

Research Progress on Cytoskeletal Protein Variation in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common tachyarrhythmia in clinical practice, which can be secondary to other diseases such as hypertension, valvular disease and heart failure, thus increasing the risk of cerebral infarction and sudden death. It has recently been recognized that 15% of individuals in the AF population are familial. Evidence from various epidemiological studies suggests that genetic factors play an important role in the pathogenesis of AF. To date, several rare variants have been identified in a range of genes related to ion channels, cytoskeletal proteins, inflammatory, calcium-treated proteins. However, the genetics of AF is quite complex, and the pathophysiological mechanisms are still unresolved. Here we focus on the genetic variation in cytoskeletal proteins associated with hereditary AF, and the underlying pathophysiological pathways that drive this arrhythmia.

Keywords

atrial fibrillation; familial; gene; cytoskeletal protein; heredity

细胞骨架蛋白变异在心房颤动中的研究进展

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摘要

心房颤动 (Atrial fibrillation, AF) 是临床上最常见的快速性心律失常, 该病可继发于其他疾病, 如高血压、心脏瓣膜病和心力衰竭, 从而增加脑梗死和猝死的风险。最近人们认识到, 在房颤人群中15%的人是家族性的。各项流行病学的研究的证据表明, 遗传因素在房颤的发病中起着重要作用。迄今为止, 在离子通道、细胞骨架蛋白、炎症、钙处理蛋白相关的一系列基因中已经发现几种罕见的变异。然而, 心房颤动的遗传学是相当复杂的, 其中的病理生理学机制仍未解开。在这里我们集中论述遗传性房颤相关的细胞骨架蛋白基因变异, 以及驱动这种心律失常的潜在病理生理途径。

关键词

心房颤动; 家族性; 基因; 细胞骨架蛋白; 遗传

1 引言

心房颤动是临床最常见的持续性心律失常。它的主要特点是心房进行无效的收缩与舒张, 继而导致心脏功能紊乱及血栓形成, 心电图主要特征是无规则的往复的基线波动^[1]。虽然在多数情况下, AF的病初发作的主要特征是可自行恢复且发作时间较短, 但随着疾病的发生发展, 逐渐表现为长期持续性发作^[2]。AF在一般人群中的患病率并不高, 并且在相关研究中表明65岁以上的人群房颤患病率呈翻倍式增长, 而在80岁以上人群其患病率可高达10%^[3], 预计到2050年, AF的患病人数与目前相比至少增加5倍, 并且AF患者的中风、心力衰竭以及死亡风险是普通人群的2倍, 接近1/3的

心脏血栓形成是由AF的并发症所引起^[4]。因此, 为了治疗这种心律失常并防止其恶化, 在早期诊断房颤和识别危险患者是至关重要的, 这就需要我们去了解AF发生的根本原因。

越来越多的研究表明, AF也是具有遗传性, 早在1943年Wolf等^[5]人发表了一个常染色体显性遗传模式的单纯性心房颤动家族。随着全基因组关联研究(GWAS)技术的应用, 越来越多AF相关的基因多态性被发现。到目前为止, 已经发现一些AF相关的基因多态性与房颤发生和卒中的风险相关, 并且在使用抗心律失常药物或射频消融治疗成功后易导致房颤复发。

2 AF相关细胞骨架蛋白变异

2.1 Lamin A/C (LMNA)

LMNA是一种编码中间丝蛋白的基因, 根据LMNA的特性可分为A型和B型, 主要参与心脏信号传导障碍、基因转录等^[6]。最近, 在意大利的一项LMNA变异与家族性心肌病相关的研究中发现, 纳入的30名受试者, 其中有18名该基因突变为阳性, 11名为阴性。在18名阳性的研究对

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象中,有11名出现了早期房颤,而11名阴性研究对象均未出现,这揭示了LMNA变异与AF发展的有着明确关联^[7]。

根据中间丝蛋白(Intermediate filament proteins, IFs)在氨基酸序列和分子结构上的相似性,将其分为6个亚群,命名为I型至VI型^[8],其中的V型层蛋白,在心肌细胞中广泛表达,V型层蛋白直接与染色质结合,负责调节与核膜相关的特定区域,并且可以与核外周的转录因子结合间接调控基因转录以及维持细胞核的形态^[9]。此外,层蛋白通过与LINC复合体的相互作用,在机械信号传导中也发挥重要作用^[10]。

在LMNAp.K219T的层状多能干细胞衍生的心肌细胞中发现突变的Lamin A/C会发生动作电位改变、钠电流峰值降低和传导速度降低,与SCN5A钠通道的基因启动子结合导致Nav1.5钠通道的表达降低,使其信号传播受损^[11]。

并且目前在对心室心肌细胞的研究中发现,LMNA基因突变可以引起细胞核形态改变、细胞骨架及其微丝、微管断裂^[12-14]和核糖聚合酶1(PARP1)激活^[15],快速起搏(TP)诱导的心肌细胞功能障碍是DNA损伤调节PARP1激活导致的,活化PARP1会增加烟酰胺腺嘌呤二核苷酸(NAD⁺)的消耗,从而加剧蛋白质和DNA的氧化损伤,这种反应的激活会导致快速心肌收缩、舒张从而增加心肌耗能,循环往复会诱导更多的DNA损伤、PARP1的过度激活以及NAD⁺耗竭^[12,16,17]。这些实验结果表明,LMNA变异导致心肌细胞电生理改变可能导致AF发生。

2.2 Desmin 蛋白(DES)

Desmin是由DES基因编码的经典III型中间丝蛋白,在心脏、心脏传导系统(包括窦房结、房室结和希氏-浦肯野系统)和肺静脉心肌袖中大量表达。它的主要作用是连接和固定桥粒、z带、细胞骨架、线粒体和细胞核等各种细胞结构及细胞器,对维持心肌细胞功能和调节多种信号通路有着重要作用^[18]。

在对DES变异相关的心肌病研究中,发现研究对象会出现心律失常等并发症,如AF,并且更容易发生恶性心律失常事件^[19]。此外,在DES相关心肌病的小鼠模型中,我们发现Desmin蛋白突变能够破坏线粒体结构、抑制线粒体活性和导致ADP/ATP比值升高,并且还发现线粒体的功能缺失与结构破坏会引起心脏重塑和收缩功能障碍^[20,21]。另一方面,我们在临床AF的实验模型中也证明了心肌细胞的重构与线粒体功能障碍密不可分^[22]。

Desmin蛋白的破坏会导致NF-κB通路激活抑制SERCA2表达,导致Ca²⁺分布异常^[23],而Brundel等人的研究发现胞质Ca²⁺异常增多是AF的触发因素。在对Desmin敲除的小鼠研究中也证实了Desmin的缺失会导致窦性心律传导延迟、心房机械和电传导完整性的破坏,使得心房不应期显著减少,AF易感性增加^[24]。以上可能是Desmin突变参与AF发生的潜在机制。

2.3 心肌肌球蛋白变异

人类心肌表达两种心肌肌球蛋白重链(MYHC)亚型

α和β,心房组织中肌球蛋白重链的补体主要是α,由MYH6基因编码。一项在英国大型全基因组关联研究表明基因MYH6的常见变异与AF密切相关^[25]。

在斑马鱼模型中,MYH6变异可引起心房收缩功能异常,触发心脏重构和心脏瓣膜形态缺陷,间接导致内质网蛋白折叠障碍(ER-stress)和未折叠蛋白反应(unfolded protein response,UPR)的激活^[26];并且最近研究发现小鼠MYH6内含子27编码的是一种心脏特异性高度保守的microRNA,而且miR-208a在维持正常心脏传导中发挥重要作用。目前研究数据已经确定了心肌肌球蛋白在心律失常发展中有关键影响。

2.4 连接蛋白40和连接蛋白43突变

缝隙连接通道是心脏作为通信电网络的电合胞体特性的基础,主要是由连接蛋白40(Cx40)或连接蛋白43(Cx43)组成,分别由GJA5和GJA1编码。他们可以转运水、离子和第二信使等,这些通道的传导性可以通过激活蛋白激酶C、蛋白激酶A或蛋白激酶G来进行调节^[27]。连接蛋白的数量、功能和定位的缺失会影响电信号的传导,并可能导致AF的折返回路的形成^[28]。GJA5被公认为与人类房颤相关,通过减少表达来影响传导和减少单通道的开放概率^[29]。在永久性房颤(PAF)患者的心房组织中观察到Cx40表达减少和Cx40分布异质性增加,而阵发性房颤(CAF)患者显示Cx40免疫染色严重减少^[30]。在心房肌细胞中Cx40突变体过度表达,如G38D、A96S、M163V会导致蛋白质不稳定和蛋白酶体加速降解,改变通道选择性,导致细胞导电性和通透性改变^[31],这可能是驱动Cx40突变体诱导AF发生。

3 结论与展望

细胞骨架蛋白作为家族性AF的变异因素,得到了越来越多的关注。多个临床研究以及动物模型均已证实,细胞骨架蛋白家族的基因变异会引起心肌细胞结构网络的破坏、线粒体功能障碍、心脏传导电生理变化、DNA损伤诱导的PARP1和NAD⁺耗竭^[13,15,17,21,22,25,26],在早发性房颤中发挥着关键作用,它们可能是房颤发生的典型病理生理途径。未来对细胞骨架蛋白变异的深入研究可能会为房颤分子根源的解剖和新药物治疗靶点的识别提供方向。

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