◆医学前沿与研究◆

组蛋白修饰与癫痫的发生发展研究进展*

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摘要：癫痫是由脑部神经元异常同步或过度放电导致的一种慢性脑部疾病。在神经系统疾病中，癫痫已成为仅次于脑血管病的第二大严重威胁人类健康的疾病，且其发病机制至今未明。表观遗传机制是调节基因表达的一种方式，其中组蛋白修饰是主要的表观遗传修饰之一。组蛋白修饰的异常与癫痫的发生发展密切相关，本文对组蛋白修饰与癫痫的关系进行综述，以期从组蛋白修饰的角度阐明两者之间的关系，为癫痫的防治提供新思路。

关键词：癫痫　表观遗传学　组蛋白修饰　组蛋白乙酰化与甲基化　JMJD6

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癫痫是一组由脑部神经元高度同步化异常放电导致的一种慢性脑部疾病。全球有 7 000 多万的癫痫患者，每年约有 240 万的新增癫痫患者[1]，癫痫的发病机制目前尚未完全明确。表观遗传是基于 DNA 序列在没有改变的情况下出现的基因功能或表达水平发生的可遗传性变化[2]。经典的表观遗传修饰主要包括 DNA 甲基化、组蛋白修饰以及非编码 RNA。近年来，组蛋白修饰与癫痫的关系成为国内外研究的热点，组蛋白修饰不仅在中枢神经系统的正常发育过程中发挥关键的作用，而且组蛋白修饰所介导的基因调控过程也参与了癫痫的发生和发展过程[3]。本文对组蛋白修饰与癫痫的关系进行综述，为癫痫的防治提供新靶点。

1　组蛋白修饰

组蛋白是参与组成真核生物染色体的结构蛋白，具有高度的保守性[4]。组蛋白主要有 H1、H2A、H2B、H3、H4 5 种。组蛋白修饰是表观遗传调控的重要形式之一。每个核心组蛋白由一个球形结构域和暴露在核小体表面的 N 端尾区组成，其中 N 端氨基末端会发生多种共价修饰，包括乙酰化、甲基化、磷酸化、腺苷酸化、泛素化和 ADP 核糖基化等。随后，相关蛋白质识别这些化学修饰并募集转录激活或抑制因子到特异的修饰位点调节基因表达[5]。组蛋白

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上能发生共价修饰的氨基酸残基称为修饰位点,修饰位点一般位于 4 种常见组蛋白(H2A、H2B、H3 和 H4,尤其是 H3 和 H4)的游离氨基酸残基上[6]。各种组蛋白修饰都有相应的酶类,不同的组蛋白修饰通过不同的作用机制调控染色质的结构和功能。组蛋白修饰不仅与染色体的重塑和功能状态紧密相关,而且在决定细胞命运、细胞生长以及致癌作用的过程中发挥重要作用[7]。组蛋白修饰主要是调控基因的表达,在基因转录以及 DNA 复制等方面起着重要的作用。

目前关于组蛋白修饰中乙酰化、甲基化的相关研究较多,因此下面将主要从组蛋白乙酰化与癫痫、组蛋白甲基化与癫痫两方面进行阐述。

2 组蛋白乙酰化与癫痫

乙酰化是组蛋白修饰的重要形式之一。组蛋白乙酰化由组蛋白乙酰化转移酶(Histone Acetyltransferase,HAT)催化,使染色质结构松解从而导致染色质结构松弛,并将转录因子结合到相应的位点上,从而激活修饰基因的表达。组蛋白去乙酰化则由组蛋白去乙酰化酶(Histone Deacetylase,HDAC)催化,HDAC 从核心组蛋白上移除乙酰基团从而抑制基因转录[8]。组蛋白乙酰化与维持突触及记忆功能密切相关。组蛋白乙酰化异常与多种神经系统疾病密切相关,如 Rubinstein-Taybi 综合征与 HAT 功能障碍相关[9]。

组蛋白 H3 乙酰化通过多种机制调控依赖 ATP 的染色质重塑[10]。研究发现,组蛋白乙酰化异常与癫痫模型的海马结构病理改变密切相关[11,12]。组蛋白 H3 赖氨酸 9 乙酰化(H3K9Ac)是存在于转录活性染色质中的表观遗传标记。研究表明,低氧大鼠海马 CA3 区 H3K9Ac 和 H3K14Ac 的表达水平降低,引起神经元神经变性和神经递质传递受损[11]。海马内单侧注射红藻酸(KA)的癫痫模型中,在急性癫痫持续状态期间(注射 KA 后 2-6 h),海马颗粒细胞和锥体细胞层中 HDAC1、HDAC2 和 HDAC11 的表达显著降低;而在慢性期(注射 KA 后 14-48 h)HDAC1 仅在颗粒细胞中轻度增加[12]。另一项研究发现,HDAC2 广泛分布在产后大鼠海马 CA1 和 CA3 区的锥体细胞中,HDAC2 敲除大鼠的这些区域中的树突棘密度显著增加,表明 HDAC2 能调节海马突触的形成并影响学习和记忆的功能[13]。有研究发现,颞叶癫痫(TLE)患者颞叶 HDAC2 的表达水平明显增高[3],表明 HDAC2 在 TLE 的发病机制中发挥着重要的作用。另外,HDAC4 可以通过上调 γ-氨基丁酸 A 型受体 α1(Gamma-Aminobutyric Acid-A Receptor alpha 1,GABAARα1)和氨基丁酸 A 型受体 α4(Gamma-Aminobutyric Acid-A Receptor alpha 4,GAB-AARα4)水平和下调谷氨酸脱羧酶抗体 65(Glutamate Decarboxylase 65,GAD65)、γ-氨基丁酸运载蛋白 1(GABA Transporter 1,GAT-1)和 γ-氨基丁酸运载蛋白 3(GABA Transporter 3,GAT-3)水平来缓解癫痫的发生[14]。在注射 KA 后的癫痫模型中,海马颗粒细胞中 HDAC5 和 HDAC9 的表达增加[15]。以上研究表明,HDAC 表达的异常在癫痫的发生过程中起着重要的作用。

癫痫持续状态后,谷氨酸受体 2(Glutamate Receptor,GluR2)的 mRNA 和蛋白质水平均下调,而 HDAC 抑制剂可逆转 GluR2 相关组蛋白的脱乙酰基作用,减弱癫痫发作引起的 GluR2 下调[16]。Glu 过度激活离子型 Glu 受体会诱发异常放电导致癫痫的发生。α-氨基-3-羟基-5-羟基-5-甲基-4-异恶唑丙酸(Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid,AMPA)受体属于离子型谷氨酸受体家族,是由 4 种亚单位(GluA1-GluA4)组成的四聚体。GluA2 亚单位是钙通透性的决定因素,含有 GluA2 受体的 Ca^{2+} 离子通道渗透性差。钙通透性(含 GluA2 亚基)AMPA 受体主要表达兴奋性投射神经元[17],因而缺乏 GluA2 的 AMPA 受体可通过钙离子进入神经元而促进神经的兴奋性。有研究表明,突触的可塑性可通过神经元突触中钙通透性的 AMPA 受体表达进行调控[18]。AMPA 受体在海马区分布密集,当过度激活 AMPA 受体时,常常会诱发颞叶癫痫[19],表明 AMPA 受体的过度表达会导致神经元的过度兴奋从而引起癫痫的发生。吡仑帕奈作为 AMPA 受体拮抗剂,是一种抗癫痫药物,是部分发作性以及全面强直-阵挛性发作的辅助治疗药物[20,21]。AMPA 受体会在其 C 末端进行赖氨酸乙酰化,从而减少 AMPA 受体的内化和降解,增加细胞表面稳定性,延长受体的半衰期,使 AMPA 受体水平增加[22]。因此,AMPA 受体可能会通过乙酰化使受体水平升高、Ca^{2+} 通透性及 Ca^{2+} 内流增加,从而增加神经元的膜电位,导致神经细胞持续去极化,降低其兴奋阈值,从而影响神经的兴奋性,诱发异常放电参与癫痫的发生发展过程。

也有研究发现,癫痫与大鼠海马组蛋白 H4 基因

启动子区域的高乙酰化有关，通过特异性地抑制CREB结合蛋白(Cap Binding Proteins，CBPS) CBP/p300的乙酰基转移酶活性，从而抑制组蛋白修饰的诱导过程并减轻癫痫的严重程度[23]。脑源性神经营养因子(Brain-derived Neurotrophic Factor，BDNF)在学习记忆过程、突触可塑性以及神经细胞存活中起关键作用[24]。BDNF在星形胶质细胞中过度表达，会导致神经兴奋性的增加或神经元细胞死亡[25]。*BDNF*启动子P1-P3位点持续高水平乙酰化以及P4位点乙酰化减少，与癫痫的转录诱导结果一致[26]。且在急性电刺激惊厥模型中发现，*BDNF*表达的上调与*BDNF* P2启动子的H4乙酰化水平相关[27]。由此可见，*BDNF*的乙酰化会导致神经兴奋性增加而参与癫痫的发生，因而*BDNF*有可能成为治疗癫痫的新靶点。组蛋白的乙酰化与癫痫的发生及发展密切相关，并且组蛋白乙酰化和去乙酰化程度可能影响大脑的认知功能，导致癫痫患者出现学习障碍或记忆力减退。

组蛋白的乙酰化与去乙酰化也可用于治疗癫痫。丙戊酸(Valproic Acid，VPA)是最常用的抗癫痫药物之一，有研究认为其机制可能是丙戊酸使H3K9/14乙酰化水平升高，去乙酰化减少[28]。伏立诺他(Vorinostat，SAHA)是一种组蛋白去乙酰化抑制酶，可使Toll样受体4 (Toll-like Receptor 4，TLR4)基因的组蛋白H3第九位赖氨酸(H3K9)低乙酰化，从而减轻KA诱导的癫痫发作[29]。生酮饮食(Ketogenic Diet，KD)是治疗癫痫的一种方式。有研究发现，生酮饮食通过提高组蛋白乙酰化来增加神经调节蛋白1 (Neuregulin-1，NRG1)的表达，从而抑制癫痫发作[30]。2-苯甲酰胺基-1，4-萘醌(2-Benzamido-1，4-Naphthoquinone，NQN1)是一种HDAC抑制剂，会减少癫痫发作等相关行为，维生素K (VK)家族与NQN1拥有相同的萘醌结构，新型维生素K类似物可减少癫痫小鼠模型的癫痫发作[31]。由此可见，目前已有一些去乙酰化酶抑制剂被应用于治疗癫痫，组蛋白的乙酰化与去乙酰化可能会成为治疗癫痫的新靶点。

3 组蛋白甲基化与癫痫

组蛋白甲基化常发生在H3和H4组蛋白的N端赖氨酸(K)或精氨酸(R)残基上，由组蛋白甲基化转移酶(Histonemethyl Transferase，HMT)完成[32]，研究表明组蛋白甲基化酶在大脑发育和突触可塑性形成过程中发挥重要的作用[33]。HMTs催化甲基从S-腺苷甲硫氨酸(S-Adenosylmethionine，SAM)转移到组蛋白上[34]。组蛋白赖氨酸甲基转移基因*2A* (The histone Lysine-methyltransferase *2A* Gene，KMT*2A*)通过H3K4的单甲基化和三甲基化来促进神经元基因的表达从而参与记忆的形成过程[35]。

目前，HMT分为3个家族，包括含有SET结构域的甲基转移酶(Methyltransferases SET Domain-containing，SET)、作用于赖氨酸的类端粒沉默干扰体-1样蛋白(Disruptor of Telomeric Silencing-1，Dot1)[36]和蛋白质精氨酸甲基转移酶(Protein Arginine Methyltransferases，PRMTs)[37,38]。研究发现，Dot1的活性及调控在转录、细胞调控和DNA损伤反应等不同的生物过程中发挥重要的作用[39]。Dot1也被称为KMT4，是一种可以使组蛋白H3赖氨酸79 (Histone H3 Lysine 79，H3K79)甲基化的催化酶[40]，H3K79甲基化普遍与基因转录相关[41]。组蛋白去甲基酶(Histone Demethylases，HDMS)在赖氨酸或精氨酸中可以脱去各种甲基化的酶[42,43]。赖氨酸去甲基酶(Histone lysine Demethylase，KDM)分为两个家族，分别为胺氧化酶和含铁依赖双加氧酶的JMJC结构域[44,45]。JMJC结构域蛋白6 (Jumonji C-Domain Containing Protein 6，JMJD6)则是一种精氨酸去甲基酶[46]。组蛋白甲基化修饰是一种常见的基因表达调控方式，组蛋白的甲基化水平会影响神经系统的突触可塑性改变，并参与癫痫的发生发展过程[47,48]。

3.1 赖氨酸甲基化与癫痫

赖氨酸残基可以被单(me)、双(me2)或三(me3)甲基化。H3K4去甲基酶包括KDM1 (KDM1A，KDM1B)和KDM5 (KDM5A，KDM5B，KDM5C)[49]，而KDM5C与癫痫及X连锁精神发育迟滞综合征密切相关[48]。H3K4的组蛋白甲基化已被证明在神经系统发生及发育过程中发挥重要作用[50]。H3K4me3、H3K9me2能够调控记忆的形成[51]，H3K4me3宽峰NeuN+调节参与学习与记忆过程中神经元连接的基因和信号传导，包括许多离子通道和突触的可塑性[52]。含*1B*基因的SET结构域(SET Domain Containing *1B*，*SETD1B*)是SET1组蛋白甲基转移酶复合物的组成部分，介导组蛋白H3K4的甲基化。研究表明，*SETD1B*基因的变异与智力缺陷及癫痫相关[53]。赖氨酸特异性去甲基酶1 (Lysine-Specific Demethylase 1，LSD1)是鉴定出

的第一个赖氨酸去甲基化酶,能使 H3K4 去甲基化[44]。LSD1 特异性缺失的小鼠癫痫敏感性降低,神经性 LSD1 缺失的小鼠对毛果芸香碱诱导的癫痫持续状态(Status Epilepticus,SE)的敏感性降低[54]。

H3K9 甲基化修饰可引起基因沉默[55]。成纤维细胞生长因子 2(Fibroblast Growth Factor 2,FGF2)已被证明可以诱导 H3K4 甲基化并减少 GFAP 启动子上的 H3K9 甲基化。H3K9 二甲基化(H3 lysine 9 Dimethylation,H3K9me2)可促进 DNA 甲基化,从而有效减少与突触可塑性相关的基因表达[56]。癫痫持续状态使组蛋白 H3K9 二甲基化水平及组蛋白 H3K9 甲基转移酶 G9a 的表达水平下调,说明 H3K9 甲基化可能在调节癫痫持续状态早期的神经网络兴奋性方面发挥重要作用[57]。基质金属蛋白酶 9(Matrix Metalloproteinase-9,MMP-9)水平与人类和啮齿动物癫痫的发病机制有关,而组蛋白 H3 上赖氨酸 27 三甲基化(Trimethylation of Lysine 27 on histone H3,H3K27me3)影响 MMP-9 在癫痫发生中的作用[58]。由此可见,赖氨酸甲基化可能参与癫痫及持续状态的发病过程并影响记忆力。

3.2 精氨酸甲基化与癫痫

组蛋白精氨酸甲基化修饰是组蛋白翻译后修饰的重要方式之一,由 PRMTs 催化精氨酸残基形成,参与许多重要的细胞过程,对基因的转录调控有非常重要的作用。精氨酸甲基化可以是单甲基化(Me)、对称双甲基化(Me2s)或不对称双甲基化(Me2a)[59]。PRMT1 可催化组蛋白 H4 第 3 位精氨酸残基(H4R3)的甲基化,而 PRMT5 可催化组蛋白 H3 第 8 位及 H4 第 3 位精氨酸(H3R8、H4R3)的甲基化[60]。蛋白质精氨酸甲基转移酶 7(Protein Arginine Methyltransferase 7,PRMT7)可催化 H2AR3 和 H4R3 上的二甲基化,并负调控相关基因的转录。缺乏 PRMT7 的细胞表现出 DNA 修复基因的表达增加,并增强了对 DNA 损伤剂的抵抗力[61]。*PRMT7* 基因的复合或纯合变异可导致一种新的智力障碍综合征,称为 SBIDDS 综合征(Short Stature,Brachydactyly,Intellectual Developmental Disability,and Seizures),主要临床表现为身材矮小、短指、智力发育障碍和癫痫发作[62]。PRMT8 主要表达在大脑的神经元上[63]。

钠通道是神经元兴奋性的基础,癫痫的发病与调控离子通道的基因表达异常有关。电压门控钠(Nav)通道是抗癫痫药物(Antiepileptic Drugs,AEDs)控制癫痫神经元高兴奋性的主要治疗靶点。Nav1.2 是人类大脑中最丰富的 Nav 通道,主要存在于轴突和神经末梢[64]。Nav1.2 是与癫痫发病相关的主要通道,也是 AEDs 的靶点[65]。颅脑中精氨酸甲基转移酶 PRMT8 表达异常导致 Nav1.2 电流显著增加[66]。因此,PRMT8 可能通过调节 Nav1.2 通道参与癫痫的发生发展。JMJC 结构域蛋白 6(Jumonji C-Domain Containing Protein 6,JMJD6)是第一个被描述的精氨酸去甲基化酶,能使精氨酸 2 上的组蛋白 H3(Histone H3 Arginine 2,H3R2)和精氨酸 3 上的组蛋白 H4(Histone H4 Arginine 3,H4R3)脱甲基[67]。JMJD6 可以调节细胞的分化和增殖,异常调节会影响细胞的成熟[68]。JMJD6 介导的组蛋白精氨酸残基的甲基化修饰会影响染色质的重组和基因表达,其在细胞分化和增殖过程中发挥重要作用[67]。有研究表明,宫内缺氧可能会导致 JMJD6 功能减弱,从而导致海马 CA3 区功能异常的神经元数量增多,大鼠的学习和记忆能力下降[69]。海马的病理改变与癫痫的发病密切相关,因此,JMJD6 可能通过影响海马区神经元的功能从而参与癫痫的发生发展。

4 展望

癫痫是一种复杂的脑部疾病,受多方面因素(如环境、遗传、睡眠等)的影响,且发病机制尚未阐明。组蛋白修饰与癫痫有密切的关系,虽然目前对于组蛋白修饰与癫痫的关系相关的研究较少,但是从现有研究可了解到组蛋白修饰与学习、记忆以及认识密切相关,并通过影响神经网络的兴奋性从而影响癫痫的发生发展。因此,组蛋白修饰也成为癫痫的重要治疗靶点之一。目前,有多种 HDAC 抑制剂已被应用于治疗癫痫,如丙戊酸钠作为一种 HDAC 抑制剂,是一种常用的抗癫痫药,不仅能减少癫痫的发作,而且在癫痫模型中具有神经保护的作用,可以减少异常的神经发生和改善认知功能[70],表明组蛋白去乙酰化酶抑制剂可能成为癫痫防治的新药物。

目前,组蛋白去甲基化与癫痫相关的研究虽然仍处于起步阶段,但是已有研究表明组蛋白去甲基化会影响神经的兴奋性及突触的可塑性,导致脑网络功能和结构改变,从而促进癫痫的发生发展。目前临床上用于治疗癫痫的方法,不仅疗效有限而且存在不同的副作用。组蛋白修饰已逐渐成为癫痫发病机制研究的热点,对表观遗传修饰异常特别是组蛋白修饰与癫

痫的相关性仍需进一步深入研究，为癫痫的发病机制提供新思路以及为癫痫的治疗提供新靶点。

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Research Progress of Histone Modification and the Occurrence and Development of Epilepsy

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Abstract: Epilepsy is a chronic brain disorder caused by abnormal synchronization or excessive discharge of neurons in the brain. In nervous system diseases, epilepsy has become the second largest serious threat to human health after cerebrovascular diseases, and its pathogenesis has not yet been understood. Epigenetic mechanism is a way to regulate gene expression, and histone modification is one of the main epigenetic modifications. Abnormal histone modifications are closely related to the occurrence and development of epilepsy. The relationship between histone modification and epilepsy is reviewed in this article to clarify the relationship between them from the perspective of histone modification and provide new ideas for the prevention and treatment of epilepsy.
Key words: epilepsy; epigenetics; histone modification; histone acetylation and methylation; JMJD6

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One Hundred Years of Progress in Clinical Xenotransplantation (Review)

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Abstract: Recently, four consecutive cases of genetically engineered pig to human renal and cardiac xenotransplantation had been sustainably reported in United States. These advances have broken the silence of clinical research in xenotransplantation for nearly 30 years. In particular, experimental pig heart transplantation has achieved initial success, which has attracted wide attention. The future clinical application of xenotransplantation has taken a key step. These four cases, whether theirs spirit of innovation, technological progress, approval process, or the synchronous follow-up of ethics, are worth learning and using for reference by peers in China. Over the past 30 years, genetically engineered (GE) animal organs have been able to survive in non-human primates (NHPs) models for a long time. In these experiments, the hyper-acute rejection reactions involved in the mechanisms of pre-existing antibodies, complement activation, and coagulation state were basically effectively controlled. Xenotransplantation has reached the starting point of clinical application. However, four major issues remain to be addressed in the future: Immune rejection, biosafety, cross-species adaptation and ethical psychology. The main progress of clinical xenotransplantation in the past 100 years has been briefly summarized in this article. The difficulty is obvious, but the hope and exploration have never ended.
Key words: xenotransplantation; genetically engineered pig; heart transplantation; kidney transplantation; organ transplantation

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