综述

NF-κB信号与白血病

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摘要 核转录因子κB(nuclear factor-kappa B, NF-κB)存在于多种组织细胞中, 具有广泛的生物学活性, 在细胞的生存、增殖、分化以及炎性因子的产生中发挥着重要的作用。NF-κB信号通过调控靶基因的表达参与多种生理过程。NF-κB信号的失调可导致炎症反应和肿瘤等疾病的发生。研究表明, NF-κB信号在多种白血病细胞中, 特别是白血病干细胞中持续活化。NF-κB抑制剂可特异性地杀死白血病干细胞, 为潜在的抗白血病药物, 但由于其潜在的毒副作用, 使其临床应用受限。该文就NF-κB信号传导的分子机理、NF-κB信号通路在白血病发生发展中的作用以及NF-κB抑制剂在临床治疗白血病中的应用作一综述。

关键词 NF-κB; 白血病; 白血病干细胞; NF-κB抑制剂

NF-κB Signal and Leukemia

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Abstract Nuclear factor-κB (NF-κB) is broadly expressed in many types of tissue cells. It is involved in the regulation of a wide range of cell biological behaviors such as cell survival, proliferation, differentiation and inflammatory cytokine production. By its control of target gene expression, the NF-κB signal participates in the regulation of a variety of physiological processes. Deregulation of NF-κB signaling has been detected in large numbers of diseases, including infectious diseases and cancers, contributing to the pathogenesis and progression of such diseases. Studies have shown that NF-κB signaling is constitutively activated in a variety of leukemic cells, especially leukemia stem cells. Inactivation of NF-κB signaling can specifically kill leukemia stem cells while at the same time causing limited toxicity to normal hematopoietic stem cells, suggesting a potential target for designing novel anti-leukemia drugs. However, because of their potential for adverse side effects affecting other organs, the clinical application of NF-κB inhibitors is limited. In this review, we summarize the molecular mechanism by which the NF-κB signal is activated and transduced. We also discuss the role of NF-κB signaling in the initiation and progression of leukemia, as well as the potential application of NF-κB inhibitors in the clinical treatment of leukemia.

Key words NF-κB; leukemia; leukemia stem cell; NF-κB inhibitor

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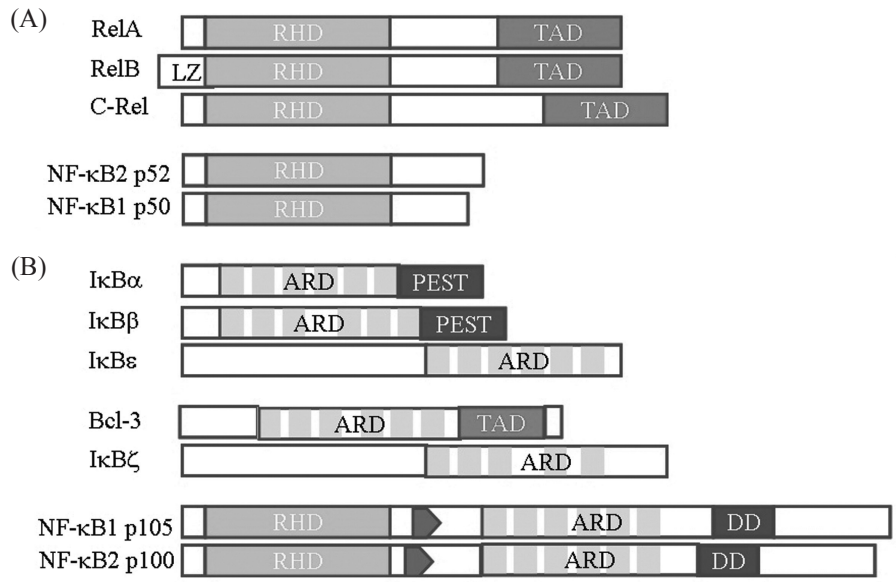
白血病是一种以某种未完全分化的幼稚造血细胞的大量增生为特征的血液系统恶性疾患, 占肿瘤总发病率的3%左右, 是儿童和青年中最常见的一种恶性肿瘤。目前, 大多数白血病的治疗仍然以大剂量化疗作为主要的手段。常用的联合化疗方案虽然可使50%~70%的患者达到缓解, 但由于缓解后患者体内的微小残留病变(minimal residual diseases, MRDs)的存在, 大多数患者经过一定缓解期后常常复发并产生耐药[1-3]。所以, 寻找新的抗白血病药物, 特别是能够清除MRDs的药物是白血病研究的重要课题。

NF-κB是一类具有多向转录调节作用的核蛋白因子, 广泛存在于多种组织细胞中, 主要调节细胞生存、增殖和分化等相关基因的表达。这主要包括: *Bcl2*、*Mcl1*、*A1*、*cFLIP*、*TRAF1*、*TRAF2*、*IAP1/2*及*Bcl-xL*等抗死亡基因, 肿瘤坏死因子-α(TNF-α)、白介素-1(IL-1)、IL-6和cyclooxygenase-2等炎性分子, 以及cyclin-D1和Myc等细胞增殖调节因子。NF-κB信号通过调节这些基因和分子的表达, 在免疫、炎症、氧化应激、细胞增殖、细胞凋亡等生理和病理过程中发挥重要的作用[4-7]。NF-κB信号的失调可导致炎症反应、肿瘤、自体免疫疾病及免疫系统失调等疾病的发生[8]。近些年, NF-κB作为肿瘤治疗的靶点引起科学家们的高度兴趣, 越来越多的研究证实, NF-κB抑制剂在治疗各类肿瘤包括白血病方面具有巨大的应用前景[9]。本文就NF-κB信号传导的分子机理、NF-κB信号通路在白血病发生发展中的作用及其在临床治疗白血病中的应用作一综述。

1 NF-κB的组成及其信号通路概述

1.1 NF-κB、IκB和IKK概述

NF-κB家族包括5个成员, 即RelA(p65)、RelB、c-Rel、NF-κB1(p105-p50)和NF-κB2(p100-p52), 它们的N末端均包含一个约300个氨基酸的高度同源序列, 称为Rel同源结构域(Rel homology domain, RHD), 该结构域介导其与DNA结合及二聚化。这5个成员可进一步分成两个亚家族。第一个亚家族包括RelA、



A: NF-κB家族共有RelA(p65)、RelB、c-Rel、p50(NF-κB1)和p52(NF-κB2)等5个成员。这5个成员可分成两个亚家族。第一个亚家族包括RelA、RelB和c-Rel这3个成员; 第二个亚家族包括p50(NF-κB1)和p52(NF-κB2)两个成员; B: IκB家族成员根据其功能和结构可分为典型性(包括IκBα、IκBβ和IκBε)、非典型性(包括Bcl3和IκBδ)以及NF-κB1和2的前体(p105和p100)三个亚家族。RHD: Rel同源结构域; TAD: 转录激活结构域; LZ: 亮氨酸拉链结构; DD: 死亡结构域; ARD: ankyrin重复结构域; PEST: 含PEST的序列。

A: NF-κB family consists of RelA(p65), RelB, c-Rel, p50(NF-κB1) and p52(NF-κB2), five members which can be further divided into two subfamilies depending on whether they contain a TAD or not. RelA(p65), RelB and c-Rel contain a TAD and thus belong to 1st subfamily, whereas p50(NF-κB1) and p52(NF-κB2) are cleavage products of p105(NF-κB1) and p100(NF-κB2) which lack a TAD, placing them in the 2nd subfamily; B: IκB family contains seven members which can be further divided into canonical (including IκBα, IκBβ and IκBε), non-canonical(including Bcl3 and IκBδ), and the precursors of NF-κB1/2(including p105 and p100) three subfamilies. RHD: Rel homology domain; TAD: transactivating domain; LZ: leucine zipper; DD: death domain; ARD: ankyrin repeat domain; PEST: proline-glutamate-serine-threonine-rich sequence.

图1 NF-κB和IκB家族成员

Fig.1 Members of the NF-κB and IκB family

RelB和c-Rel这3个成员, 它们均含有转录激活结构域(transactivating domain, TAD)。第二个亚家族包括p50(NF-κB1)和p52(NF-κB2)两个成员, 这两个成员分别是其相应的前体p105(NF-κB1)和p100(NF-κB2)的降解产物, 它们无TAD结构域(图1A)。TAD结构域能直接作用于转录元件而激活转录过程, 所以, 活化的NF-κB通常为一个第一亚家族成员和一个第二亚家族成员形成的异源二聚体, 如RelA/NF-κB1(p50)和RelB/NF-κB2(p52)异二聚体分别为介导经典和非经典NF-κB信号的主要活化成分; 而p50和p52形成的同源或异源二聚体不但缺乏转录激活活性甚至可能具有转录抑制活性[10-11]。

需要指出的是, 在无外界刺激时, NF-κB二聚体通常与IκB(inhibitor of kappa B)结合而被扣留于胞浆中。IκB蛋白家族成员有IκBα、IκBβ、IκBδ、IκBε、Bcl-3以及NF-κB1和2的前体(p105和p100), 这些家族成员的共同特点为都具有能与Rel蛋白相互作用的锚蛋白重复序列(ankyrin repeat domain, ARD), 其中部分IκB蛋白家族成员的C-端还含有PEST序列, 该序列可被其相应的E3泛素连接酶识别而介导其被蛋白酶体降解。7个IκB成员根据其功能和结构可分为典型性(包括IκBα、IκBβ和IκBε)、非典型性(包括Bcl3和IκBδ)以及NF-κB1和2的前体(p105和p100)等三个亚家族(图1B)。典型性和NF-κB1/2的前体主要起到抑制NF-κB活性的功能, 而非典型性IκB根据细胞不同可起到抑制或激活两种相反的功能[12-13]。

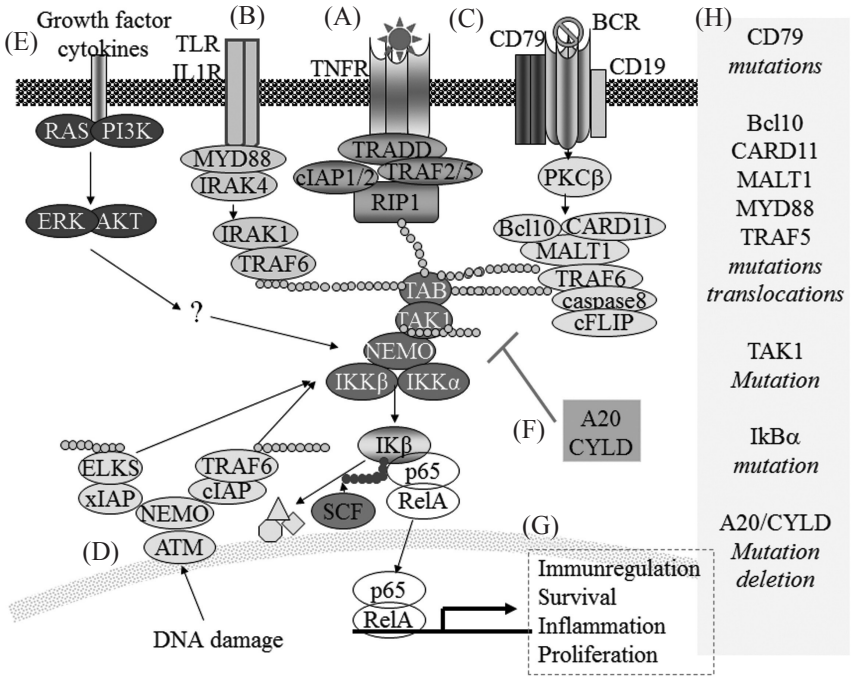
IκB的降解过程受到IKK激酶(IκB kinases)复合物的磷酸化调节。IKK激酶复合物磷酸化IκB蛋白, 使其暴露于蛋白酶体降解体系而被降解, 从而释放NF-κB复合体, 使其进入细胞核而诱导靶基因的表达。所以, IKK激酶复合物是NF-κB信号传导通路的关键性激酶。在细胞中存在着两种IKK激酶复合物, 分别由三个亚基组成。其中, 介导经典NF-κB信号通路的IKK复合物由具有催化活性的IKKα(IKK1)、IKKβ(IKK2)和一个有调节功能IKKγ(NEMO)组成。在该复合物中, IKKα和IKKβ都能磷酸化IκB, 但磷酸化位点不同; 然而, 具有调节功能的IKKγ其本身虽然没有催化活性, 但IKK复合物的酶活性依赖IKKγ亚单位的完整性。另外, 介导非经典NF-κB信号通路的IKK复合物由两个IKKα和一个NIK(NF-κB inducing kinase)组成。该复合物主要介导蛋白酶体对p100的剪切和NF-κB2的成熟和活化[14-15]。

1.2 NF-κB信号通路

NF-κB信号通路有两条主要的活化途径, 即经典的(以p50/RelA-p65异二聚体为主)和非经典的(p52/RelB异二聚体组成)NF-κB信号活化途径[16]。

经典的NF-κB信号主要是指通过激活IKK激酶复合物(由IKKα和IKKβ激酶及调节元件NEMO组成的三聚体)活化, 进而通过磷酸化诱导IκB降解而激活NF-κB的信号通路。在未受刺激的细胞中, NF-κB二聚体通常和IκB结合而被扣留在细胞浆中而不能发挥其转录调节活性。当受到特定刺激时, 细胞中将形成由接头蛋白(adaptor)和泛素化酶形成的复合物。在这些复合物中, 泛素化酶催化泛素化反应, 在接头蛋白上形成K63型线性泛素链。这种线性泛素链为TAK1激酶和其结合蛋白TAB及IKK激酶复合物提供可以共同结合的着床, 使得这些激酶聚集在一起。TAK1在TAB的作用下被激活。激活的TAK1进一步通过磷酸化IKKβ而激活IKK复合物。被激活的IKK复合物通过磷酸化IκB使其被泛素化连接酶b-TrCP识别, 并通过诱导被称为SCF的泛素化酶体系泛素化(K48)。被泛素化的IκB被蛋白酶体降解体系降解。从而解放NF-κB使其进入细胞核, 通过调控靶基因的表达而发挥其生物学效应[16](图2)。

已知有多种刺激可激活经典的NF-κB信号。比如, 炎性分子TNFα通过其特异性受体而募集TRADD、CIAP1/2、TRAF2/5和RIP1等组成的复合物到受体上, 接头蛋白RIP1被泛素化酶CIAP和TRAF泛素化, 通过TAK1激活IKK激酶[17](图2A); TLR和IL1R在其相应的配体诱导下通过接头蛋白MYD88将IRAK4、IRAK1和TRAF6复合物募集到受体上, 通过IRAK4激活IRAK1而诱导NF-κB信号活化[18](图2B); T细胞受体(TCR)、B细胞受体(BCR)及其辅助受体CD79a/b和CD19诱导PKCb的活化, 再可通过诱导CARD11:MALT1:Bcl-10复合物的形成而激活IKK/NF-κB介导的经典通路的活化[19](图2C); 化学药物或放射线等所引起的DNA损伤可通过ATM激酶诱导NEMO/CIAP/TRAF6或/和XIAP/ELKS复合物激活NF-κB信号(图2D); 此外, 许多生长因子和细胞因子如表皮生长因子(EGF)、造血干细胞生长因子(SCF)、粒单核细胞生长因子(GM-CSF)和IL-3等可通过PI3K/AKT和TAK1-IKK依赖或非依赖性通路诱导经典型NF-κB信号通路的活化, 其具体机制尚不清楚[16](图2E)。



A-E: 各类不同刺激活化经典型NF-κB信号通路的过程; F: 接头蛋白的K63泛素化对NF-κB信号的激活起到关键作用, 通常这种信号可被去泛素化酶A20和CYLD等通过去除泛素化链而抑制; G: NF-κB信号通过调节靶基因的表达而参与免疫调节、细胞生存、炎性反应和细胞增殖等生物学功能; H: NF-κB信号中, 一些重要调节分子在淋巴瘤和淋巴细胞白血病中发现有突变, 这些基因的突变造成NF-κB信号的持续过度活化, 在这些血液系统恶性肿瘤的发生和发展中起到至关重要的作用。

A-E: the activation of canonical NF-κB signaling pathway by many different types of stimulation; F: K63 ubiquitination of adaptor proteins is critical for NF-κB signal activation. Such signaling can be inactivated by A20 and CYLD deubiquitinases which remove unbiquitin from adaptor proteins. G: NF-κB signal regulates many biological activities including cell survival, cell proliferation, immunity and inflammation through modulation of expression of target genes; H: mutations of several key mediators in the canonical NF-κB signaling pathway are detected in many lymphomas and lymphocytic leukemias. Such mutations result in the constitutive activation of NF-κB signaling, which plays a critical role in the pathogenesis and progression of hematopoietic malignancies.

图2 经典的NF-κB信号通路

Fig.2 Canonical NF-κB signaling pathway

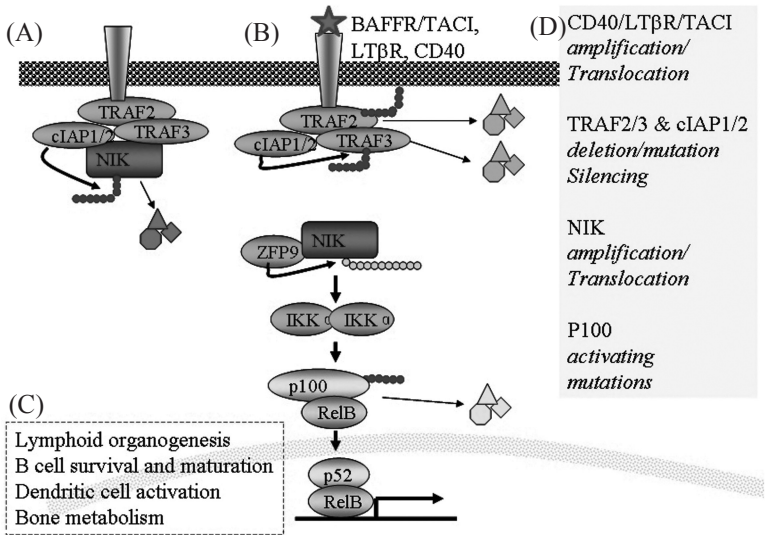
与经典途径不同, 非经典的NF-κB信号通路主要是指含有p100和RelB的二聚体的NF-κB的激活。NF-κB诱导激酶(NIK)为这一信号通路的关键激酶。由于NIK蛋白相对不稳定, 其在细胞中含量受TRAF2和CIAP1/2组成的泛素化调节复合物调节。在未受刺激的细胞中, NIK通常与TRAF2/CIAP1/TRAF3形成复合物。在这一复合物中, NIK非常不稳定, 多被CIAP1介导的K48泛素化蛋白酶体降解体系降解。所以其在细胞中含量极低, 不能诱导NF-κB信号的活化(图3A)。当细胞受到BAFF(B-cell activating factor)、LTβ(lymphotoxin β)、TWEAK(TNF-like weak inducer of apoptosis)、CD40配体和RANKL(receptor activatot of NF-κB ligand)等刺激后, CIAP通过泛素化降解TRAF2和TRAF3, 从而将NIK释放到细胞浆中, 导致细胞浆中NIK表达上调和活化, 从而激活IKKα磷酸激酶。活化的IKK进一步激活p100, 导致p100发生磷酸化依赖性剪切, 生成有活性的p52/RelB复合物并进入细胞核, 通过调控靶基因的表达而参与调节包括淋巴细胞生存、淋巴组织的发育和免疫细胞激活等重要生物学功能[20-21](图3B和3C)。

所以, NF-κB的经典信号通路和非经典信号通路的主要区别在于: 在NF-κB的经典信号通路中, IκB蛋白的降解使NF-κB二聚体得到释放; 而在NF-κB非经典信号通路中, 则是通过p100到p52的加工处理, 使信号通路激活[16]。

2 NF-κB信号通路在白血病发生发展中的作用

2.1 白血病干细胞是白血病发生、发展和复发的根源

白血病是一广义术语, 泛指所有的血液及骨髓



A: 未受刺激的细胞中, NIK通常与TRAF2/CIAP1/TRAF3形成复合物, 不能诱导NF-κB信号的活化; B: 当细胞受到刺激时, CIAP通过泛素化降解TRAF2和TRAF3, 从而将NIK释放到细胞浆中激活NF-κB信号; C: 非经典NF-κB信号的重要生物学功能; D: 在多发性骨髓瘤中通常检测到的基因突变。这些突变多由于过度激活非经典NF-κB信号, 在多发性骨髓瘤的发病中起关键作用。

A: without stimulation, NIK normally forms a complex with TRAF2/CIAP1/TRAF3, thus can't induce NF-κB activation; B: upon stimulation, CIAP mediates the ubiquitination and degradation of TRAF2 and TRAF3, thus releasing NIK to the cytoplasm and inducing NF-κB activation; C: the important biological function of non-canonical NF-κB signaling; D: mutations of several critical mediators of non-canonical NF-κB signaling pathways have been detected in multiple myelomas. Such mutations induce a constitutive activation of non-canonical NF-κB signaling which plays a key role in the pathogenesis of multiple myeloma.

图3 非经典NF-κB信号和多发性骨髓瘤

Fig.3 Non-canonical NF-κB signaling pathway and multiple myeloma

癌变, 其发病机制是由于基因突变而造成造血干细胞或祖细胞(hematopoietic stem cells or hematopoietic progenitors, HSCs或HPs)的恶性增殖、分化障碍及凋亡/坏死受抑的综合结果。根据增生细胞类型, 可将白血病分为淋巴系和髓系两类。按白血病细胞分化程度又可分为急性和慢性。急性白血病发病急, 骨髓和外周血中主要是原始细胞, 若不治疗病人常于半年内死亡; 慢性白血病虽然起病缓慢, 早期多无症状, 但仍是一种致死性疾病, 多数慢性白血病患者可生存3~5年[22]。

事实上, 白血病细胞(LCs)并非单一的一群细胞, 它由白血病干细胞(leukemia stem cells, LSCs)、白血病祖细胞(leukemia progenitors, LPs)和相对较成熟的白血病细胞(leukemia blasts, LBs)组成。LSCs是一小群特殊的LCs(占所有LCs的0.1%~1%)[23-24]。同正常HSCs一样, 它们增殖相对较慢、具有自我更新和无限增殖等特性。与LPs和LBs不同, 少量甚至单一LSCs即可在受体小鼠体内重建白血病。研究提示, MRDs中可能为富集的相对静止和耐药的LSCs[25-26]。所以, LSCs是白血病发生、发展和复发的根源。彻底清除患者体内LSCs是根除白血病复发乃至治愈白血病的最终目标[27]。

2.2 NF-κB信号在多种白血病细胞中持续活化

研究发现, NF-κB在多种类型的血液系统恶性肿瘤中均有持续活化, 包括急性髓系白血病(AML)、急性淋巴系白血病(ALL)、慢性髓系白血病(CML)、慢性淋巴系白血病(CLL)、多发性骨髓瘤(MM)、淋巴瘤和骨髓增生异常综合征(MDS)[28-33]。临床标本研究发现, 在骨髓细胞中, NF-κB的活性在MDS向白血病转化过程中明显增加[34]。在白血病患者的骨髓细胞中, NF-κB的活性明显高于正常骨髓细胞, 且其活性的高低与白血病细胞的数量成正比, 提示NF-κB的活化与白血病的发生相关[35]。2001年, Guzman等[29]研究发现, NF-κB活性在AML的LSCs中明显高于正常HSCs, 体外研究发现, LSCs对NF-κB抑制剂(MG-132, 蛋白酶体抑制剂或thalidomide和lenalidomide等)诱导的凋亡的敏感性明显高于正常HSCs。但在这些恶性细胞中, 造成NF-κB信号持续活化的原因目前尚不清楚。

在部分淋巴瘤和淋巴细胞白血病细胞中,

NF-κB信号的持续活化可能与该信号途径中某些重要调节分子发生突变有关。比如, 在MALT淋巴瘤和弥漫性大B细胞淋巴瘤(DLBCL)等部分恶性B细胞淋巴瘤细胞中, 发现有*MALT1*、*Bcl-10*和*CARD11*等基因突变[36-37]。在正常B和T淋巴细胞中, 这些基因编码的蛋白组成CARD11:MALT1:Bcl-10复合物, 通过IKK/NF-κB信号通路介导B和T细胞受体及抗原等激活的关键生存信号[38]。这些基因的突变常常引起IKK/NF-κB信号的持续过度活化, 可能是导致这种类型淋巴瘤发病的主要原因[39]。

在部分多发性骨髓瘤细胞中发现*TRAF3*、*NIK*、*cIAP1*/*cIAP2*和*TRAF2*等基因的突变[40]。这些基因所编码的蛋白为调节非经典NF-κB信号的关键成分。已知, NIK(MAP3K家族成员)非常不稳定。在未受刺激的正常细胞中, NIK通常被TRAF3募集到由泛素化连接酶cIAP1/cIAP2和TRAF2等组成的复合物中而被泛素化介导的蛋白酶体系统降解[21]。这些基因的突变通过影响NIK和TRAF3的结合、或降低cIAP1/cIAP2和TRAF2的表达, 从而导致NIK蛋白由于稳定性增加而过度聚集。NIK通过激活IKKα进一步将NF-κB2/p100加工, 使其成为NF-κB2/p52而引起该信号的持续活化[41]。

此外, 在部分B细胞慢性淋巴细胞白血病、B和T细胞淋巴瘤及Hodgkin's淋巴瘤中, 分别检测到*Bcl-3*、*NF-κB2*和*IκBα*等基因的突变。同时发现, 在DNA和RNA病毒感染相关的淋巴瘤和白血病中, 病毒蛋白LMP1(latent membrane protein 1)、vFLIP(病毒型cFLIP蛋白)和Tax等分别通过激活NIK和IKK而诱导NF-κB的活化, 分别在Epstein-Barr病毒、Kaposi肉瘤相关的疱疹(KSHV)及人类T-淋巴瘤病毒(HTLV)等诱导的淋巴细胞恶性肿瘤的发生发展中起重要作用[42-47]。

但在绝大多数淋巴细胞白血病和粒细胞白血病中, 尚未检测到NF-κB信号成分的突变。在这些白血病中, NF-κB信号的活化可能受白血病蛋白的调节, 同时, 白血病细胞及骨髓基质细胞分泌的炎性分子如TNF、IL6和GM-CSF等也可能是激活NF-κB信号的原因。Guzman等[29]的研究发现, 在AML患者的LSCs中IKK信号的调节异常可能是导致NF-κB信号持续活化的原因。但另外有研究发现, 在白血病细胞中, 许多炎性分子和造血细胞生长因子还可刺激IKK非依赖性NF-κB的持续活化[48]。

在25%~30%的成人和5%的儿童的B-ALL病人以及95%的CML病人中都有t(9;22)的染色体易位, 这导致了Bcr/Abl白血病融合蛋白的表达, 该蛋白是NF-κB的丝氨酸苏氨酸激酶[30]。Munzert等[30]发现, NF-κB信号在Bcr/Abl阳性B-ALL病人标本的白血病细胞中持续活化, 同样, 在CML病人的白血病细胞中也发现有持续激活的NF-κB信号, 但IKK活性却很低, 提示在这种细胞中NF-κB信号的激活可能不依赖于IKK。Bueso-Ramos等[31]研究证明, 由于CML的幼稚细胞中内在的NF-κB的持续活化, 导致了用酪氨酸激酶抑制剂STI571治疗的8位CML病人耐药和疾病的复发, 所以NF-κB的活化也是部分患者白血病细胞对化疗药物耐药的直接原因。在T-ALL中, NF-κB信号的活化可能为Notch信号激活的直接结果。Notch信号通过抑制NF-κB负调节因子CYLD的表达而引起NF-κB的持续激活。研究提示, NF-κB信号为Notch信号诱导的T-ALL发生和发展所必需。抑制NF-κB信号可引起T-ALL细胞的凋亡[49-51]。此外, 也有研究提示, 在AML细胞中, Notch可能通过诱导炎性分子的表达而诱导NF-κB的活化[52]。在B-CLL中, Furman等[33]和Cuni等[53]的研究均发现, NF-κB信号在B-CLL病人的淋巴细胞中持续活化。NF-κB信号的激活可能受骨髓微环境中C40和CD40L的旁分泌作用的调节。另外, PI3K和Akt/蛋白激酶B也可激活NF-κB信号[53-54]。

总之, 越来越多的证据证实, NF-κB信号通路的持续激活是白血病发生、发展及复发的重要特征, 在临床中抑制其活性将对白血病的治疗有重要作用[55](表1)。

3 NF-κB信号通路的抑制在临床治疗白血病中的应用

由于NF-κB在白血病中举足轻重的作用, 所以通过对NF-κB抑制来治疗白血病也越来越受到科学家们的关注。NF-κB的活化是多种信号途径综合的结果, 对NF-κB的抑制可以针对信号途径中的不同靶点, 其中IKK在NF-κB信号途径中起着至关重要的作用。IKK功能的丧失可引起NF-κB经典或非经典信号的失活, 因此IKK可以作为一个研制抗肿瘤药物的重要靶点[55-56]。许多科学家正致力于研究IKKβ的抑制剂, 已经有报道证明了其能够杀死肿瘤细胞和诱导早期细胞的凋亡, 如焦煤油衍生物PS-1145可抑制多发性骨髓瘤(MM)中NF-κB活性[57]; 苯胺嘧啶

碱衍生物AS602868有效地抑制AML中NF-κB的活性, 从而诱导白血病干细胞和外周血白血病幼稚细胞的凋亡[58]。一些抗炎药物如阿司匹林和水杨酸可以通过抑制IKK的活性来抑制NF-κB[59]。白藜芦醇、姜黄素、小白菊内酯、长春新碱、雷公藤甲素等一些天然化合物也已被证明可抑制IKK的活性[60-62]。

另一种途径是通过蛋白酶体抑制剂来直接抑制NF-κB的活化, 如MG-132、硼替佐米PS341、4-羟基查耳酮, 它们通过阻碍IκBs、NF-κB1/p105或NF-κB2/p100的降解来抑制NF-κB的活化[63-65]。其中, 硼替佐米已被FDA和欧洲监管机构(EMEA)通过可用于MM的临床治疗[64]。其他途径还包括抑制NF-κB的DNA结合活性, 如BAY11-7082可通过快速有效地阻止NF-κB与DNA的结合来诱导HTLV-1感染的T细胞系和成人早期ATL细胞的凋亡[66]; 白叶藤素是一种具有抗炎作用的藤本植物, Olajide等[67]发现其具有抑制NF-κB活性的作用, 这种抑制作用在于减少NF-κB的DNA结合活性。近年来研究表明, miRNA也可以通过锚定IKK或NF-κB亚基来抑制NF-κB信号通路, 从而给白血病的治疗提供的新的思路[68](表2)。

4 NF-κB抑制剂用于白血病临床治疗的潜在问题及解决方法

4.1 NF-κB抑制剂用于白血病临床治疗的潜在问题

由于NF-κB信号参与调节组织发育、组织再生、免疫反应和炎性反应等多种关键的生物学功能, 对维持许多组织功能的正常运行起着重要作用。所以, NF-κB抑制剂不但可以杀死肿瘤细胞, 也可以造成部分正常组织的严重损害。如肠道上皮细胞、肝脏细胞和淋巴细胞的生存多依赖于NF-κB信号[69-71]。NF-κB信号的抑制可引起由于严重的淋巴细胞减少所致的免疫缺陷, 肠道上皮损伤所致的胃肠反应以及由于肝脏细胞受损所致的肝脏功能异常[69,72]。更为重要的是, 在某些组织, 如肝脏和皮肤上皮组织, NF-κB具有抑癌功能。转基因小鼠研究发现, NF-κB信号的持续抑制可引起肝脏和皮肤上皮的恶性肿瘤的发生[70,73]。所以, 如何预防这些潜在的毒副作用

表1 NF-κB在白血病发生中的作用

Table 1 The function of NF-κB in the development of leukemia

白血病类型 Leukemia type	NF-κB参与白血病发病的机制 Mechanisms of NF-κB involved in the pathogenesis of leukemia
MM	The mutations of TRAF3, NIK, cIAP1/cIAP2 and TRAF2 lead to the aggregation of NIK protein to activate the non-canonical NF-κB signaling pathway
AML	Inflammatory molecules such as TNF-α secretion by leukemia cells excessively activate of the IKK-NF-κB signaling through its receptor activation; leukemia pathogenic genes constitutively activate IKK-NF-κB by inhibiting the negative regulators such as A20 and CYLD
T-ALL	Notch signaling constitutively activates NF-κB by suppressing the expression of negative regulator CYLD
CML	Leukemia fusion protein Bcr/Abl activates IKK-NF-κB signaling through MEKK1
B-CLL	PI3K-Akt and Bcr/Abl activate IKK-NF-κB signaling
B-cell lymphoma	The mutation of CD79, MALT1, Bcl-10 and CARD11 causes the activation of chronic B cell receptor signal and excessive activation of TLR signaling caused by the MyD88 mutation, then causes constitutively activation of the IKK/NF-κB signaling
Hodgkin's lymphoma	The mutation of IκBα gene induces the activation of NF-κB

表2 NF-κB信号通路抑制剂在治疗白血病的作用机制

Table 2 The mechanism of NF-κB inhibitors in clinical treatment of leukemia

抑制剂种类 Inhibitor species	作用机制 Mechanisms
PS-1145, AS602868, aspirin, salicylic acid and other anti-inflammatory drugs as well as resveratrol, curcumin, parthenolide, vincristine, triptolide and other natural compounds	Inhibit NF-κB signaling through inhibition of the activity of IKKβ
MG-132, boron bortezomib PS341, 4-hydroxy chalcone ketone	Inhibit NF-κB signaling by blocking the degradation of IκBs, NF-κB1/p105 or NF-κB2/p100
BAY11-7082, cryptolepine	Inhibit DNA binding of NF-κB

是临床应用NF-κB抑制剂治疗白血病需要解决的首要问题。

TAK1-IKK为TNFα等炎性分子诱导NF-κB活化的主要分子通路, 所以较多研究试图通过抑制TAK1或IKK活性来抑制NF-κB的活化, 从而达到治疗白血病的目的。但由于其他细胞因子或造血细胞生长因子可通过TAK1-IKK非依赖性途径激活NF-κB, 所以TAK1-IKK的抑制多不能达到抑制NF-κB活性的作用。此外, 除NF-κB外, TAK1-IKK还具有NF-κB非依赖性功能, 这些功能多对正常细胞的生存和功能所必须, 而白血病细胞多可通过其他通路代偿TAK1-IKK信号抑制所引起的生存和增殖障碍。我们的研究提示, TAK1-IKK抑制剂不但对部分白血病治疗无好处, 同时对正常组织的功能造成严重损失。所以, 直接抑制NF-κB蛋白的活性和功能可能会得到较特异杀伤白血病细胞的作用。

4.2 解决毒副作用的方法

正常情况下, NF-κB信号通过调节生存基因的表达, 在保护正常组织细胞免受炎性和应急分子等诱导的细胞凋亡和坏死中起着至关重要的作用。抑制NF-κB信号可引起细胞对炎性和应急分子等诱导的细胞凋亡和坏死过度敏感。NF-κB抑制剂的许多毒副作用可能与炎性分子特别是TNF-α所诱导的死亡信号有关[74-76]。此外, NF-κB抑制所引起的肝脏和皮肤细胞癌症的发生也与炎性分子所诱导的细胞死亡及其代偿性细胞过度增生有关[77]。这种代偿性过度增生主要是由于死亡细胞诱导的周围其他细胞分泌大量的炎性分子如IL-1-α、IL6和TNF-α等, 这些炎性分子通过诱导JAK/STAT和JNK等信号的活化而刺激残余细胞的过度增生[75,78-79]。因此, TNF-α等炎性分子活性的抑制有可能特异地保护NF-κB抑制剂对正常组织的毒副作用。

此外, 我们的研究发现, NF-κB抑制剂主要通过诱导凋亡而杀死LCs。而在正常造血干/祖细胞(HSCPs)中, NF-κB抑制剂还可诱导部分细胞发生RIP1/RIP3介导的necroptosis, 一种特殊的程序化坏死。值得重视的是, 与细胞凋亡不同, 坏死的细胞可诱导淋巴细胞和单核巨噬细胞在受损组织中的侵润。通过引起周围组织的强烈炎性反应, 坏死的细胞可进一步促进组织损伤。因此, 在不影响对LCs杀伤作用的前提下, 抑制细胞坏死也有可能特异地保护NF-κB抑制剂对正常组织的毒副作用。

5 展望

核因子NF-κB作为一种在各组织器官细胞中广泛存在的细胞转录调控因子, 在免疫、炎症等过程中发挥核心性的调控作用, 已经被大量的研究所证实。NF-κB信号通路在白血病发生发展中的作用也越来越受到重视。NF-κB抑制剂将成为新的抗白血病药物, 但其潜在的毒副作用不可忽视。通过对其信号通路更深入的研究, 找出产生毒副作用的根源, 从而来缓解毒副作用将是之后研究的重心。我们相信, 针对NF-κB信号通路的深入研究有望为白血病的早期诊断、预防和治疗提供新的、更为有效的作用靶点, 进而帮助人类早日解除白血病对人类生命和健康的威胁。

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