急性髓系白血病发生机制研究进展

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摘要 急性髓系白血病(acute myeloid leukemia, AML)是一种骨髓造血干细胞的克隆性扩增和分化缺失导致的恶性增生性疾病, 发病率和死亡率高。阐明AML的发生机制, 开发治疗药物将有效提高患者存活率, 但目前其具体发生机制不明。研究报道, AML的发生与相关基因突变、信号通路异常、表观遗传调控、白血病微环境或免疫失衡等密切相关。该文主要对与AML发生相关的基因(如*FLT3*、*IDH1*/*IDH2*和*BCL-2*等)突变或异常表达, 信号通路(如ROS信号通路、受体酪氨酸激酶途径、非受体酪氨酸激酶途径、Ser/Thr激酶活性和细胞表面受体等)异常, 以及相关免疫细胞(如NK细胞、T细胞、巨噬细胞等)失衡或免疫分子(如CD33、PD-1、CD47、CD70等)表达异常进行综述, 在分子细胞水平总结AML发生机制的研究进展, 为AML的靶向治疗药物开发提供参考依据。

关键词 急性髓系白血病; 发生机制; 基因突变; 信号通路; 免疫; 靶向治疗

Advances in the Pathogenesis of Acute Myeloid Leukemia

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Abstract AML (acute myeloid leukemia) is a malignant hyperplastic disease caused by clonal expansion and loss of differentiation of hematopoietic stem cells in bone marrow, with high morbidity and mortality. Clarifying the pathogenesis and developing the therapeutic drugs will improve effectively the survival rate of AML patients. However, the occurrence mechanism of AML is still unknown. Studies have reported that the occurrence of AML is closely related to gene mutations, signal pathway abnormalities, epigenetic regulation, leukemia microenvironment and immune imbalance. This review mainly discusses the related gene mutations or abnormal expression such as *FLT3*, *IDH1/IDH2* and *BCL-2*, abnormal signaling pathways such as ROS signaling pathway, receptor tyrosine kinase pathway, non-receptor tyrosine kinase pathway, Ser/Thr kinase activity and cell surface receptors, as well as the imbalance in related immune cells such as NK cells, T cells and macrophages or abnormal immune molecules such as CD33, PD-1, CD47, CD70. In this review, the research progress of pathogenesis in AML is summarized at the molecular and cellular level, which will provide a reference for the development of targeted therapeutic drugs for AML.

Keywords acute myeloid leukemia; pathogenesis; gene mutation; signal pathway; immune; targeted therapy

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白血病(leukemia)俗称“血癌”, 是一类造血干细胞克隆性增殖的血液恶性疾病。克隆性白血病细胞在骨髓和其他正常造血组织中增殖累积, 抑制造血功能, 还可通过血液循环渗入其他非造血组织和器官, 造成器官衰竭, 预后差。临床表现常有贫血、出血、感染发热等症状。急性髓系白血病(acute myeloid leukemia, AML)是常见的白血病类型, 占急性白血病的80%, 在儿童中发病率高[1]。70%的65岁以上AML患者在诊断后一年内会死亡, 死亡率较高[2]。AML的发生机制复杂多样, 化学物质、放射性物质、遗传因素、基因突变、信号通路异常、表观遗传调控、白血病微环境或免疫失衡等都能引起AML发生。本文将主要阐述基因突变或异常表达、信号通路异常和免疫分子异常介导AML发生的研究进展。

1 基因突变或异常表达与AML发生

AML发生与特定的基因突变或异常表达密切相关, CHEN等[3]通过新一代测序技术发现AML相关基因突变谱, 其中某些基因的改变可能引起AML发生, 并与白血病的预后有关。本文主要概述常见的参与AML发生的基因突变或异常表达如FMS样酪氨酸激酶3(FMS-like tyrosine kinase 3, *FLT3*)、异柠檬酸脱氢酶1/异柠檬酸脱氢酶2(isocitrate dehydrogenase 1/isocitrate dehydrogenase 2, *IDH1*/*IDH2*)和B细胞淋巴瘤2(B-cell lymphoma-2, *BCL-2*)。

1.1 *FLT3*基因突变

FMS样酪氨酸激酶3(FLT3)是III型受体酪氨酸激酶, 由胞外区的五个免疫球蛋白样结构域、一个膜旁结构域和一个酪氨酸激酶(tyrosine kinase, TK)结构域组成, 在造血细胞的存活、增殖和分化中起重要作用[4]。FLT3在髓样和淋巴谱系发育的早期阶段均发挥重要作用, 由FLT3配体结合并激活FLT3[5]。FTL3与其配体结合后, 会发生二聚化并自磷酸化, 从而激活酪氨酸激酶活性, 进而激活PI3K/Akt和Ras/MAPK途径, 导致DNA损伤和修复缺陷, 并增加细胞增殖和抗凋亡能力[6]。临床上*FLT3*基因突变是AML患者最常见的基因改变和预后不良的因素, 在大多数AML细胞中都有*FLT3*突变, 进而激活抗凋亡和促生长信号, 刺激AML细胞增殖[4]。而内部串联重复(internal tandem duplication, ITD)是最常见的*FLT3*突变类型(*FLT3-ITD*), 约占AML患者的25%[5]。DJAMAI等[7]研究表明, 在AML细胞中FLT3-ITD能激活Rho激酶, 从而导致LIM激酶(LIM kinase, LIMK)磷酸化, 影响细胞骨架动力学、细胞生长和细胞凋亡。NGUYEN等[8]报道, FLT3-ITD通过磷酸化SPRED1蛋白和抑制miRNAs的核–质转运, 从而干扰AML细胞中微小RNA(microRNAs, miRNAs)的产生, 促进AML发生。BJELOSEVIC等[9]也证明FLT3-ITD可促进丝氨酸合成, 新合成的丝氨酸能选择性地抑制AML细胞增殖。

因此, 靶向*FLT3*突变可有效治疗AML, 总结见表1。WEI等[10]发现, midostaurin是FLT3酪氨酸激酶的有效抑制剂, 可诱导细胞凋亡并导致细胞周期停滞, 从而抑制AML细胞生长[11]; 研究也表明, midostaurin可显著提高AML患者四年总生存率。DHILLON等[12]发现, 一种口服的小分子受体酪氨酸激酶抑制剂吉利替尼(gilteritinib)能抑制*FLT3*突变的AML细胞中FLT3信号转导, 导致AML细胞凋亡。另外, PERL等[13]发现相比挽救性化疗, gilteritinib可显著延长复发难治*FLT3*突变AML患者的生存期且缓解率更高。因此, 深入了解*FLT3*相关突变在AML中的作用, 能为AML治疗提供新方法。

1.2 *IDH1*/*IDH2*基因突变

异柠檬酸脱氢酶(isocitrate dehydrogenase, IDH)是三羧酸循环中细胞呼吸所必需的酶, 其中IDH1和IDH2分别在细胞质和线粒体中催化异柠檬酸转化为α-酮戊二酸, 并产生烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)[14]。与肿瘤相关的*IDH*突变能阻止正常细胞分化, 并通过代谢物羟戊二酸(D-2-hydroxyglutarate, 2-HG)的异常产生促进肿瘤的发生[15]。*IDH1*或*IDH2*突变在AML中普遍存在, 约占所有AML患者的20%[16], 其中*IDH1*突变占6%~16%, *IDH2*突变占8%~19%[17]。DANG等[18]研究表明, *IDH2*突变与致癌性*FLT3*或*NRAS*等位基因的杂交可减弱髓样细胞的分化从而驱动白血病转化, 在继发性AML细胞中发现*IDH1/2*突变发生在恶性转化的早期。CHIFOTIDES等[19]研究发现, *IDH1/2*突变导致肿瘤代谢物2-羟基戊二酸的积累, 引起DNA和组蛋白甲基化, 促进AML的发生。

因此, 靶向*IDH*突变能有效治疗AML, 总结见表1。艾伏尼布(ivosidenib)是一种口服靶向*IDH1*突变的小分子抑制剂, 靶向IDH1的代谢途径, 可防止因正常代谢物2-HG的积累而引发的AML发生, 用于

治疗*IDH1*突变的AML患者[20]。DINARDO等[21]通过临床实验证明, 在晚期*IDH1*突变的复发或难治的AML患者中, 用ivosidenib治疗能降低相关不良事件发生率, 增加缓解率。恩西地平(enasidenib)是IDH2的抑制剂, 用于*IDH2*突变的AML患者, 安全且耐受性良好, 减少了异常组蛋白的高甲基化, 并恢复骨髓分化[22]。靶向*IDH1/2*突变的抑制剂在AML治疗中潜力巨大, 随着研究的深入, 能为AML治疗带来新的方向。

1.3 *BCL-2*基因异常表达

B细胞淋巴瘤2(B-cell lymphoma-2, BCL-2)蛋白家族成员可分为三类: 凋亡抑制蛋白如BCL-2等、凋亡促进蛋白如Bax等及仅含BH3区域的蛋白如Bad和Bid等。BCL-2是与细胞凋亡相关的BCL-2蛋白家族成员之一, 是抗癌治疗的主要靶标[23]。BCL-2的主要作用是调节细胞凋亡, 其中促凋亡蛋白和抗凋亡BCL-2蛋白之间的平衡决定了细胞对凋亡刺激的敏感性[24]。研究表明, 在AML中*BCL-2*的高表达与患者的预后不良有关[25]。VU等[26]报道抗凋亡*BCL-2*的过度表达将导致在化疗期间AML细胞难以根除, 产生化学耐药性。

目前发现, 靶向*BCL-2*具有治疗AML的潜在价值, 总结见表1。临床上已发现BCL-2的抑制剂venetoclax是一种新型口服药, 对BCL-2的BH3结合域具有高亲和力, venetoclax通过抑制AML细胞中*BCL-2*的高表达, 从而促进细胞凋亡和抑制细胞增殖[27]。VARTAK等[28]研究表明, BCL-2的特异性小分子抑制剂disarib结合BH1结构域, 这是一种新型的BCL-2抑制模式, 其不仅在体外可特异性地破坏BCL-2-BAK的相互作用, 还可促进AML细胞的凋亡。以上研究表明, 靶向*BCL-2*的抑制剂对AML治疗具有良好疗效。因此, 阐明*BCL-2*参与AML发生机制, 有助于推进AML治疗药物开发的研究。

2 信号通路异常与AML发生

2.1 ROS信号通路

活性氧(reactive oxygen species, ROS)是具有氧化活性的分子或离子的总称。ROS作为信号分子调节氧化还原敏感的转录因子、酶、致癌基因和其他下游效应因子, 其介导的信号通路调控正常生理过程, 维持细胞内氧化还原平衡。ROS水平的变化可引起氧化还原失衡, DNA发生氧化损伤, 增加DNA突变, 导致基因组不稳定, 从而促进细胞增殖、分化, 或改变基因组和表观遗传学等, 导致癌症发生[29]。研究报道, 在60%的AML患者体内发现ROS过度产生是由于烟酰胺腺嘌呤二核苷酸磷酸氧化酶(NADPH oxidase, NOX)持续激活引起的, 而且ROS升高与谷胱甘肽水平降低和抗氧化防御蛋白耗竭有关。ROS的大量积累促进了AML细胞系及原代AML细胞的增殖, 并在较小程度上促进了正常$CD34^+$细胞的增殖[30-31]。AML细胞中*FLT3-ITD*突变导致Akt激活、ROS水平增加和DNA损伤, 且FLT3-ITD信号增强NOX4的表达, 导致ROS持续积累, DNA双链断裂、损伤和突变积累, 引起基因组不稳定, 促进AML增殖和浸润。因此, 干扰FLT3-ITD-STAT5-NOX4介导的ROS过量产生和酪氨酸磷酸酶失活可能具有治疗AML的潜力[32]。

AGRAWAL-SINGH等[29]提出, AML中新发现的抑癌基因过氧化物酶2(peroxiredoxin-2, *Prdx2*)启动子上组蛋白H3乙酰化缺失、甲基化增加, 表观水平沉默导致*Prdx2*低表达, 氧化还原失衡, 进而ROS持续积累引起基因组不稳定, AML细胞恶性增殖, 患者不良预后。上调*Prdx2*表达能降低ROS水平抑制AML细胞生长。研究发现, 在AML复发患者中ROS水平增加, 与氧化应激相关的指标也显著改变, 且ROS水平增加诱导c-Jun激活区结合蛋白1(c-Jun activation domain-binding protein l, *Jab1*)基因和硫氧还原蛋白1(thioredoxin 1, *Trx1*)基因高表达, 促进AML细胞恶性增殖, 加速疾病进展[33-34]。

以上研究表明, ROS参与调控AML的发生发展(图1), 调控ROS水平抑制AML增殖可能是AML治疗的有效措施之一(表1)。已有研究表明, 化合物5-羟黄酮(tricetin)通过ROS介导的c-Jun N-端激酶活化通路诱导白血病HL60细胞凋亡[35]。我们也发现复方苦参注射液和天然无毒的小分子化合物壬二酸(azelaic acid, AZA)都可以降低ROS水平, 通过调控Prdxs/ROS/信号通路抑制AML的增殖[36-37]。因此, 深入探索AML发生机制, 可能为AML治疗提供新的思路。

2.2 受体酪氨酸激酶途径——Ras/Raf/MEK/ERK信号通路

促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)级联是一个关键的信号转导级联途径, 常常是通过配体与细胞表面的受体酪氨酸

激酶(receptor tyrosine kinases, RTK)结合并通过启动Ras蛋白, 将信号传递到Raf/细胞外信号调节激酶(extracellular signal-regulated kinase, MEK), 最终通过细胞外信号激酶(extracellular signal-regulated kinase, ERK)来调控细胞核内基因转录[38]。该信号通路可调节多种细胞功能, 包括细胞增殖、分化、存活和凋亡, 其异常通常是关键成分基因或上游生长因子受体突变导致的, 该通路的激活与白血病细胞无限增殖、白血病治疗的敏感性和耐药性有关, 会导致AML发生[39](图1)。MAPK级联途径在70%~80%的AML患者中被上游突变蛋白如FLT3和RAS激活, 通过调节BCL-2家族蛋白参与调控AML的发生[40]。研究显示, 有10%~25%的AML患者存在*RAS*突变, 具有*RAS*突变的AML患者体内MAPK级联和PI3K信号通路被上调, 且MAPK能调控细胞凋亡抑制因子, 从而导致AML的耐药性[41]。MAPK信号的抑制会导致处于G_0/G_1期的AML细胞周期停滞[42], 从而抑制AML细胞增殖。

因此, 可针对MAPK信号通路进行AML靶向治疗药物开发。目前, 针对Raf蛋白ATP结合位点开发的小分子竞争性抑制剂如L-779、ZM 336372和Bay 43-9006等能结合Raf激酶结构域, 阻止Raf激酶活性(表1); 还有一种靶向Raf的方法是通过靶向激酶如Src、PKC和PKA等及磷酸酶如蛋白磷酸酶2A来阻止Raf激活, 从而影响AML细胞发生[43]。此外, MOSHOFSKY等[44]实验结果显示, MAPK通路的激活能诱导T细胞死亡, 反之, 抑制MAPK通路能保护T细胞, 激活细胞免疫, 从而影响AML的发生与发展。靶向MAPK通路与免疫的联合治疗可能在未来会成为一种AML治疗的新方法。

2.3 非受体型酪氨酸激酶途径——JAK/STAT信号通路

Janus激酶(Janus kinase, JAK)及信号转导和转录激活因子(signal transducers and activators of transcription, STAT)信号通路, 属于非受体型酪氨酸激酶途径即细胞质因子受体途径, JAK家族包含JAK1、JAK2、JAK3和TYK2四个成员[45], STAT家族包含七个成员, 分别是STAT1、STAT2、STAT3、STAT4、STAT5A、STAT5B和STAT6[46]。JAK/STAT信号通路在细胞增殖、分化、迁移和凋亡的调控中起着关键作用, 在实体瘤和血液系统恶性肿瘤发生发展中起着重要作用。

异常激活的JAK-STAT信号通路参与了血液恶性肿瘤的发生发展并与T细胞急性淋巴细胞白血病(T-cell lymphoblastic leukemia)形成密切相关[47]。该通路持续激活会导致白血病细胞过度增殖、抗凋亡、分化受阻[48]。慢性期的骨髓增生性肿瘤(myeloproliferative Neoplasms, MPN)会发展为AML[49], 这一过程中JAK-STAT信号通路相关的基因突变导致了不受控制的下游信号通路被激活, 促使STAT1蛋白S727位点磷酸化, 而STAT1 S727磷酸化可调节肿瘤的生长和分化, 从而导致AML细胞的恶性增殖[50](图1)。在AML细胞中, JAK/STAT通路通过转录激活因子STAT3/5直接与*TET1*启动子结合促进*TET1*的转录, 且TET1蛋白也直接结合在*JAK1*的启动子上激活*JAK1*转录, 表明JAK1/STAT/TET1通路在AML中形成了反馈环路[51]。此外, JAK2也可能直接通过下游效应物或间接通过诱导靶基因表达来激活其他多种信号分子。例如, SHA等[52]研究发现, 当miR-486在AML细胞中过表达时, 其直接靶点细胞因子信号通路抑制因子2(suppressor of cytokine signaling 2, *SOCS2*) mRNA水平下降, miR-486的过表达会激活STAT3, 促进细胞的增殖, 因此, miR-486-SOCS2-STAT3轴参与了AML的发生, 为AML的诊断和治疗提供了新的分子机制和靶点。

调控JAK-STAT通路抑制AML增殖是治疗AML的重要策略之一。KARJALAINEN等[53]研究报道, JAK1/2抑制剂ruxolitinib能增加AML患者对BCL-2抑制剂venetoclax的敏感性, 逆转耐药。通过数据分析和药物筛选鉴定出化合物NSC-370284能选择性地抑制*TET1*的转录和5-羟甲基胞嘧啶(5hmC)的修饰, 并能有效地抑制高表达TET1的AML细胞活性。NSC-370284及其结构类似物即UC-514321都直接作用于*TET1*的转录激活因子STAT3/5, 抑制*TET1*的表达, 进而抑制AML细胞增殖[51]。

2.4 Akt信号通路

Akt, 即蛋白激酶B(protein kinase, PKB), 是一种在细胞存活和凋亡之间保持平衡的丝氨酸/苏氨酸激酶, 包含Akt1、Akt2和Akt3三种亚型。常见的PI3K/Akt/mTOR信号转导通路参与细胞生长、增殖和分化, 在肿瘤的发生、发展、和预后中起着重要作用。PI3K/Akt/mTOR通路在AML细胞中发生异常变化, 处于持续激活状态, 导致肿瘤细胞恶性增殖, 患者预后差[54-55]。PI3K/Akt/mTOR通路的激活

还与AML患者的整体生存率下降有关, 该通路整合了多个受体和级联信号转导[56-57]。CHENG等[58]发现, AML患者骨髓间充质干细胞中趋化因子配体8(C-X-C motif chemokine ligand 8, CXCL8)通过PI3K/Akt信号通路促进AML生成。此外, 在AML患者骨髓和血清中显著高表达的长链非编码RNA如LINC00265也可激活AML细胞中PI3K/Akt信号通路, 通过调控PI3K/Akt通路促进AML增殖和浸润[59]。

因此, PI3K/Akt/mTOR信号通路在AML发生发展中有至关重要的作用(图1), 抑制该通路能有效抑制AML细胞增殖, 该通路中的关键分子可以作为AML治疗的靶点[56]。WU等[60]发现, 苦参碱(matrine)既能诱导AML细胞凋亡, 也能抑制Akt的磷酸化, 抑制mTOR及其下游底物p70S6K和4EBP1, 从而导致AML细胞自噬。PEI等[61]发现, 丹酚酸A (salvianolic acid A, SAA)能显著抑制AML细胞内Akt的磷酸化, 从而抑制小鼠皮下肿瘤的生长。LI等[62]发现, 同时抑制PI3K和组蛋白去乙酰化酶活性的抑制剂CUDC-907在体内外实验中均能诱导AML细胞凋亡。此外, ZHANG等[63]还发现, miR-139-5p通过靶向Tspan 3抑制AML细胞的PI3K/Akt通路, 抑制AML细胞的生成。

2.5 Notch信号通路

Notch信号系统是细胞增殖和分化的主要调节器。Notch的表达受缺氧和炎症细胞因子如IL-1、IL-6等调控, Notch与配体结合后激活Notch信号通路。该通路有四个Notch受体, 分别是Notch-1、Notch-2、Notch-3和Notch-4; 有五个相关配体, Jagged-1、Jagged-2、Delta-like-1(Dll-1)、Dll-3和Dll-4, 这些分子都是膜结合的蛋白, 转导旁分泌信号[64]。AML中Notch信号通路是沉默的, Notch通路中分子表达的高低与AML患者的预后生存有关[65], 如AML患者高危组中丝氨酸/苏氨酸蛋白激酶D2(serine-threonine protein kinase D2, *PRKD2*)高表达, 促使*Notch1*高表达, 可促进AML细胞增殖和化疗耐药(图1)。

Notch通路可作为AML预后指标和治疗靶标[66]。激活Notch是治疗AML的策略之一[67], 已有研究报道激活Notch能改善AML, 如上皮生长因子样蛋白7(epidermal growth factor-like protein 7, EGFL7)抗体与Dll4受体竞争性结合, 导致Notch信号重新被激活, 诱导AML细胞凋亡[68]。运用小分子激活Notch信号通路, 也能实现治疗AML的目的, 如*N*-甲基庚啶氯化物(*N*-methylhemeanthidine chloride, NMHC)可与Notch配体Dll4结合激活Notch信号通路[69]。我们也发现小分子壬二酸(AZA)可作为潜在的Notch激活剂, AZA能促进NK和T细胞的增殖, 促进*Notch1*和*Notch2*表达上调, 导致Notch信号通路被激活从而发挥抗AML效应[70]。

3 免疫失衡与AML发生

免疫细胞的存活与凋亡、免疫调节因子的表达和肿瘤微环境(tumor microenvironment, TEM)的变化都会影响AML的发生与发展[71]。免疫细胞监视机体异常细胞, 并发挥免疫效应将其清除[72], 如自然杀伤(nature killer, NK)细胞通过介导细胞毒性作用识别和杀死肿瘤细胞[73]。肿瘤细胞可通过对自身表面抗原的修饰及改变肿瘤组织周围的微环境来逃避机体的免疫识别与攻击, 即肿瘤的免疫逃逸, AML发生也与免疫逃逸密切相关, 通过改变免疫细胞的活性或调节免疫分子的表达, 影响免疫细胞功能, 进而实现AML细胞的免疫逃逸, 导致AML细胞恶性增殖[74]。抑制AML细胞免疫微环境[75], 增强免疫应答, 可有效治疗AML。阐明AML发生与免疫应答之间的关系, 对AML患者的免疫疗法开发具有重要意义。

3.1 免疫细胞失衡与AML发生

3.1.1 NK细胞 NK细胞属于先天性淋巴样细胞家族的成员, 是介导肿瘤免疫监视和清除的关键效应淋巴细胞, 也是抗肿瘤防御系统的关键组成部分[76]。AML细胞通过抑制NK细胞的发育和功能实现免疫逃逸[77]。GONCALVES等[78]报道, 促使AML细胞免疫逃逸的分泌途径Tim-3-galectin-9可减弱淋巴细胞包括NK细胞的活性, 从而促使AML细胞免疫逃逸。AML细胞本身对NK细胞受体的缺陷表达也可导致NK细胞介导的抗白血病反应的减弱[79]。

靶向NK细胞的疗法在AML治疗中越来越受关注。KOERNER等[80]发现, Fc优化的CD133单抗(293 C3-SDIE)可显著增强NK细胞对原代CD133阳性AML细胞的激活、脱颗粒和溶解, 从而促进NK细胞对AML细胞的清除(表1)。WILLIAMS等[81]发现, $CD16^{+}$NK-92细胞与抗白血病干细胞抗原的抗体联合使用可提高AML模型小鼠的存活率。SHANG等[82]还报道关于靶向NK细胞治疗AML的临床试验正在进行中。靶向NK细胞治疗AML将是一种新的免疫

疗法。

3.1.2 T细胞 T淋巴细胞(T细胞)是适应性免疫系统的主要组成部分, T细胞介导的免疫应答在白血病中起着重要作用。SUN等[83]研究发现, AML骨髓微环境中有许多细胞因子异常, T亚群细胞因子的失衡被认为是AML发病的重要原因之一。AML患者T细胞表面缺陷的TCR受体导致T细胞功能更弱, 增强TCR ζ的表达, 将恢复T细胞功能[84]。

针对T细胞抗AML的治疗, 主要是嵌合抗原受体(chimeric antigen receptor, CAR) T细胞免疫疗法备受关注。采用基因工程技术诱导改造患者T细胞, 在T细胞中表达嵌合蛋白, 即制备CAR-T细胞, 再回输到AML患者中, CAR-T细胞靶向识别肿瘤细胞的抗原, 引发细胞免疫反应实现对AML细胞的杀伤[85]。DRIOUK等[86]通过利用含天然免疫受体NKG2D的CAR-T细胞作为抗原结合域, 表明针对NKG2D配体的CAR-T细胞具有显著的抗AML细胞活性(表1)。LIN等[87]证明靶向C型凝集素样分子-1的CAR-T细胞联合PD-1沉默治疗AML具有显著疗效。KIM等[88]发现, CD33缺陷细胞不受靶向CD33的CAR-T细胞影响, 允许在没有骨髓毒性情况下有效地消除白血病。因此, CAR-T细胞疗法用于AML治疗具有较大的应用前景。

3.1.3 巨噬细胞 巨噬细胞是先天性免疫细胞, 起源于循环单核细胞, 存在于所有组织中, 并参与多种病理过程, 巨噬细胞表达所有类型的Fcγ受体, 它们具有通过抗体依赖性吞噬作用破坏肿瘤的巨大潜力[89]。巨噬细胞也参与AML的发生, 研究表明肿瘤区巨噬细胞主要由M2表型组成, 可在肿瘤细胞生长、生存、侵袭、转移、耐药、炎症、血管生成和免疫抑制等方面促进肿瘤的进展[90-91]。XU等[92]系统地分析了536例AML患者体内肿瘤浸润性白细胞(tumor infiltrating lymphocytes, TIL)如单核细胞、B细胞、T细胞、中性粒细胞和巨噬细胞等的分布情况, 结果表明相比骨髓增生异常综合征、慢性髓系白血病、急性淋巴细胞白血病和慢性淋巴细胞白血病, AML患者体内TILs的分布发生显著改变, 且AML患者M2巨噬细胞的比率增加; 还发现M2的标志分子CD206在AML中高表达, 表明巨噬细胞大量浸润与AML预后不良有关。

针对巨噬细胞治疗AML的研究还较少, 需要更深入的探究。YANG等[93]研究发现, pyridoxine(维生素B6)可选择性地诱导单核–巨噬细胞程序性细胞死亡, 在U937细胞中依赖caspase-3介导细胞凋亡或在THP-1细胞中由GSDME介导的细胞焦亡, 结果表明低毒性的天然小分子pyridoxine可作为一种潜在的AML治疗药物。

3.2 免疫分子异常与AML发生

3.2.1 CD33 CD33是唾液酸结合受体家族和髓样分化抗原的成员之一, 在大多数白血病中广泛表达[94]。研究表明, CD33在AML原始幼稚细胞中的表达量超过85%, 且CD33水平高的AML患者存活率低[95]。CD33在几乎所有AML患者细胞中都高表达和持续表达, 因此也是一种常用于AML诊断的骨髓标记物[96]。

靶向CD33治疗AML具有重要的应用前景, 见表1所示。靶向CD33的治疗药物如吉妥珠单抗mylotarg(gemtuzumab ozogamicin, mylotarg)是一种抗体–药物偶联物, 是卡奇霉素的衍生物, 可促进单链和双链DNA的断裂从而导致AML细胞死亡[97]。CD33也是CAR-T细胞在临床前试验中最显著的靶抗原。在NSG小鼠的移植模型中, 抗CD33 CAR-T细胞治疗可显著减轻白血病负担, 延长存活时间[98]。KENDERIAN等[99]用CAR-T细胞靶向吉妥珠单抗中的抗CD33单链可变片段(CAR-T 33), 结果显示, CAR-T 33具有显著抗AML作用, 可延长小鼠的存活时间。ROTIROTI等[100]研究也表明, 制备表达CD33分子的细胞因子诱导杀伤细胞(cytokine-induced killer, CAR-CIK)细胞, 作为“早期治疗”使用时, 可减缓AML的发展, 增加缓解率。CAR-NK细胞如CD33-CAR-NK-92细胞也用于复发难治AML的临床试验[101]。

目前有几种针对CD33的疗法正在早期测试中, 靶向CD33的治疗剂在临床开发中包括Fc工程化的未偶联抗体、放射免疫偶联物、双特异性及三特异性抗体和嵌合抗原受体(CAR)修饰的免疫效应细胞[102]。这些疗法未来可能用于临床, 为AML治疗提供新方案。上述研究阐明了CD33在临床开发上的巨大潜力, 甚至可能会出现新的治疗方法。

3.2.2 PD-1 程序性细胞死亡受体1(programmed cell death-protein 1, PD-1)是一种免疫检查点抑制剂, 在免疫效应细胞表面表达[103]。程序性细胞死亡配体1(programmed cell death-ligand 1, PD-L1)为PD-1的一个重要配体, 在抗原呈递细胞表面广泛表达[104]。当PD-1与其配体PD-L1和PD-L2结合时可抑制细胞活化[105]。

表1 AML治疗药物和治疗方法总结

Table 1 Summary the therapeutic drugs and methods of AML

相关的基因、信号通路或免疫细胞与分子 Related gene, signaling pathways or immune cells and molecules		治疗药物或方法 Therapeutic drugs or methods	类别 Category	治疗效果或机制 Therapeutic effects or mechanisms	参考文献 References
Gene	FLT3	Midostaurin	TKI	Improve the four-year survival rate from 44.3% to 55.4%	[10-11]
		Gilteritinib	TKI	Prolong the survival time, and improve the remission rate	[12-13]
	IDH1/IDH2	Ivosidenib	IDH1 inhibitor	Reduce the incidence of adverse events, and improve the remission rate	[20-21]
		Enasidenib	IDH2 inhibitor	Reduces hypermethylation of abnormal histones and restores the differentiation of bone marrow	[22]
	BCL-2	Venetoclax	Inhibitor	Inhibit the high expression of BCL-2 in AML cells, and promote the cell apoptosis and inhibit the cell proliferation of AML cells	[27]
		Disarib	Inhibitor	Promote the cell apoptosis of AML cells	[28]
Signal pathway	ROS	Tricetin	Compound	Induce the cell apoptosis of HL60 cells by ROS-mediated c-Jun N-terminal kinase activation	[35]
		CKI	Mixture of chinese medicine	Reduce the ROS level, and regulate the Prdxs/ROS signal pathway to inhibit the cell proliferation of AML cells	[36-37]
		AZA	Small molecule compound		
	Ras/Raf/MEK/ERK	L-779, ZM 336372, Bay 43-9006	Small molecule inhibitor	Binding to the Raf kinase domain and inhibit the Raf kinase activity	[43]
	JAK/STAT	Ruxolitinib	JAK1/2 inhibitor	Increase the sensitivity of venetoclax and reverse the drug resistance in AML	[51,53]
		NSC-370284, UC-514321	Compound	Act directly on STAT3/5 that a transcriptional activator of TET1, and inhibits the expression of TET1 and inhibit the cell proliferation of AML cells	
	Akt	Matrine	Alkaloid	Induce the cell apoptosis of AML cell, or inhibit the Akt phosphorylation, and inhibit the mTOR and its downstream substrates p70S6K and 4EBP1, leading to the cell autophagy in AML	[60]
		SAA	Compound	Inhibit significantly the Akt phosphorylation of AML cells and inhibit the tumor growth	[61]
		CUDC-907	Inhibitor	Induce the cell apoptosis of AML cells	[62]
	Notch	AZA	Small molecule inhibitor	Promote the higher expression of Notch 1 and Notch 2, activating the Notch pathway and exerting the anti-AML effect	[70]

续表1

相关的基因、信号通路或免疫细胞与分子 Related gene, signaling pathways or immune cells and molecules			治疗药物或方法 Therapeutic drugs or methods	类别 Category	治疗效果或机制 Therapeutic effects or mechanisms	参考文献 References
Immune	Immune cells	NK cells	Fc-optimized CD133antibody (293 C3-SDIE)	McAb	Enhance the activation, degranulation and dissolution of primary $CD133^+$ AML cells, and promote the clearance of AML cells by NK cells	[80]
		T cells	CAR-T	Cell immunotherapy	CAR-T cells targeting NKG2D ligand against AML. And CAR-T combined with PD-1 silencing therapy has a significant effect on AML	[86-87]
		Macrophage	Pyridoxine	Compound	Induce selectively the programmed cell death of monocytes-macrophages	[93]
	Immune molecules	CD33	Mylotarg	Antibody-drug conjugate	Promote the breakage of single-and double-stranded DNA, leading to AML cell death	[97]
			CAR-T 33	Cell immunotherapy	Anti-AML	[99]
			CAR-CIK	Cell immunotherapy	Slower the progress of AML and improve the remission rate	[100]
		PD-1	Nivolumab, Pembrolizumab	McAb	Activation the antitumor activity of T cells	[108]
		CD47	CD47 antibody	McAb	Block the CD47/SIRPα signal and promote the phagocytosis, and enhance the clearance of AMLcells	[111]
		CD70	Cusatuzumab	McAb	Block the CD70/CD27signal transduction to eliminate the LSCs for AML treatment	[118]

TKI(tyrosine kinase inhibitor): 酪氨酸激酶抑制剂; CKI(compound kushen injection): 复方苦参注射液; AZA(azelaic acid): 壬二酸; SAA(salvianolic acid A): 丹酚酸A; McAb(monoclonal antibody): 单抗; LSC(leukemia stem cells): 白血病干细胞。

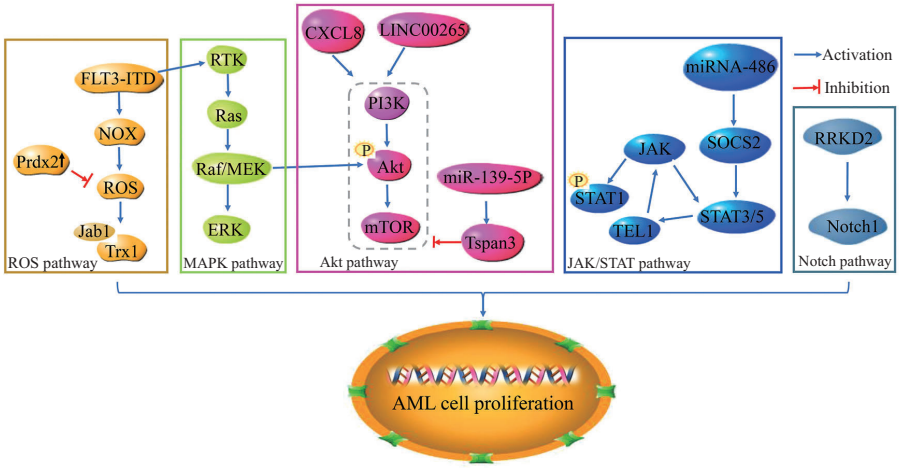

图1 调控AML发生的信号通路

Fig.1 The signaling pathways that regulating the occurrence of AML

许多癌细胞通过上调PD-1, 从而导致T细胞失活, 继而发生免疫逃逸, 致使肿瘤发生[106]。HAROUN等[107]研究表明, 在AML患者中, PD-L1和PD-1分别在非肿瘤的造血干细胞和T细胞中表达增加。因此, 抑制PD-1可激活T细胞免疫活性从而有效治疗AML。最常见临床试验中采用的PD-1抑制剂是Nivolumab和

Pembrolizumab, 可用于复杂难治的白血病[108]。

3.2.3 CD47 CD47是一种广泛表达的跨膜蛋白, 也是信号调节蛋白α(signal regulatory protein α, SIRPα)的配体, 该蛋白在吞噬细胞包括巨噬细胞和树突细胞中表达, 被激活后启动信号转导级联反应, 抑制吞噬作用。此外, 除了巨噬细胞, CD47分子在NK细胞、树突状细胞、T细胞中均有识别癌细胞或参与免疫应答的作用[109]。CD47在AML中过表达, 通过与SIRPα结合来抑制吞噬作用[110]; MAJETI等[111]研究发现, AML细胞系中CD47的表达抑制吞噬作用; 而抑制CD47的表达可恢复对AML细胞的免疫监视, 用针对CD47的抗体或抗体衍生物阻断CD47/SIRPα轴可增强吞噬作用并增强抗肿瘤免疫作用。例如, 用已建立的新型完全人源抗CD47单克隆抗体阻断CD47/SIRPα信号可增加体外巨噬细胞对AML细胞的吞噬作用, 并增强对AML细胞的清除能力[112]。CD47有潜力作为AML的新型治疗靶标[113], 相关研究证明CD47在筛选针对AML的新药方面具有重要潜力, 巨噬细胞免疫检查点阻断有望成为新的AML免疫治疗策略[114-115]。

3.2.4 CD70 CD70分子, 也被称为整合素相关蛋白(intergrin-associated protein, IAP), 是免疫超家族成员, 广泛表达于多种细胞表面。CD70是肿瘤坏死因子(tumor necrosis factor, TNF)超家族的成员之一, 在调控免疫应答过程中发挥重要作用, CD70的异常表达导致炎性细胞因子的分泌增加和免疫功能障碍, CD70还可通过与其配体CD27相互作用参与调控肿瘤细胞和调节性T细胞的存活[116]。RIETHER等[117]研究发现, CD70/CD27在AML原始幼稚细胞和AML干细胞/祖细胞上表达, 而在健康细胞中不表达; AML细胞中的CD70/CD27信号转导激活干细胞基因表达程序, 包括Wnt途径, 促进对称细胞分裂和增殖, 通过单克隆抗体阻断CD70/CD27相互作用可诱导AML原始幼稚细胞和AML干/祖细胞中的不对称细胞分裂和分化, 抑制细胞生长和集落形成, 并显著延长AML小鼠的存活时间。靶向CD70/CD27信号也是有潜力的AML治疗策略(表1)。RIETHER等[118]研究还发现, 人αCD70单克隆抗体(cusatuzumab)可靶向表达CD70分子的白血病干细胞(leukemia stem cells, LSCs), 阻断CD70/CD27信号通路, 在体外和异种移植实验中消除LSCs, 从而达到治疗AML的目的。

4 结语

虽然随着医疗技术的发展, AML作为一种难治的恶性血液疾病, 其治愈率和缓解率都有很大提高, 但患者预后较差、死亡率高。本综述重点阐述了与AML发生相关的突变基因、信号通路及免疫分子的调控机理, 并概述了相应治疗药物或免疫疗法。AML的发生受多个信号通路的共同调控, 是信号通路交叉网络调控的结果, 关于AML细胞中信号通路的交叉还有待深入探究。此外, 各信号通路与免疫系统密切相关, 相互调节和影响, 共同调控AML的发生。靶向信号通路和免疫系统的联合治疗方案会给AML治疗带来新的前景, 具有巨大潜力。阐明AML的发病机制将为AML治疗药物的开发提供新的靶点和思路, 期待更有效的治疗方案或免疫疗法应用于AML患者的临床治疗。

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