周期蛋白D与CDK4/6在细胞周期进程中的调控机制

张宇飞[1] 潘剑锋[2] 乔永华[3] 戎友俊[2] 马荣[2] 尚方正[2] 张燕军[2, 4, 5, 6, 7]*

([1]内蒙古农业大学职业技术学院, 包头 014109; [2]内蒙古农业大学动物科学学院动物遗传育种与繁殖系, 呼和浩特 010018; [3]内蒙古赤峰市敖汉旗农牧局, 赤峰 026000; [4]农业农村部肉羊遗传育种重点实验室, 呼和浩特 010018; [5]内蒙古自治区山羊遗传育种工程技术中心, 呼和浩特 010018; [6]内蒙古自治区羊遗传育种与繁殖重点实验室, 呼和浩特 010018; [7]内蒙古自治区高校动物遗传育种与繁殖重点实验室, 呼和浩特 010018)

摘要 细胞周期(cell cycle)是指细胞从一次分裂完成开始到下一次分裂结束所经历的全过程。细胞周期包括G_0期(静止期)、G_1期(DNA合成前期)、S期(合成期)、G_2期(DNA合成后期)和M期(细胞分裂期)。通常, 阻止细胞进行异常复制主要有三个检查点, 分别为G_1/S检查点、G_2/M检查点和有丝分裂中/后期检查点。其中, G_1/S检查点又称起始点, 是细胞周期进程起始的关键节点。G_1/S检查点可通过周期蛋白D与CDK4/6结合所形成的复合物调节细胞周期起始, 影响细胞周期进程。活性异常的周期蛋白D与CDK4/6会诱导癌细胞的异常增殖, 引发癌症恶性发展。因此, 了解CDK4/6活性变化情况、周期蛋白D与CDK4/6的组装以及CDK4/6抑制剂的作用, 将有助于了解细胞周期进程中潜在的调控过程, 并为癌症与疾病的治疗提供一种新方案。该综述对CDK4/6活性调控过程的关键条件, 周期蛋白D-CDK4/6在G_1期到S期转换中的关键过程, 以及CDK4/6类抑制剂治疗药物在癌症及疾病中的研究进展进行了描述与总结, 最后阐述了周期蛋白D与CDK4/6在细胞周期进程中所面临的问题及存在的挑战, 旨在为后续细胞周期的深入研究提供科学参考。

关键词 细胞周期; G_1/S检查点; 周期蛋白D; CDK4/6; CDK4/6抑制剂

Regulation Mechanism of Cyclin D and CDK4/6 in Cell Cycle Progression

ZHANG Yufei[1], PAN Jianfeng[2], QIAO Yonhua[3], RONG Youjun[2], MA Rong[2], SHANG Fangzheng[2], ZHANG Yanjun[2,4,5,6,7]*

([1]*College of Vocational and Technical, Inner Mongolia Agricultural University, Baotou 014109, China*; [2]*Department of Animal Genetic Breeding and Reproduction, College of Animal Science, Inner Mongolia Agricultural University, Hohhot 010018, China*; [3]*Agriculture and Animal Husbandry Bureau of Aohan Banner, Chifeng 026000, China*; [4]*Key Laboratory of Mutton Sheep & Goat Genetics and Breeding, Ministry of Agriculture and Rural Affairs, Hohhot 010018, China*; [5]*Inner Mongolia Engineering Research Center for Goat Genetics and Breeding, Hohhot 010018, China*; [6]*Inner Mongolia Key Laboratory of Sheep & Goat Genetics, Breeding and Reproduction, Hohhot 010018, China*; [7]*Inner Mongolia Key Laboratory of Animal Genetics Breeding and Reproduction in Universities, Hohhot 010018, China*)

Abstract The cell cycle is the entire process that a cell undergoes from the completion of one decelerated division to the end of the next decelerated division. The cell cycle consists of G_0 phase (stationary phase), G_1 phase (DNA pre-synthesis phase), S phase (synthesis phase), G_2 phase (late DNA synthesis phase) and M phases (cytokinesis). Normally, there are three main checkpoints that prevent cells from undergoing abnormal replication, namely the G_1/S checkpoint, the G_2/M checkpoint and the metaphase/anaphase mitotic checkpoint. The G_1/S checkpoint,

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*通讯作者。 Tel: 0471-4300651, E-mail: imauzyj@163.com

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*Corresponding author. Tel: +86-471-4300651, E-mail: imauzyj@163.com

also known as the initiation point, is a critical point for cell cycle initiation, and the G_1/S checkpoint regulates cell cycle initiation through a complex formed by the binding of cyclin D to CDK4/6, which affects cell cycle progression. In addition, abnormal activity of cyclin D and CDK4/6 can induce abnormal proliferation of cancer cells and trigger malignant development of cancer. Therefore, understanding the changes in CDK4/6 activity, the assembly of cyclin D with CDK4/6 and the role of CDK4/6 inhibitors will help to understand the underlying regulatory processes in cell cycle progression as well as provide a new option for the treatment of cancer. This review describes and summarizes the key conditions for the regulation of CDK4/6 activity, the key processes of cyclin D-CDK4/6 in the G_1 to S phase transition, and the progress of CDK4/6 inhibitor in cancer, and finally describes the problems and challenges of cyclin D and CDK4/6 in cell cycle progression, aiming to provide a scientific reference for further research on the cell cycle.

Keywords cell cycle; G_1/S checkpoint; cyclin D; CDK4/6; CDK4/6 inhibitor

细胞周期是生命活动的基本过程, 是细胞分裂成两个子细胞所经历的全过程[1]。细胞周期进程依赖于各级调控因子精确而严密的调控, 这些调控因子的核心是周期蛋白(cyclin)和周期蛋白依赖性蛋白激酶(cyclin dependent kinase, CDK)结合形成的周期蛋白-CDK复合物[1-2]。在整个细胞周期调控过程中, 起核心调控作用的周期蛋白-CDK复合物有: 周期蛋白D-CDK4/6、周期蛋白E-CDK2、周期蛋白A-CDK2、周期蛋白H-CDK7、周期蛋白A-CDK1和周期蛋白B-CDK1等[2-4]。其中周期蛋白D-CDK4/6在细胞周期启动中发挥着重要作用[5]。

细胞周期蛋白D(cyclin D)于1991年第一次在酵母细胞和小鼠巨噬细胞中被发现, 其可通过诱导细胞从G_1期到S期的转变, 进而调控细胞周期进程[5-7]。随着研究深入, 发现周期蛋白D在细胞周期进程中的调控过程, 主要是通过激活与其相结合的CDK4/6, 影响G_1期到S期转变而实现的[5]。在被鉴定的人类周期蛋白D1、D2和D3中发现, 周期蛋白D具有潜在肿瘤调控作用, 并且这些调控过程与其相结合的CDK4/6有着直接联系[8-9]。CDK4/6的过度活化, 会引起细胞异常增殖的现象发生[5]。在乳腺癌等癌细胞中, CDK4/6的过度活化导致癌细胞异常增殖, 促进癌症进展[10]。此外, CDK4/6抑制剂可有效阻滞癌细胞从G_1期进展到S期, 将细胞异常分裂控制在G_0/G_1阶段, 从而抑制癌细胞分裂增殖[11]。因此, CDK4/6可能成为癌症治疗中的关键靶点, CDK4/6抑制剂有望成为一种新的靶向治疗药物。

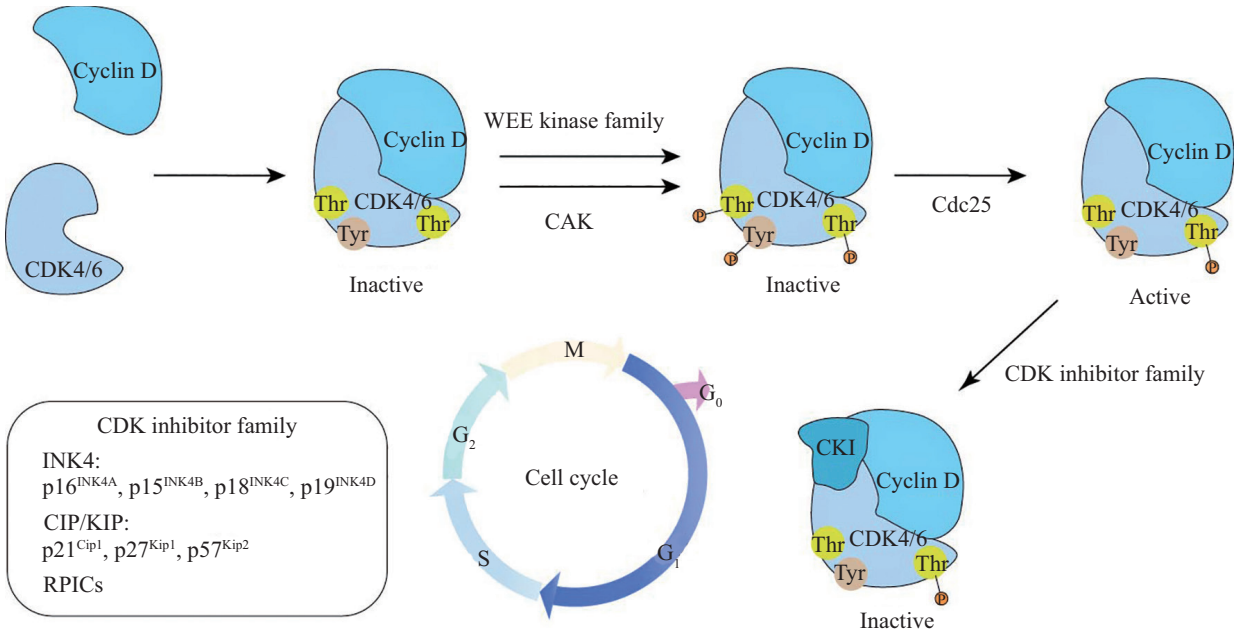
本综述主要描述了CDK4/6活性调控过程的关键事件、G_1期到S期转换过程中周期蛋白D-CDK4/6的研究进展、相关CDK4/6抑制剂在疾病和癌症中的应用情况。该文对现阶段周期蛋白D-CDK4/6复合物和CDK4/6抑制剂研究面临的问题和存在的挑战进行阐述, 旨在为细胞周期领域的发展及研究提供有价值的科学参考。

1 CDK4/6激活的关键事件

细胞周期蛋白D-CDK4/6是细胞周期起始的关键复合物, 只有细胞周期进程中的CDK4/6被激活, 周期进程才可得以进行。而CDK4/6的激活则需同时满足以下条件: (1) 与细胞周期蛋白D结合; (2) CDK4/6激活位点的磷酸化和抑制位点的去磷酸化; (3) 不与CDK抑制剂(cyclin-dependent kinase inhibitors, CKI)结合等。CDK4/6激活过程示意图见图1。

1.1 与细胞周期蛋白D结合形成复合物

细胞周期蛋白D是细胞分裂周期启动因子, 也是生长因子感应器。细胞周期蛋白D的过表达可加速细胞从G_1向S期转换, 并快速通过G_1/S检查点, 缩短S期; 阻断或敲除细胞周期蛋白D, 可使细胞周期阻滞, 诱导细胞发生凋亡[12]。然而, 近年的研究则发现细胞周期蛋白D通过与CDK4/6结合激活CDK4/6活性, 才是诱导周期进程的关键事件[11]。随着结构生物学的发展, 细胞周期蛋白D的结构得到相应的解析, 发现其拥有氨基酸结构域、破坏框、PEST序列等结构[13]; 另外也发现, 这些结构调控着细胞周期蛋白D与CDK4/6结合、细胞周期蛋白D的泛素化降解等生物学过程[13]。此外, 发挥完作用的细胞周期蛋白D会随着细胞周期进程的进展而逐渐降解, 然而这一过程CDK4/6的浓度不会随着细胞周期蛋白D的降解而变化[14]。这些结果揭示, 细胞周期蛋白D通过充当CDK4/6的启动因子与CDK4/6结合, 激活



WEE激酶家族使CDK4/6抑制位点磷酸化, CAK使CDK4/6激活位点磷酸化, Cdc25去除CDK4/6抑制位点磷酸化基团, 从而激活CDK4/6活性; 内源性CDK抑制剂与细胞周期蛋白D-CDK4/6结合, 抑制CDK4/6活性。

The WEE kinase family phosphorylates the CDK4/6 inhibitory site, CAK phosphorylates the CDK4/6 activation site, and Cdc25 removes the CDK4/6 inhibitory site phosphorylation motif to activate CDK4/6 activity; endogenous CDK inhibitors bind to cyclin D-CDK4/6 to inhibit CDK4/6 activity.

图 1 细胞周期蛋白D-CDK4/6的激活过程

Fig.1 Activation process of cyclin D-CDK4/6

CDK4/6活性, 从而驱动细胞周期进程的发展。

1.2 CDK4/6特定位点的磷酸化修饰状态

CDK4/6与细胞周期蛋白D结合是CDK4/6激活的必要前提, 而CDK4/6达到激活状态, 则还需要结合后特定位点发生磷酸化或去磷酸化修饰[15]。研究发现, WEE激酶家族(WEE1、PKMYT1和WEE1B等)可通过驱动CDK4/6抑制位点的磷酸化, 从而抑制CDK4/6的活性[16]。而磷酸酶细胞分裂周期因子25(cell division cycle 25, Cdc25)则可通过移除这种由WEE激酶介导的抑制性磷酸基团, 从而重新激活CDK4/6[17-18]。有趣的是, 当CDK4/6的抑制位点磷酸化基团被去除时, 暴露出的CDK4/6激活位点则会被CDK激活激酶(CDK-activating kinase, CAK)磷酸化, 从而完全激活细胞周期蛋白D-CDK4/6复合物[19]。经过连续的去除和激活CDK4/6特定位点磷酸基团, CDK4/6的活性才得以完全激活。综上所述, CDK4/6激活需要如下两种激活模式: (1) 去除CDK4/6抑制位点的抑制性磷酸基团; (2) 激活CDK4/6激活位点的磷酸基团。因此, 可以得出, CDK4/6特定位点磷酸化状态的探究对细胞周期进程研究具有重要意义。

1.3 CDK活性抑制剂

在细胞周期进程中存在多种内源性CDK抑制剂, 当这些内源性CDK抑制剂与激活的细胞周期蛋白D-CDK4/6复合物结合时, 细胞周期蛋白D-CDK4/6的激活状态则被抑制, 细胞分裂“开关”被关闭, 细胞周期进程被控制[20]。当前, 已有这些内源性CDK抑制剂家族, INK4家族(p16^{INK4A}、p15^{INK4B}、p18^{INK4C}、p19^{INK4D})、CIP/KIP家族(p21^{Cip1}、p27^{Kip1}、p57^{Kip2})以及核糖体蛋白抑制CDKs(ribosomal protein-inhibiting CDKs, RPICs)家族等[2,20]被发现在细胞周期进程中起关键作用。其中, 细胞周期蛋白D-CDK4/6复合物中的CDK4/6活性的负调控主要受到INK4细胞周期抑制剂家族介导, 它们与复合物中的CDK4和CDK6结合形成非活性复合物, 从而调控细胞周期进程的进展[2,21-22]。另外, CIP/KIP家族蛋白, 如p21^{Cip1}、p27^{Kip1}, 也可抑制CDK4和CDK6, 并诱导细胞周期停滞[23-24]。有趣的是, p21^{Cip1}和p27^{Cip1}的抑制特性还可被用作细胞周期进程的稳定剂, 通过抑制异常表达的CDK4/6, 稳定细胞周期蛋白D-CDK4/6复合物, 从而使细胞周期进程得以继续稳定进行[25]。因此, 开展内源性CDK抑制

剂的研究对解析细胞周期进程, 具有重要意义。

2 周期蛋白D与CDK4/6的分子调控过程

细胞周期蛋白D与CDK4/6是驱动细胞周期进程的核心分子。胞外生长因子信号(如EGF)通过与细胞表面酪氨酸激酶受体(如EGFR)结合, 激活MAPK(mitogen-activated protein kinases)信号转导途径, 启动细胞周期进程[26-27]。而随着细胞周期的启动, 细胞周期蛋白D也开始迅速合成, 并与CDK4/6结合调控细胞周期进程[28]。在细胞分裂过程中, 过表达细胞周期蛋白D使活化的CDK4/6浓度升高, 促使细胞G_1期向S期转换加快, S期缩短[29]。而敲除或阻断周期蛋白D则使活化的CDK4/6浓度降低, 细胞周期进程停滞, 诱导细胞进入G_0期或出现凋亡[30-31]。在G_1期向S期转换过程中, 活化的细胞周期蛋白D-CDK4/6通过使底物视网膜母细胞瘤蛋白(retinoblastoma protein, Rb)磷酸化, 促使E2F释放。而游离的E2F则进入细胞核中, 促进周期蛋白E及进入S期所需基因的转录, 保证G_1期向S期正常转换[32-34]。此外, 非磷酸化的Rb则与E2F紧密结合, 抑制E2F释放, 从而诱导G_1期停滞[35]。这表明磷酸化的Rb在G_1期向S期转换过程中起着关键作用。

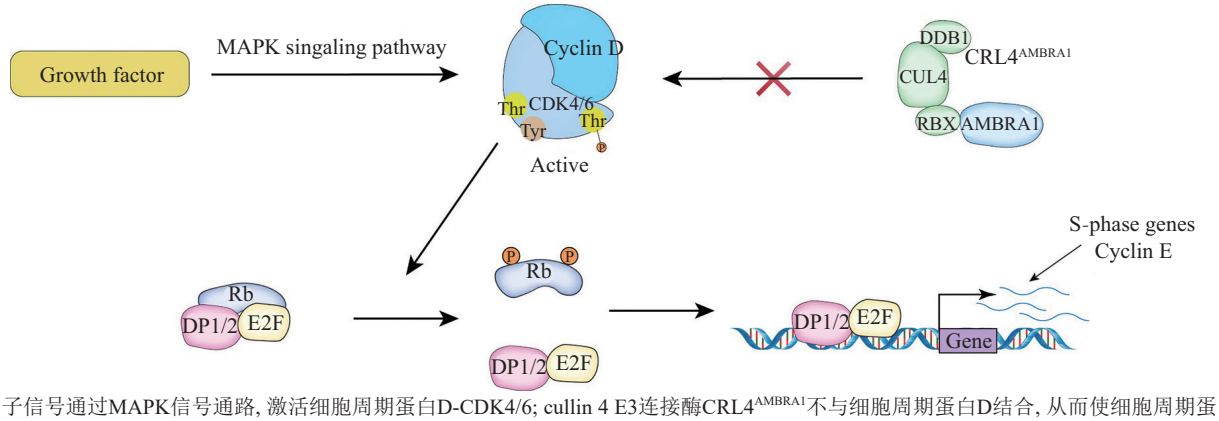
此外, 异常表达的细胞周期蛋白D会导致DNA损伤、细胞周期进程紊乱[36]。因此, 使异常表达的周期蛋白D恢复稳定, 将是促使细胞周期进程正常进行的关键。研究发现, cullin 4 E3连接酶$CRL4^{AMBRA1}$(cullin 4-based RING-type)是介导周期蛋白D泛素化和蛋白酶体降解的主要调节因子[36-37]。在细胞周期进程中, $CRL4^{AMBRA1}$连接酶复合物的底物受体AMBRA1(activating molecule in beclin-1-regulated autophagy)的缺失导致周期蛋白D水平升高和Rb过度磷酸化, 促进细胞增殖并降低其对CDK4/6抑制剂的敏感性[37-38]。此外, AMBRA1有助于细胞在周期进程DNA复制过程中维持基因组完整性, 从而抵消发育异常和抑制肿瘤生长[36]。综上所述, 在细胞周期进程中可通过AMBRA1控制细胞周期蛋白D稳定性调控细胞的正常分裂。细胞周期蛋白D与CDK4/6分子调控过程示意图见图2。

3 CDK4/6抑制剂在癌症及其他疾病中的应用

近几年, CDK4/6抑制剂出色的治疗效果, 吸引了无数医药学家的关注。当前已有多类高特异性CDK4/6抑制剂, 包括帕博西尼(Palbociclib)、瑞博西尼(Ribociclib)和阿贝西利(Abemaciclib)等[39-40], 被批准用于癌症及其他疾病的治疗。但在临床研究中发现癌症等疾病对这些抑制剂有耐药性, 虽开展了许多研究, 但仍有许多耐药性病例缺乏分子研究基础[41]。

3.1 Palbociclib

Palbociclib(PD0332991)于2015年被美国食品药品监督管理局(Food and Drug Administration, FDA)



生长因子信号通过MAPK信号通路, 激活细胞周期蛋白D-CDK4/6; cullin 4 E3连接酶$CRL4^{AMBRA1}$不与细胞周期蛋白D结合, 从而使细胞周期蛋白D不被泛素化降解, 促进细胞周期蛋白D-CDK4/6激活; 激活的细胞周期蛋白D-CDK4/6通过使Rb磷酸化, 将Rb从Rb-DP1/2-E2F复合物解离, 从而促进细胞周期蛋白E与S期基因转录。

Growth factor signaling activates cyclin D-CDK4/6 through the MAPK signaling pathway; the cullin 4 E3 ligase $CRL4^{AMBRA1}$ does not bind to cyclin D, thus keeping cyclin D from ubiquitinated degradation and promoting cyclin D-CDK4/6 activation; activated cyclin D-CDK4/6 promotes cyclin E transcription with S-phase proteins by phosphorylating Rb and dissociating Rb from the Rb-DP1/2-E2F complex.

图2 细胞周期蛋白D-CDK4/6的分子调控

Fig.2 Molecular regulation of cyclin D-CDK4/6

批准上市, 并且是全球首个被批准上市的CDK4/6抑制剂, 可应用于激素受体阳性(hormone receptor-positive, HR^+)、人表皮生长因子受体2阴性(human epidermal growth factor receptor 2-negative, $HER2^-$)晚期乳腺癌患者的治疗, 以及可与芳香化酶抑制剂联用作为绝经后女性患者的初始内分泌治疗[42-45]。MARZEC等[46]在细胞淋巴瘤(mantle cell lymphoma, MCL)中发现Palbociclib可通过抑制周期蛋白D1-CDK4复合物, 抑制MCL细胞G_0/G_1期的Rb磷酸化, 阻滞细胞周期进展, 表明Palbociclib对MCL具有抗性作用。BAUGHN等[47]在多发性骨髓瘤(multiple myeloma)中发现Palbociclib可通过抑制CDK4/6, 有效地诱导原代骨髓瘤细胞的G_1期停滞, 抑制播散性人骨髓瘤异种移植物中的肿瘤生长。这表明周期蛋白D1-CDK4/6可作为癌症治疗的重要生物靶点。

越来越多的临床研究发现, 许多癌症等疾病对Palbociclib的耐药性是不可避免的, 而如何去克服这种耐药性就成为众多研究者所关注的方向[48-49]。CAI等[50]在乳腺癌细胞中发现, 高表达的周期蛋白D1和CDK4是导致CDK4/6抑制剂耐药的关键, 而PI3K/mTOR抑制剂与CDK4/6抑制剂联合治疗可恢复乳腺癌细胞对CDK4/6抑制剂的敏感性。LI等[51]在肝内胆管细胞癌(intrahepatic cholangiocarcinoma, ICCA)中发现PF-04691502(PI3K/mTOR抑制剂)与Palbociclib联合治疗对周期蛋白D1、CDK4/6和PI3K信号通路的抑制作用更强、更稳定, 从而保持ICCA细胞对治疗药物有效的敏感性。此外, 与单一疗法相比, 联合用药对常见的下游信号通路具有更明显的抑制作用。这表明CDK4/6抑制剂和PI3K/mTOR抑制剂的联合使用可提高CDK4/6抑制剂的敏感性, 克服CDK4/6抑制剂的耐药性。ER^+乳腺癌是乳腺癌最常见的亚型。WANG等[52]在ER^+乳腺癌中发现, 可通过降低PFKFB4水平改善药物的敏感性, 克服Palbociclib的耐药性。GOODWIN等[53]在胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)中发现Palbociclib和ERK-MAPK抑制剂(ERK-MAPK inhibitor, ERKi)联合治疗, 可增强细胞对治疗药物的敏感性, 提高治疗效果。三阴性乳腺癌(triple-negative breast cancer, TNBC)是一种侵袭性很强的乳腺癌亚型, 预后差, 有效的治疗选择有限[54]。ESTEPA-FERNÁNDEZ等[55]在侵袭性TNBC小鼠异种移植模型中发现, Palbociclib和衰老剂NAV-Gal的联合治疗可以延缓肿瘤生长和抑制肿瘤转移, 表明Palbociclib在侵袭性TNBC治疗中具有关键的疗效。

3.2 Ribociclib

Ribociclib在2017年被FDA批准上市, 是全球第2款获批上市的CDK4/6抑制剂, 商品名为Kisqali, 用于绝经后$HR^+/HER2^-$的局部晚期或转移性乳腺癌的治疗[56-57]。一项名为MONALEESA-2的III期临床研究, 发现Kisqali联合芳香化酶抑制剂治疗相比内分泌药物单药治疗, 可以使疾病进展或死亡风险显著降低, 使中位无进展生存期(prolonged progression-free survival, PFS)显著延长[58]。此外, MONALEESA-3和MONALEESA-7两项临床研究也进一步证明了Ribociclib在乳腺癌中的疗效。MONALEESA-3是首个用于评估CDK4/6抑制剂联合氟维司群(Fulvestrant)治疗晚期乳腺癌疗效的III期临床研究[59-60]。该研究评估了Ribociclib与氟维司群联合用于绝经后$HR^+/HER2^-$晚期乳腺癌患者的疗效, 结果表明Ribociclib与氟维司群联合治疗可显著延长患者的中位PFS, 并且Ribociclib联合氟维司群治疗比单药氟维司群的总生存期明显延长[59]。MONALEESA-7 III期临床研究评估了Ribociclib联合内分泌治疗他莫昔芬(Tamoxifen)或非甾体类芳香化酶抑制剂(nonsteroidal aromatase inhibitor, NSAI)用于晚期$HR^+/HER2^-$乳腺癌治疗的疗效[61]。研究结果发现, 在内分泌治疗中加用Ribociclib比单独使用内分泌治疗的总生存期显著延长, 并且在后续针对治疗患者的跟踪回访中也未发现毒性作用问题的存在, 表明在内分泌治疗中加用Ribociclib具有更好的疗效及安全性[61]。随后的多期临床试验也进一步证明, CDK4/6抑制剂与内分泌治疗联合治疗比单独内分泌治疗更有疗效[62-63]。

3.3 Abemaciclib

Abemaciclib是一种CDK4/6抑制剂, 于2017年9月被FDA批准上市, 用于治疗$HR^+/HER2^-$晚期或转移性乳腺癌, 商品名为Verzenio, 是目前唯一一种在转移性乳腺癌中即可单用也可联合使用的CDK4/6抑制剂[64]。对于HR^+的乳腺癌患者, 主要治疗手段为内分泌治疗。但是CDK4/6的异常激活会造成内分泌治疗耐药的发生, 如能阻断CDK4/6异常激活, 则可有效控制肿瘤生长[53]。MONARCH-3 III期临床试验评估了Abemaciclib在$HR^+/HER2^-$的晚期或转移性

乳腺癌绝经后女性患者中的疗效及安全性[65]。结果表明，接受Abemaciclib和芳香酶抑制剂联合治疗的患者，中位PFS显著延长[65]。这表明Abemaciclib加芳香化酶抑制剂的联合疗法可显著延缓$HR^+/HER2^-$转移性乳腺癌女性的疾病进展。此外，Abemaciclib联合内分泌治疗，在治疗高危$HR^+/HER2^-$早期乳腺癌患者的III期临床试验中显著降低了乳腺癌复发或死亡风险[66]。这表明Abemaciclib联合内分泌治疗可降低乳腺癌患者的复发及死亡风险。新辅助化疗(neoadjuvant chemotherapy, NAC)是提供给$HR^+/ERBB2^-$高危早期乳腺癌患者的一种术前治疗方法，为实现保乳带来希望[67]。但是大多数$HR^+/ERBB2^-$乳腺癌患者在接受NAC后仍有残留疾病，尽管辅助内分泌治疗可以降低这些患者的复发风险，但仍存在相当大的风险[67]。因此，需要新的治疗选择来预防这些患者疾病的复发。2022年，MARTIN等[67]在MONARCHE III期临床试验中评估了Abemaciclib联合内分泌治疗与单独内分泌治疗方法用于$HR^+/ERBB2^-$和淋巴结阳性高危早期乳腺癌患者的疗效。结果显示，联合Abemaciclib和内分泌治疗方法可显著改善无侵袭性疾病生存(invasive disease-free survival, IDFS)和远处无复发生存期(distant relapse-free survival, DRFS)[67]。这表明在随机临床试验MONARCHE中，对于在试验前接受了NAC的$HR^+/ERBB2^-$和淋巴结阳性高危早期乳腺癌患者，辅助Abemaciclib与内分泌治疗联合的方法可明显改善IDFS和DRFS。许多患有$HR^+/HER2^-$早期乳腺癌的患者在目前可用的标准治疗下不会复发或远处复发，但在高危临床和/或病理特征的患者中，则有多达30%的患者可能会经历远处复发[67]。综上所述，Abemaciclib可作为单一药物，也可与其他治疗药物联合使用，用于治疗接受内分泌治疗和既往化疗后疾病仍进展的患者，且Abemaciclib的联合疗法有望为高危$HR^+/HER2^-$早期乳腺癌患者提供一种新的治疗选择。

4 问题与展望

细胞周期进程是一种复杂的机制调控过程，在这一过程中有许多细胞周期调控因子，例如细胞周期蛋白D、CDK4/6，发挥作用。当生长信号转导到细胞周期G_1/S检查点后，周期蛋白D与CDK4/6启动，从而开启细胞周期进程。当前，关于周期蛋白D与CDK4/6的研究多集中在体细胞中，而在胚胎干细胞以及其他类型细胞中的研究还相对较少。然而，胚胎干细胞在胚胎发育过程中起着至关重要的作用，可诱导分化为机体内各类细胞，并维持着机体的生长。此外，胚胎干细胞与体细胞相比具有独特的细胞周期运行模式，并且这一独特的运行模式与其自我更新及多向分化潜能等特性密切相关[68]。因此，从细胞周期研究角度探究周期蛋白D与CDK4/6对胚胎干细胞自我更新、多向分化潜能和维持多能性等方面的影响，及周期蛋白D与CDK4/6在胚胎干细胞中的周期运行模式，将对胚胎干细胞周期进程以及分化研究具有重要意义。

近几年的研究，发现CDK4/6抑制剂是抗癌及疾病治疗药物研发中重要的药理学靶点，当前已有Palbociclib、Ribociclib、Abemaciclib等CDK4/6抑制剂被研发和投入临床治疗中。这些CDK4/6抑制剂治疗药物在临床研究中可作为单一药物进行治疗，也可与其他治疗药物或方法联合使用进行治疗。但癌症对CDK4/6抑制剂的高耐药性，一直是癌症治疗中CDK4/6靶向药物研发的重要挑战。因此，在设计及研发CDK4/6抑制剂时要充分考虑其耐药性，并且在设置治疗方案时应尽量减少CDK4/6抑制剂耐药性的发生。

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