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· 综述 ·

慢性胰腺炎遗传致病机制研究进展

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[摘要] 慢性胰腺炎是一种以组织萎缩和不可逆纤维化为特征的复杂炎症性疾病, 疾病后期出现胰腺内外分泌功能受损。自第1个慢性胰腺炎相关致病基因突变被发现以来, 胰腺炎的遗传学研究取得了重大进展。多数慢性胰腺炎风险基因编码胰蛋白酶、胰蛋白酶抑制因子或胰腺内高表达的其他蛋白, 其通过不同致病机制对胰腺造成损害。现回顾近年来慢性胰腺炎的遗传学研究进展, 针对其遗传致病机制进行综述。

[关键词] 慢性胰腺炎; 遗传学; 致病机制; 基因模型

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Genetic pathogenesis of chronic pancreatitis: research progress

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[Abstract] Chronic pancreatitis is a complex inflammatory disease characterized by tissue atrophy and irreversible fibrosis. In the late course of the disease, a progressive loss of endocrine and exocrine function occurs. Since the discovery of the first pathogenic mutation of chronic pancreatitis, great progress has been made in the genetic study of pancreatitis. Most of the chronic pancreatitis-related risk genes encode trypsin, trypsin inhibitors or other proteins highly expressed in the pancreas. Herein we reviewed the genetic research progress of chronic pancreatitis in recent years and summed up its genetic pathogenesis.

[Key words] chronic pancreatitis; genetics; pathogenesis; genetic model

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慢性胰腺炎是一种由遗传、环境等因素引起的慢性炎症性疾病, 临床治疗难度大, 严重影响患者的生活质量。全球范围内慢性胰腺炎的年发病率为10/10万, 年死亡率为0.09/10万^[1]。随着研究的深入, 遗传因素在慢性胰腺炎发生、发展过程中的作用日益受到关注。根据致病机制不同, 慢性胰腺炎的遗传致病通路主要分为胰蛋白酶相关通路、蛋白质错误折叠相关通路和胰腺导管相关通路3类。本文就近年来慢性胰腺炎的遗传学研究进展进行综述。

1 胰蛋白酶相关的通路

胰腺自身消化的概念最先由奥地利病理学家

Chiari提出, 他认为胰腺炎是由腺体自身消化引起的^[2]。腺泡细胞以无活性的前体形式分泌胰蛋白酶原, 后者被十二指肠中的肠肽酶水解为有活性的胰蛋白酶; 如果胰蛋白酶原通过自激活或溶酶体组织蛋白酶B介导的活化在胰腺内提前转变为活性胰蛋白酶, 即可损伤胰腺^[3]。防止胰蛋白酶原过早激活的保护机制包括: (1) 丝氨酸蛋白酶抑制因子Kazal 1型 (serine peptidase inhibitor Kazal type 1, SPINK1) 对胰蛋白酶的抑制作用; (2) 胰凝乳蛋白酶C (chymotrypsin C, CTRC) 和组织蛋白酶L介导的胰蛋白酶原降解^[4]。尽管CTRC的主要作用是促进胰蛋白酶原降解, 但它还通过将胰蛋白酶原激活肽加工成较短的形式来增强胰蛋白酶原

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的活化^[5]。胰蛋白酶原自身激活和CTRC依赖的胰蛋白酶原降解是决定胰腺内胰蛋白酶活性的关键环节。

1.1 阳离子胰蛋白酶原 (serine protease 1, *PRSS1*) 基因突变 1996年, Whitcomb等^[6]发现 *PRSS1* R122H突变与遗传性胰腺炎相关。Archer等^[7]在腺泡细胞表达 *mPRSS1* p.R122H的转基因小鼠中观察到慢性胰腺炎的病理改变。此后研究发现, 约90% *PRSS1* 突变阳性的遗传性胰腺炎患者家族携带杂合状态的 *PRSS1* 基因 p.N29I、p.R122C或 p.R122H突变, 其中 p.R122C和 p.R122H突变抑制CTRC介导的胰蛋白酶原降解, p.N29I突变通过增加氨基末端处理、减少CTRC依赖性降解和增加自激活等多种作用使胰蛋白酶原自身活化增强^[3]。Huang等^[8]发现 *PRSS1* p.R122H在小鼠胰腺中的转基因表达促进了胰腺炎症, 且与酒精、高脂等常见环境危险因素存在协同致病效应。

1.2 阴离子胰蛋白酶原 (serine protease 2, *PRSS2*) 基因突变 尽管 *PRSS1* 和 *PRSS2* 在氨基酸水平上的一致性可达90%, 但在遗传性胰腺炎或散发性慢性胰腺炎中未鉴定出致病性 *PRSS2* 突变^[9]。其原因可能是CTRC介导的 *PRSS2* 降解更高效, 即使突变也不足以使 *PRSS2* 在胰腺内过度激活^[10]。有研究发现 *PRSS2* 基因 p.G191R突变有约3~6倍的保护效应, 该突变将新的水解位点引入 *PRSS2*, 从而促进催化蛋白水解和失活^[9,11]。

1.3 *SPINK1* 基因突变 *SPINK1* 是一种胰蛋白酶抑制因子, 能够抑制过早激活胰蛋白酶的活性。*SPINK1* p.N34S突变是欧洲慢性胰腺炎人群中常见的遗传突变^[12-13]。功能实验提示 *SPINK1* p.N34S突变及相关的4个内含子突变不影响其胰蛋白酶抑制活性和蛋白在细胞内的表达, 其造成慢性胰腺炎风险的机制仍不明确^[14]。*SPINK1* 是我国慢性胰腺炎人群中最常见的易感基因, 44.9%的特发性慢性胰腺炎患者携带 *SPINK1* c.194+2T>C突变^[15]。功能实验表明该突变导致 *SPINK1* 基因在转录过程中直接跳过外显子3, 使蛋白表达减少^[16]; Sun等^[17]发现 *Spink1* c.194+2T>C突变的杂合小鼠发生自发性慢性胰腺炎。

1.4 *CTRC* 基因突变 Rosendahl等^[18-19]通过DNA测序分析发现, 44%的非酒精性慢性胰腺炎患者携带 *CTRC* 基因杂合突变, 携带该突变的人群患慢性

胰腺炎的风险增加。突变导致CTRC功能丧失, 包括分泌缺陷、活化受阻或降解增加等, 如 p.A73T突变使得CTRC分泌减少, p.K247_R254del突变使编码蛋白无活性且易于降解, p.V235I突变使蛋白活性降低^[20]。此外, p.G60G的杂合突变使慢性胰腺炎风险增加2.5倍, 纯合突变使其增加10倍, 该突变与 *CTRC* mRNA 表达降低相关^[3]。

2 蛋白质错误折叠相关通路

蛋白质错误折叠相关通路是一种独立于胰蛋白酶依赖通路的慢性胰腺炎遗传致病机制^[21], 变异引起消化酶错误折叠并导致内质网应激, 进而促进腺泡细胞死亡。这一致病通路近年来引起了研究者的广泛关注。

2.1 错误折叠相关的 *PRSS1* 突变 Kereszturi等^[22]在2009年首次提出突变引起的胰蛋白酶原错误折叠可能会导致慢性胰腺炎。他们发现与 *PRSS1* p.N29I、p.R122C和 p.R122H等突变不同, *PRSS1* p.R116C和 p.C139S突变会导致编码的胰蛋白酶原分泌减少、滞留于细胞内并导致内质网应激。随后的研究发现 *PRSS1* p.L104P突变的编码蛋白也存在类似的错误折叠表型^[23]。错误折叠相关的 *PRSS1* 突变在临床上较为罕见, 主要存在于散发型胰腺炎患者和部分遗传性胰腺炎家族^[21]。

2.2 羧肽酶 A1 (carboxypeptidase A1, *CPA1*) 基因突变 羧肽酶原 A1 在胰液中的含量仅次于胰蛋白酶原。2013年的一项研究显示, *CPA1* 突变与慢性胰腺炎相关 ($OR=24.9$), 尤其是早发性慢性胰腺炎 ($OR=84.0$)^[24]。多数致病性 *CPA1* 突变发生率较低, 见于散发病例, 其中 p.S282P突变在2个遗传性胰腺炎家族中被报道^[25]。体外实验表明致病性 *CPA1* 变异可引起蛋白错误折叠, 导致其分泌受阻、滞留于细胞内并发生内质网应激^[24-25]。Hegyí和 Sahin-Tóth^[26]研究发现, 携带人类 *CPA1* p.N256K突变的基因编辑小鼠会产生自发和进行性的慢性胰腺炎病变, 伴随 *CPA1* 蛋白的错误折叠和内质网应激。

2.3 羧基酯脂肪酶 (carboxyl ester lipase, *CEL*) 基因变异 *CEL* 由胰腺腺泡细胞分泌, 参与胆固醇酯的水解。*CEL* 基因最后一个外显子中由单核苷酸缺失引起的框移突变可导致青春晚期糖尿病8型 (maturity onset diabetes of the young type 8,

MODY8),引起胰腺内外分泌功能损害^[27]。变异的CEL-MODY8蛋白分泌受阻,并且在胞内形成蛋白聚集体,提示变异蛋白存在错误折叠。此外,CEL与其串联排列的假基因(carboxyl ester lipase pseudogene, CELP)形成的杂合等位基因CEL-HYB1在欧洲特发性慢性胰腺炎患者中的携带率约为正常人群的5倍,细胞实验发现CEL-HYB1杂合蛋白同样存在分泌受阻、胞内留滞,并且诱导自噬激活^[28]。这些发现表明CEL-HYB1变异可能通过蛋白错误折叠增加慢性胰腺炎的风险。然而,Zou等^[29]没有在亚洲人群中发现CEL-HYB1的携带者,提示这是一种人种特异的遗传致病因素。

3 胰腺导管相关通路

3.1 囊性纤维化跨膜传导调节因子(cystic fibrosis transmembrane conductance regulator, CFTR)基因突变 CFTR是一种跨膜蛋白,主要调节胰腺导管细胞分泌富含碳酸氢盐的液体,将腺泡细胞分泌的酶原转运至十二指肠。CFTR基因的异常被认为是囊肿性纤维化病变的主要原因^[30]。一项对CFTR基因的分析研究显示,慢性胰腺炎患者中异常CFTR等位基因的频率为18.6%,而对照组为9.2%,提示CFTR基因突变增加慢性胰腺炎发生风险^[31]。CFTR p.F508del突变和CFTR p.R117H突变的杂合携带者患慢性胰腺炎的风险升高,而同时携带2个突变的复合杂合状态则被认为是慢性胰腺炎的直接致病因素^[32]。动物实验提示CFTR^{-/-}小鼠有轻度的胰腺外分泌功能不全,雨蛙素处理后的CFTR^{-/-}小鼠出现了更严重的急性胰腺炎表现^[33]。

3.2 密封蛋白2(claudin-2, CLDN2)基因突变 CLDN2是一种能密封上皮细胞之间空隙的紧密连接蛋白,在胰腺导管细胞间形成水和钠离子通道。一项全基因组关联分析研究发现,CLDN2基因座的变异与慢性胰腺炎存在关联,且风险变异与CLDN2的非典型定位有关^[34]。另一项研究发现CLDN2-MORC4基因座中的部分单核苷酸多态性与慢性胰腺炎发生风险相关,且与酒精性慢性胰腺炎的关联性比非酒精性慢性胰腺炎更强^[35]。

3.3 钙感受受体(calcium-sensing receptor, CASR)基因突变 CASR可以感受胞外钙水平,并激活细胞内多种调节功能。CASR在胰腺导管细胞中表达,通过增加导管液分泌来稀释胰液中高浓度的

钙,从而防止结石形成和胰腺炎^[36]。一项在美国人群中开展的研究发现,CASR p.R990G突变可增加慢性胰腺炎发生风险,特别是对于中度或重度饮酒的人群^[37]。一项在法国人群中开展的研究发现,特发性慢性胰腺炎患者中稀有CASR突变的比例较高,CASR p.A986S纯合突变与慢性胰腺炎显著相关^[38]。

4 小结

急性胰腺炎、复发性胰腺炎和慢性胰腺炎是疾病发展的不同阶段,存在连续性^[1]。慢性胰腺炎的发生与遗传、环境及其他多种致病因素有关,其防治属于世界性医学难题^[39]。近年来,随着分子遗传学和人类基因组研究的迅速发展,慢性胰腺炎风险基因逐渐被鉴定出来,其遗传致病机制研究也逐渐深入。然而目前针对慢性胰腺炎的治疗方法仅能缓解症状和延缓病程,仍无逆转或治愈手段。遗传致病机制研究的成果或能为慢性胰腺炎的治疗提供新思路。

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