 坏死细胞会释放大量炎症因子导致强烈的炎症反应, 坏死性凋亡具有坏死和凋亡共同的特征, 而与坏死不同的是其有着固定的信号传导通路, 可以对其进行研究和调控<sup>[18,19]</sup>. 焦亡与凋亡有类似的形态学变化, 部分学者<sup>[20,21]</sup>已经证明焦亡有促进炎症反应的作用. AP腺泡细胞发生损伤, 胰酶激活, 对周围胰腺组织造成损伤, 从而引发胰腺局部的炎症反应. 如局部炎症反应轻, 可能进展为轻型AP, 若局部炎症反应重, 可进一步大量激活单核巨噬细胞, 上调细胞黏附分子和各种趋化因子, 并触发更多的细胞因子和炎症因子, 产生“瀑布样”连锁反应, 导致机体免疫系统失衡, 进展为SAP, 引起SIRS和MODS<sup>[22]</sup>. 因此在AP发病早期若有效的遏制促进炎症反应的死亡方式, 或有效的诱导其转变为抑制炎症反应的死亡方式, 即可抑制炎症反应, 控制病情.

## 2 凋亡、坏死与AP

凋亡是一种经典的程序性细胞死亡方式, 形态学特征为细胞核固缩、DNA片段降解、凋亡小体形成以及不伴有细胞膜与溶酶体破裂. 因此通常不引起炎症反应及继发性组织损伤<sup>[23]</sup>. 细胞凋亡的启动和进展均受到精确的基因调控, 其调控通路主要包括线粒体通路、死亡受体通路和内质网通路, 三条通路可相互作用、相互影响<sup>[23,24]</sup>. 三条通路最终都激活caspase, 因此caspase也常被视为凋亡通路的核心. 目前发现的与凋亡相关的caspase主要包括caspase-2、caspase-3、caspase-6、caspase-8及caspase-9等<sup>[25]</sup>. 值得注意的是, 敲除caspase基因后细胞还存在凋亡代偿通路, 其中机制有待于进一步实验研究<sup>[26,27]</sup>.

坏死的形态学特征为细胞核固缩、溶酶体破裂、各种细胞器损坏、细胞膜破坏、细胞丧失原有结构以及大量炎症细胞浸润组织. Kaiser等<sup>[28]</sup>的实验发现SAP

大鼠模型中存在大量坏死的腺泡细胞, 轻型AP则有大量凋亡的腺泡细胞, 即认为轻型AP时腺泡细胞死亡方式以凋亡为主, SAP时坏死的腺泡细胞以坏死为主, 坏死比例越高AP病情越重. 长期以来, 坏死被认为是细胞受刺激产生的不可调控的被动型死亡过程, 调节坏死的细胞传导通路不固定, 并且机制不明, 很难对其进行干预<sup>[29,30]</sup>.

Zhang等<sup>[22]</sup>认为凋亡几乎不引起AP炎症反应. 研究人员发现凋亡腺泡细胞比例高于坏死比例时, 则AP炎症相对较轻, 病情较轻, 而腺泡细胞坏死比例相对较高时, AP炎症反应则较重, 病情较重. 一些专家持有相似观点: AP病程早期如果大部分受损伤的腺泡细胞死亡方式都趋向凋亡, 那么AP病情将减轻很多<sup>[31-36]</sup>. Bhatia等<sup>[37]</sup>用肿瘤坏死因子- $\alpha$ (tumor necrosis factor alpha, TNF- $\alpha$ )处理AP小鼠, 发现小鼠腺泡细胞凋亡比例多于坏死比例, 胰腺组织病理学评分降低, 病情减轻. Zang等<sup>[38]</sup>认为小剂量的TNF- $\alpha$ 可诱导AP腺泡细胞的死亡方式趋向凋亡, 减轻AP病情. Kaneto等<sup>[39]</sup>用一氧化氮(nitric oxide, NO)处理大鼠胰腺腺泡细胞, 发现NO会引发凋亡, 血清NO浓度增加会使AP炎症反应减轻.

### 3 坏死性凋亡与AP

细胞坏死广泛参与了多种疾病的病理生理过程, 但其不可调控的特点使相关性研究未受到学者足够的重视. 近年在研究缺血性脑损伤的机制时发现了可被调控的特殊类型的坏死, Degterev等<sup>[40]</sup>将其命名为坏死性凋亡. 坏死性凋亡是受特殊死亡受体-配体介导的程序性细胞坏死方式, 具有独特的信号传导途径, 还具备典型坏死细胞的形态学表现: 细胞膜破裂、细胞器肿胀、细胞器损坏和细胞结构破坏<sup>[41]</sup>. He等<sup>[42]</sup>发现RIPK3基因敲除小鼠的胰腺病理学评分明显低于未敲除组. 提示RIPK3可以介导AP腺泡细胞坏死性凋亡的发生. Wu等<sup>[43]</sup>的研究发现MLKL基因敲除的AP消除坏死的腺泡细胞数量少于普通AP小鼠. 表明MLKL也可引发胰腺腺泡细胞坏死性凋亡. Ma等<sup>[44]</sup>的研究表明AP小鼠中存在RIPK3介导的腺泡细胞坏死性凋亡, 并且miR-21表达明显上调. 抑制miR-21表达即可阻断RIPK3介导的坏死性凋亡, 减轻AP炎症反应. 目前关于AP坏死性凋亡的研究仅仅从初步探讨了关键基因对于胰腺组织学改变的影响, 而引发形态学功能学变化以及具体的分子机制尚不明确. 有待于众多学者的进一步探究.

### 4 焦亡与AP

焦亡是近年发现的一种新的细胞程序性死亡方式, 目前大部分学者<sup>[45-47]</sup>认为焦亡是由Caspase-1与Caspase-11介导的. 焦亡在1992年被Zychlinsky等<sup>[48]</sup>发现, 2001年

Cookson等<sup>[49]</sup>对其命名. 近年来有关Gasdermin D蛋白的研究<sup>[50]</sup>使关于焦亡机制的研究更进一步, 研究认为凋亡减轻炎症反应而焦亡促进炎症反应, 对疾病的转归影响截然不同, 因此区分炎症反应中细胞的死亡方式是焦亡还是凋亡, 关系到是抑炎或促炎, 是维持机体免疫平衡、改善预后的重要环节. 焦亡广泛发生于单核巨噬细胞和树突状细胞等其他细胞中, 细胞焦亡早期, 细胞膜上形成许多直径为1-2 nm的微孔, 其完整性丧失, 随后水分内流、细胞膜内外离子梯度消失, 细胞发生肿胀、渗透性溶解最终导致细胞破裂死亡<sup>[51,52]</sup>. 此外, 焦亡过程还伴有细胞核浓缩及染色体DNA的断裂、降解<sup>[53,54]</sup>. 与凋亡不同的是: 虽然焦亡细胞发生核固缩, 但细胞核保持完整, 不发生核裂解. 目前认为焦亡存在caspase-1介导的需炎症小体参与和caspase-11介导的不需炎症小体参与两种通路<sup>[45-47]</sup>. 目前研究较多的是前者.

大部分学者认为焦亡会加重炎症反应. Mazzolini等<sup>[19]</sup>关于肝脏炎症的研究发现焦亡会加重炎症反应, Labbé等<sup>[20]</sup>也认为焦亡会加重炎症反应. Shao等<sup>[54]</sup>研究发现AP病程中存在腺泡细胞焦亡现象. 目前关于焦亡对AP炎症反应的作用尚不清楚. 有待于进一步研究发现和证明.

### 5 结论

腺泡细胞死亡方式对于AP病情以及炎症反应有重要作用, 面对AP可调控的死亡方式带给研究者希望的同时, 也引起了诸多思考: (1)AP病程中存在氧化应激、钙离子超载、炎症介质过度生成等因素. 那么这些因素对于AP腺泡细胞坏死性凋亡和焦亡的作用如何, 目前仍不清楚; (2)内质网和线粒体在腺泡细胞死亡方式中也起到了关键作用. 其对于坏死性凋亡和焦亡的作用和机制也需要进一步研究; (3)除以上提到的细胞死亡方式外, 铁死亡、Parthanatos(又称PARP-1 dependent cell death, 是基于DNA损伤, PARP-1激活的一种新的程序性细胞坏死形式)<sup>[55]</sup>等分别通过不同的细胞通路和靶点对于细胞死亡起到重要作用. AP时是否存在这些死亡方式, 这些死亡方式与凋亡、坏死、坏死性凋亡和焦亡的关系以及是否存在相互作用值得进一步深入研究.

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