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·文献综述·

急性胰腺炎腺泡细胞损伤机制研究进展

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摘　要　急性胰腺炎（AP）是胰腺的炎症性疾病，由于发病机制尚未完全阐明，临床对重症 AP 仍缺乏有效的治疗方法。目前认为，钙超载、酶原异常活化、内质网应激、自噬、线粒体损伤及炎症反应与胰腺腺泡细胞损伤关系密切，现就其研究进展进行综述。

关键词　胰腺炎；腺泡细胞；损伤；综述文献
中图分类号：R657.5

Mechanism for injury of pancreatic acinar cells during acute pancreatitis: recent progress

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Abstract　Acute pancreatitis (AP) is an inflammatory disorder of the pancreas. Because the mechanism is not yet fully elucidated, there is clinically no effective treatment for the severe AP. Calcium overload, premature trypsinogen activation, endoplasmic reticulum stress, autophagy, mitochondrial dysfunction and inflammatory response are considered to be closely associated with the injury of pancreatic acinar cells. Here, the authors address the research progress in this field.

Key words　Pancreatitis; Acinar Cells; Injury; Review
CLC number: R657.5

急性胰腺炎（acute pancreatitis，AP）是临床上常见的急腹症，通常认为是多种因素引起腺泡细胞内酶原异常激活而导致胰腺局部的自身消化，甚至诱发全身炎症反应综合征（SIRS），进展为重症急性胰腺炎（SAP）[1]。由于AP病程进展迅速，有关疾病始发过程的机制难以从临床上获得，因此，目前有关AP的机制研究仍以动物实验及基于人体标本的体外研究为主。现就AP发病机制的最新研究进展综述如下。

1　钙超载与线粒体损伤

生理性钙离子振荡在AP时受到破坏，腺泡细胞内Ca^{2+}浓度病理性升高是AP的核心事件，在调节促细胞死亡和促炎信号通路中起到重要作用，包括未成熟胰蛋白酶原的活化[2]，NF-κB的激活[3]，线粒体功能障碍[4]等。酒精、胆汁酸等物质可通过开放内质网的三磷酸肌醇受体（inositol

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1，4，5- trisphosphate receptor，IP3R），使得内质网钙池的Ca^{2+}过度释放，引起细胞质钙超载[5-6]。激活腺泡细胞膜上的钙释放激活钙通道蛋白1（ORAI1）促使细胞外Ca^{2+}内流，造成细胞内病理性钙超载状态[5, 7]。ERCP后胰腺炎及胆源性胰腺炎均被认为通过胆道梗阻造成胆道压力升高，激活腺泡细胞膜上的机械性刺激感受器PIEZO1，引起Ca^{2+}内流而加剧钙超载，进而导致腺泡细胞损伤[8]。

钙超载造成线粒体膜通透性转运孔（mitochondrial permeability transition pore，MPTP）持续开放，线粒体膜间隙的质子或者阳离子不断进入线粒体基质，使得线粒体内膜两侧离子梯度消失，导致合成ATP所需的线粒体膜电位逐渐下降甚至消失，氧化磷酸化发生解偶联，ATP生成减少[4, 9-11]，ATP依赖性滑面内质网Ca^{2+}通道（SERCAs）和胞膜Ca^{2+}通道（PMCAs）功能受损，无法清除细胞内过剩的Ca^{2+}，并削弱依赖ATP供能发挥细胞保护作用的自噬效应和未折叠蛋白反应（UPR）[12]，最终导致细胞死亡。考虑到钙超载的毒性作用，应用ORAI1通道抑制剂可以减少AP小鼠腺泡细胞和人腺泡细胞的坏死[5-6]。此外，Javed等[13]应用 MPTP抑制剂TRO40303来阻断线粒体膜电位缺失并有效减少AP小鼠腺泡细胞和人腺泡细胞发生坏死。此外，精氨酸诱导的啮齿类动物AP模型中，亲环素D调控ATP合成酶发生构象改变而失去活性亦可导致线粒体MPTP持续开放[12]。多中心双盲随机对照研究表明，通过早期高热量营养支持来维持ATP生成，有望成为缓解AP病情的有效途径[14]。

2 腺泡细胞和巨噬细胞内酶原活化

胰腺创伤、胰管梗阻或者酒精等因素既可增加溶酶体酶和消化酶的合成，又导致腺泡细胞酶原颗粒正常胞吐过程受限，若酶原颗粒与溶酶体发生共定位，胰蛋白酶原将被溶酶体内的组织蛋白酶B（cathepsin B，CTSB）激活成为胰蛋白酶，胰蛋白酶活化导致胰腺及其他组织的自我消化，此外，随着细胞质内CTSB增多，细胞死亡方式由凋亡向坏死过渡[15]。细胞坏死性凋亡由受体相互作用蛋白激酶（receptor-interacting protein kinase，RIPK）与下游的混合谱系激酶结构域（mixed lineage kinase domain-like，MLKL）调控，MLKL被RIPK3磷酸化后形成低聚体，再转运到细胞膜上，使得细胞膜破裂而细胞内容物溢出，细胞发生坏死性凋亡，通过基因敲除RIPK1/RIPK3或应用RIPK1抑制剂necrostatin可以减少腺泡细胞的坏死性凋亡，减轻损伤程度[16-17]。最近Sendler等[18]研究发现，AP发生时，损伤的腺泡细胞释放的趋化因子，巨噬细胞是第一个受趋化作用向胰腺聚集的免疫细胞，浸润的巨噬细胞高表达CTSB，也通过吞噬胰蛋白酶原并使其活化，再经NF-κB通路进一步释放促炎因子，加重AP炎症反应程度，而CTSB基因敲除小鼠的胰腺炎明显改善，将野生型小鼠的巨噬细胞移植到CTSB基因敲除小鼠体内同样可以加重胰腺炎。因此，未成熟的酶原的激活不仅存在腺泡细胞内，而且在巨噬细胞内，且该过程都依赖于CTSB的作用。

3 细胞自噬与内质网应激

腺泡细胞需要内质网、高尔基体等高效并大量合成蛋白质以满足生理需求。大自噬通过处理多种衰老的、有缺陷的、被破坏的细胞器及错误折叠的蛋白成分发挥细胞保护作用，促进细胞存活[19]。生理条件下，内质网、高尔基体与细胞膜等双膜结构包裹细胞内容物形成自噬体，该过程受自噬相关蛋白（ATGs）调控，自噬体与溶酶体融合后其内容物降解，若自噬反应受损则可诱发炎症反应[20]。腺泡细胞特异性敲除ATG5与ATG7小鼠可导致自噬反应受损，酶原颗粒堆积并在细胞内活化而发生严重的胰腺炎[19, 21-22]。此外，溶酶体相关膜蛋白（LAMPs）缺失导致腺泡细胞溶酶体功能障碍，自噬反应异常，未成熟酶原活化，炎症反应加剧[23]。自噬反应受损还可导致线粒体功能障碍、内质网应激和脂质代谢异常，使得腺泡细胞易受损伤因素影响而死亡[12, 24]。因此，修复腺泡细胞的自噬反应有望成为AP的治疗靶点。Biczo等[12]在精氨酸和雨蛙素诱导的小鼠AP模型中发现，应用海藻糖可以减少异常自噬，减轻腺泡细胞损伤，从而改善AP严重程度。但是海藻糖如何干预自噬过程的具体机制仍不明确。

错误折叠的蛋白质在内质网腔内过度聚集，超过了细胞正常的处理能力将发生内质网应激（endoplasmic reticulum stress，ERS），ERS发生后，腺泡细胞激活UPR过程来促进多余的蛋白降解和正确折叠以维持细胞稳态，当ERS超过了细胞UPR的保护限度后将诱发细胞死亡[25]。笔者既往

研究[26-28]发现，4-苯基丁酸作为ERS抑制剂，能够有效减轻大鼠的AP的脏器损伤和炎症反应程度。他汀类药物作为HMG-CoA抑制剂，能起到促进UPR效应的作用，临床回顾性队列研究发现，他汀类药物可以减少AP的发病率并改善预后[29-30]。

4　导管细胞功能障碍

腺泡细胞和导管细胞的跨膜水通道蛋白（aquaporin 1，AQP1）和囊性纤维跨膜调控因子（cystic fibrosis transmembrane regulator，CFTR）对维持胰液的生理性分泌至关重要[31]。酒精和胆汁酸可以显著破坏CFTR的功能，减少碳酸氢盐的分泌而酸化导管内环境，造成导管内胰液淤积，引起未成熟消化酶原在导管内活化[32-33]。此外，Husain及其团队研究发现，导管内高压通过激活钙调磷酸酶促进炎症反应、STAT3通路活化和破坏胰腺细胞紧密连接的完整性，诱发腺泡细胞损伤，进而引起AP，而基因敲除钙调磷酸酶或应用钙调磷酸酶抑制剂可以明显减轻导管内高压诱导的腺泡细胞损伤[34-35]。胆汁酸还可以导致线粒体功能障碍，减少ATP产生而造成ATP依赖性碳酸氢盐分泌不足，损伤导管细胞，进而使得腺泡细胞暴露于胆汁酸而死亡[36]。

5　免疫细胞反应

受损的腺泡细胞释放趋化因子、细胞因子和多种粘附分子来募集免疫细胞向炎症区域浸润[3, 37]，之后坏死的腺泡细胞释放细胞内容物进一步激活炎性细胞并使得炎症播散[38]。单核细胞趋化蛋白（monocyte chemoattractant protein 1，MCP1）促进单核细胞迁移，巨噬细胞炎性蛋白（macrophage inflammatory protein 2α，MIP2α）和CXC趋化因子配体（CXCL1）招募中性粒细胞[39-40]。中性粒细胞可以产生中性粒细胞外诱捕网络（neutrophil extracellular traps，NETs），进一步激活促炎信号和未成熟酶原，加重脏器损伤和AP病情[41]。在动物实验中，抑制趋化因子及其受体可以有效减轻AP时胰腺及胰外脏器损伤[42-43]。AP时，单核-巨噬细胞的活化受到坏死腺泡细胞释放的损伤相关分子模式（damage associated molecular patterns，DAMPs）调节。包括高迁移率族蛋白B1（HMGB1），热休克蛋白70（HSP70）以及Toll样受体（TLRs）在内的DAMPs可以经NF-κB调控促炎因子、趋化因子和黏附分子的转录翻译过程。此外，ATP和NAD等DAMPs还可与P2X7受体结合而活化炎性小体，使得IL-1β和IL-18转化为活性形式，形成级联放大效应[44-45]，而抑制NF-κB和炎性小体通路可以减轻AP的炎症反应水平[46]。在小鼠AP模型中，坏死腺泡细胞释放出DNA，作为DAMP激活干扰素基因刺激器（STING），促进干扰素β和肿瘤坏死因子（TNF）等促炎因子的表达，加重AP严重程度[47]。在AP的炎症反应阶段也伴随着代偿性抗炎反应综合征（CARS），IL-10作为最主要的抗炎因子，可由腺泡细胞、单核巨噬细胞，淋巴细胞产生，并通过抑制STAT3通路和T细胞增殖减少促炎因子合成[48]。当CARS占据优势时，胰腺可由无菌性坏死向感染性坏死转变[49]。

己酮可可碱作为一种非选择性磷酸二酯酶抑制剂，通过下调NF-κB通路而减少TNF的合成，有小规模的临床研究表明，己酮可可碱可以减少AP患者的住院时长[50]，具体效果仍有待大规模临床试验证实。此外，Chen等[42]在大鼠AP模型中发现，IL-6受体拮抗剂Tocilizumab可以减轻AP严重程度及AP相关肺损伤等并发症，既往Tocilizumab在巨细胞动脉炎、移植物抗宿主反应的临床应用中具有良好的疗效和安全性[51-52]，有望进入临床试验用于治疗AP。

6　不饱和脂肪酸和肠系膜淋巴液的毒性作用

既往临床研究表明，病态肥胖是AP预后不良的危险因素[53]，内脏脂肪堆积可以作为AP向SAP进展的可靠预测因素[54]，而高甘油三酯血症是AP时持续器官功能衰竭的独立危险因素[55]。Noel等[56]研究发现，AP发作时，酶原颗粒的正常顶浆分泌途径被破坏，从基底侧分泌的脂肪酶进入胰腺间质、胰周及血流中，分解胰腺内、胰周脂肪和血液中的甘油三酯生成脂肪酸，其中不饱和脂肪酸（UFAs）通过抑制线粒体复合体的功能，增加TNF、IL-1β和IL-8表达水平而加剧炎症反应程度。因此，应用脂肪酶抑制剂来抑制内脏脂肪和血甘油三酯的水解有望成为阻止AP向SAP进展的治疗策略。

AP病程随着肠道受损而进一步恶化，特别是

肠梗阻和肠道缺血再灌注损伤导致的肠道细菌易位和菌群失调。近年来，含有毒素的淋巴液引流在AP中的作用逐渐受到研究者的重视。Windsor等[57-58]研究表明，在大鼠AP模型中，肠道缺血条件下的肠系膜淋巴液（mesenteric lymph，ML）可导致心脏功能不全和多器官功能障碍。但是，目前ML中何种成分在起作用仍不清楚。在动物实验中，已证实结扎胸导管可以减轻AP大鼠ML的有害效应[57, 59]。随着介入放射和超声内镜下定位胸导管的技术不断进步，在AP患者中让ML改变流动方向有望成为减少远隔脏器损伤的有效手段[60-61]。

7 总结与展望

AP的发生发展是一个复杂的生物学过程，目前临床治疗仍以补液、抑制胰酶分泌、营养支持及手术等综合治疗为主，对于该病的防治还缺乏特效方法和策略。钙超载、内质网应激、自噬、线粒体损伤及炎性反应等在发病过程中相互影响，单纯解决某个环节的问题仍难以起到以点带面的作用，若能深入研究，厘清这些机制之间内在的联系，可为临床治疗AP开辟一条新的治疗途径，这对AP的确切治疗有着重要的意义。

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