靶向CD30治疗经典霍奇金淋巴瘤的研究进展

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摘要 CD30属于肿瘤坏死因子受体超家族的一员, 是一种定位在细胞膜上的I型跨膜蛋白质。正常情况下CD30仅在部分活化的B淋巴细胞和T淋巴细胞中表达, 参与维持机体免疫系统的功能。值得注意的是, CD30在多种淋巴瘤亚群, 尤其是经典霍奇金淋巴瘤(classical Hodgkin's lymphoma, cHL)中高表达。高表达的CD30可通过多种机制影响cHL的进展, 例如激活NF-κB、MAPK-ERK信号通路, 影响肿瘤微环境等促进cHL肿瘤细胞的增殖和抗凋亡能力。CD30是cHL进展的重要驱动分子, 结合它在cHL肿瘤细胞膜上特异性高表达, 因此CD30是一个极具潜力的治疗cHL的靶点。CD30抗体偶联药物维布妥昔单抗已被批准用于复发难治性cHL的临床治疗, 其临床适应症不断扩大, 显著改善了cHL患者的预后。此外, 有多项研究正在尝试开发其他靶向CD30(例如CD30单抗、CD30 CAR-T细胞等)治疗cHL的方法, 部分临床前研究以及临床试验展示出令人振奋的疗效。该文将综述CD30在cHL中的表达、功能以及靶向CD30治疗cHL的研究进展。

关键词 细胞分化抗原30; 维布妥昔单抗; 嵌合抗原受体T细胞; 霍奇金淋巴瘤; 靶向治疗

Advances in Targeting CD30 for Classic Hodgkin Lymphoma Therapy

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Abstract CD30, a member of TNFR (tumor necrosis factor receptor) superfamily, is a type I transmembrane protein that is localized to cell membrane. CD30 is only expressed in some activated B lymphocytes and T lymphocytes and involved in regulating the function of immune system. However, it is upregulated in a variety of lymphomas, especially in cHL (classical Hodgkin's lymphoma). Highly expressed CD30 promotes cHL progression through various mechanisms, such as activation of NF-κB, MAPK-ERK signaling pathway, and influence of tumor microenvironment to promote the proliferation and anti-apoptosis of cHL tumor cells. As it is highly overexpressed in cHL tumors and promotes disease progression, CD30 is a promising therapeutic target for cHL. BV (Brentuximab vedotin), a kind of CD30 related antibody-drug conjugate, has been approved for the clinical treatment of relapsed/refractory cHL. The clinical indications of BV have been rapidly expanded and significantly improved the prognosis of cHL patients. In addition to BV, several studies are working to develop other CD30-targeted therapies for cHL, such as CD30 monoclonal antibodies and CD30 CAR-T cells. The effectiveness of these treatments has confirmed by many preclinical studies and clinical trials. This review will summarize the expression and function of CD30 in cHL and cover the advances in targeting CD30 for cHL.

Keywords CD30; Brentuximab vedotin; CAR-T; Hodgkin's lymphoma; targeted therapy

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霍奇金淋巴瘤(Hodgkin's lymphoma, HL)是来源于生发中心B细胞的恶性淋巴瘤, 约占每年新诊断淋巴瘤患者的10%[1]。HL有两个高发年龄阶段, 第一个发病高峰在15至34岁之间, 另一个是在60岁以后[2]。根据肿瘤细胞形态可将HL分为经典型霍奇金淋巴瘤(classical Hodgkin's lymphoma, cHL)和结节性淋巴细胞为主型霍奇金淋巴瘤(nodular lymphocyte predominant Hodgkin's lymphoma, NLPHL), 其中cHL是霍奇金淋巴瘤的主要类型(约占95%), 以单核的霍奇金淋巴瘤细胞和多核的里德–斯德伯格氏(Hodgkin Reed-stainberg, H-RS)细胞为特征, 镜下可见肿瘤细胞被淋巴细胞、嗜酸性粒细胞、中性粒细胞等炎性细胞包绕, 具有明显的嗜酸性包涵体样核仁[3]。大部分cHL患者经过化疗可治愈, 临床一线化疗方案主要包括两种: 第一种是多柔比星、博来霉素、长春碱和达卡巴嗪的联合使用(adriamycin, bleomycin, vinblastine, dacarbazine, ABVD), 第二种为博莱霉素+依托泊苷+阿霉素+环磷酰胺+长春新碱+丙卡巴肼+泼尼松(bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, BEACOPP)的联合使用。值得注意的是, 约30%的患者因化疗效果不好进展为复发难治性霍奇金淋巴瘤(relapse and refractory Hodgkin's lymphoma, R/R HL), 其中约50%的R/R HL患者可通过自体造血干细胞移植(autologous stem cell transplantation, ASCT)获得长期缓解[4]。然而对于分期较晚、复发风险较大以及不可移植或移植后复发的患者, 如何实现长期疾病控制以及改善预后仍然是一个巨大的挑战。

细胞分化抗原30(cluster of differentiation 30, CD30)高表达是cHL肿瘤细胞重要的分子特征, 因此是一个极具前景的治疗cHL的靶点[5]。靶向CD30的抗体偶联药物维布妥昔单抗(Brentuximab vedotin, BV)于2011年批准上市, 显著改善了cHL患者的预后, 其治疗cHL的适应症包括: 自体造血干细胞移植失败或不适合自体造血干细胞移植、接受过至少2种化疗方案无效的cHL患者, 复发或进展高风险的cHL患者接受造血干细胞移植后的巩固治疗以及联合化疗用于复发难治性cHL的初治[6]。除了BV外, 目前还开展了多个以CD30为靶点治疗cHL的临床前研究和临床试验, 这些研究可能为cHL治疗带来新的选择和思路[7-8]。本文将对CD30在cHL中的表达、功能以及CD30相关的靶向治疗进行综述。

1 CD30结构及生物学功能

1982年SCHWAB等[9]利用能特异性结合HL肿瘤细胞的单克隆抗体鉴定出CD30。CD30又称肿瘤坏死因子受体超家族成员8(tumor necrosis factor receptor superfamily, member 8, TNFRSF8), 是属于肿瘤坏死因子受体(tumor necrosis factor receptor, TNFR)超家族的I型跨膜蛋白(图1)。CD30胞外段由6个半胱氨酸重复序列组成, 与TNFR超家族其他成员有高度同源性[10]。CD30胞外段可以被蛋白水解酶切割成可溶性的CD30片段(soluble CD30, sCD30)并分泌至血浆中[11]。CD30胞内段有3个具有独立功能的结构域(D1~3), 其中D2和D3结构域可以与肿瘤坏死因子受体相关因子(TNF receptor-associated factor, TRAF)结合激活NK-κB通路, 而D1则无需结合TRAF可直接激活NF-κB信号通路[12]。CD30的配体为CD30L, 又称细胞分化抗原153(cluster of differentiation 153, CD153), 是属于肿瘤坏死因子(tumor necrosis factor, TNF)家族的II型跨膜蛋白质。CD30与配体结合后可以形成三聚体, 发挥其生物学作用[13]。

CD30在正常组织中表达水平较低, 仅在部分活化的B淋巴细胞和T淋巴细胞中表达, 包括淋巴结和胸腺中的记忆性T细胞(CD45RO$^+$ T)亚群以及位于生发中心边缘和滤泡外区域的少数受刺激的B淋巴母细胞[14]。AMAKAWA等[15]发现, *CD30*敲除后小鼠胸腺变大, 循环CD4/CD8双阳性T细胞增加, 但*CD30*敲除对记忆性T细胞功能以及T辅助细胞依赖的B细胞类别转化没有影响。另外一项研究发现, CD30-OX40共缺陷小鼠对抗原刺激的初级免疫应答正常, 但是产生二次抗体的能力受损, 失去持续的生发中心反应[16]。这些研究提示CD30在免疫监视以及T、B淋巴细胞类别转化中发挥作用。CD30还可以调节T淋巴细胞免疫应答, 作为次级T细胞应答的共刺激受体促进外周T细胞的增殖, 刺激T细胞产生白细胞介素-2(interleukin-2, IL-2)、肿瘤坏死因子(tumor necrosis factor, TNF)、干扰素-γ(interferon-γ, IFN-γ)等细胞因子[17]。CD30/CD30L通过调节辅助性T细胞(T helper cells, Th)在自身免疫和炎症过程中发挥作用[18]。CD30/CD30L还可抑制CD4$^+$ T细胞介导的同种异体移植排斥反应[19]。综上, CD30在维持机体免疫系统功能中发挥重要作用。

CD30在多种淋巴瘤, 包括cHL、间变大细胞淋

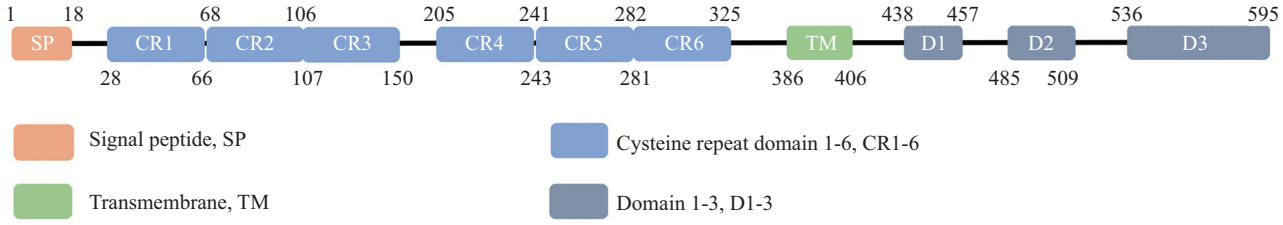

图1 CD30结构示意图

Fig.1 Schematic diagram of CD30 protein structure

巴瘤(anaplastic large cell lymphoma, ALCL)、外周T细胞淋巴瘤(peripheral T-cell lymphoma, PTCL)、蕈样真菌病(mycosisfungoides, MF)和弥漫性大B细胞淋巴瘤(diffuse large B-cell lymphoma, DLBCL)等细胞中表达上调, 其中在cHL和ALCL中表达特异性最高[20]。有意思的是, CD30在不同类型淋巴瘤中的作用也不相同, CD30抗体Ki-1可以抑制ALCL细胞增殖, 促进细胞凋亡, 但是对HL细胞没有影响[21-22]。转录组学分析发现, CD30激活后HL和ALCL细胞的基因转录水平也存在显著差异[23]。有研究者认为CD30在不同肿瘤中功能的多效性可能是胞内段不同区域介导的, 但具体机制仍然需要进一步研究。

2 CD30在cHL中的表达及功能

2.1 CD30在cHL中的表达

cHL的H-RS细胞高表达CD30, 因此可以根据CD30的表达差异区分NLPHL和cHL[24]。此外, cHL患者血清中sCD30水平可作为预后和治疗反应不良的标志[25]。CD30和JUNB形成的正反馈通路可能是CD30在cHL中高表达的分子基础。一方面, CD30可以激活细胞外信号调节激酶–丝裂原活化蛋白激酶通路(extracellular signal regulated kinase-mitogen activated protein kinases, ERK-MAPK)上调原癌基因*JUNB*(JunB proto-oncogene)的表达, 另一方面, JUNB反过来结合*CD30*启动子上的CpG岛抑制其DNA甲基化, 促进CD30表达[26]。研究人员发现接受CD30 CAR-T细胞治疗的cHL患者肿瘤细胞中CD30表达水平降低, 但分子机制目前尚不清楚[27]。类似的现象在接受克拉屈宾(Cladribine)治疗的T幼淋巴细胞白血病(T cell prolymphocytic leukaenia, T-PLL)患者和接受BV治疗的ALCL患者中也会出现[28-29]。

2.2 CD30在cHL中的功能及机制

核因子-κB(nuclear factor kappa-B, NF-κB)通路介导CD30在cHL中的生物学作用, CD30能够招募肿瘤坏死因子受体相关因子1/2/5(TNF receptor associated factor 1/2/5, TRAF1/2/5), 激活下游NF-κB通路, 促进cHL细胞的存活[30-31](图2)。表达不含胞内段的CD30截短体可阻断NF-κB活化并下调IL-13表达, 诱导cHL细胞凋亡[32]。有研究发现CD30介导的热休克蛋白90(heat shock protein 90, HSP90)表达可能是调控cHL细胞信号通路的中心枢纽, CD30可以通过促进热休克因子1(heat shock factor 1, HSF1)磷酸化诱导HSP90表达, 敲减CD30或者HSP90抑制cHL细胞系NF-κB、丝氨酸苏氨酸蛋白激酶(serine/threonine-protein kinase, AKT)和信号转导及转录激活蛋白(signal transducer and activator of transcription, STAT)通路[33]。此外, 使用CD30的抗体刺激霍奇金淋巴瘤细胞可以上调C-X-C基序趋化因子受体4(chemokine C-X-C-motif receptor 4, *CXCR4*)的mRNA水平, 增强其对CXCR4配体C-X-C基序趋化因子配体12(chemokine C-X-C-motif ligand 12, CXCL12)的趋化活性[34]。CD30对这些通路及分子的调控可能与cHL细胞的恶性转化有关。

除了能够直接促进cHL肿瘤细胞恶性转化外, CD30还可以通过影响肿瘤微环境促进cHL的进展。研究发现, H-RS细胞可以通过CD30相关的相互作用抑制T细胞的增殖和活化。当CD30存在时, 与H-RS细胞共培养的T细胞不能表达CD25和CD26且分泌IL-2。添加外源性IL-2或用抗CD30预处理H-RS细胞可以促进T细胞增殖[35]。由此可见, H-RS细胞和T细胞之间存在CD30依赖的相互作用, 这种细胞间的互作能够抑制肿瘤免疫, 促进肿瘤细胞的生长和存活。

2.3 可溶性CD30和外泌体上CD30在cHL中的作用

CD30可以通过两种方式分泌到细胞外, 一种是被解整合素金属蛋白酶(a disintegrin and metalloprotease, ADAM)(主要是ADAM10)切割脱落

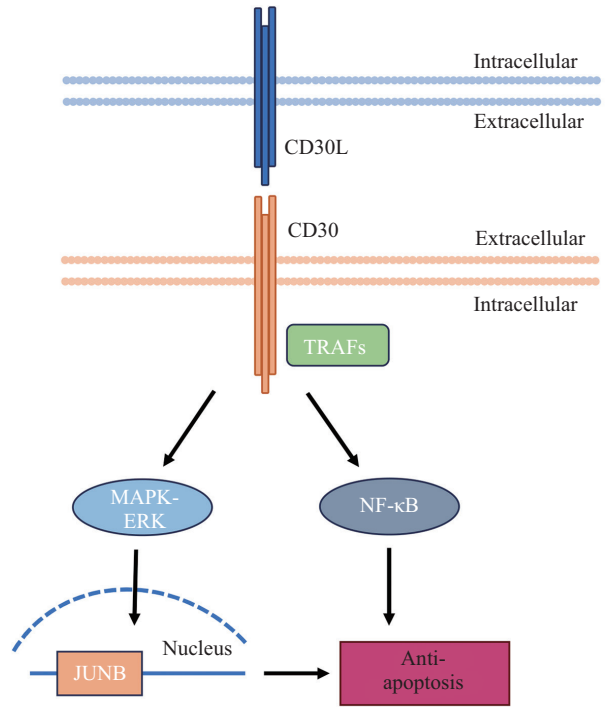

图2 CD30在经典霍奇金淋巴瘤细胞中的作用机制示意图

Fig.2 Schematic representation of the mechanism of CD30 in classical Hodgkin's lymphoma

成sCD30, 另一种是可作为一个完整的CD30跨膜蛋白质通过外泌体囊泡(extracellular vesicles, EVs)分泌至细胞外。目前sCD30在cHL进展中的作用尚不清楚, 但人们发现抑制sCD30切割可以增强CD30靶向治疗效果, 金属蛋白酶抑制剂BB-3644可显著降低cHL异种肿瘤小鼠模型血液中sCD30的浓度, 提高CD30靶向治疗的疗效[36]。然而, 由于BB-3644的特异性不高, I期剂量递增临床研究因发现存在剂量依赖的肌肉骨骼毒性被终止。因此, 选择特异性更强的ADAM10抑制剂, 如LT4、INCD8765、ADAM10抗体可能副作用更小[37]。ADAM10抑制剂与BV联合使用能够提高BV的抗肿瘤效果[38]。值得注意的是, 在cHL中抑制ADAM10可能是一把双刃剑, 它一方面改善了CD30靶向治疗的疗效, 另一方面可能激活促癌的上皮细胞[39]。另外一研究表明sCD30不会影响CD30 CAR-T细胞的抗肿瘤效果, 这可能是由于CD30 CAR-T细胞主要识别细胞膜上的CD30造成的[40]。EVs上表达的CD30与肿瘤微环境中CD30L阳性的支持细胞存在功能互作, EVs相关的CD30可以影响BV在cHL患者中的疗效。具体的机制可能是BV不仅靶向杀伤cHL肿瘤细胞, 而且对装载CD30阳性EVs的肿瘤周围支持细胞也有杀伤效果[41]。

3 靶向CD30治疗cHL

CD30在正常组织细胞中的表达仅限于小部分活化的T、B淋巴细胞, 但在cHL的H-RS细胞上特征性高表达, 因此是一个理想的治疗靶点[42]。目前开发了多种针对CD30的治疗方法, 包括CD30抗体、CD30抗体偶联药物、CD30 嵌合抗原受体T细胞疗法(chimeric antigen receptor T-cell immunotherapy, CAR-T)细胞等(图3)。

3.1 CD30单克隆抗体

目前开展了多个利用CD30单克隆抗体治疗cHL的临床试验, 但治疗效果不尽人意。1992年FALINI等[43]利用鼠源性的抗CD30单克隆抗体Ber-H2治疗cHL, 尽管Ber-H2能够特异性结合H-RS细胞, 但是由于它识别的区域不是与配体结合的位点, 因此在小鼠淋巴瘤模型中无明显的杀伤效果。此外, 在6例接受该抗体治疗的患者中没有观察到有效的抗肿瘤效果[44]。研究人员在该抗体的基础上开发了小鼠–人嵌合抗体SGN-30以及人源化的抗体MDX-060。临床前研究发现, SGN-30和MDX-060均能有效抑制cHL细胞生长, 在小鼠肿瘤模型中也能观察到肿瘤消退和生存率提高。临床试验表明SGN-30耐受性良好, 但临床获益一般, 38例复发或难治性cHL患者中, 11例患者病情稳定(stable disease, SD), 没有

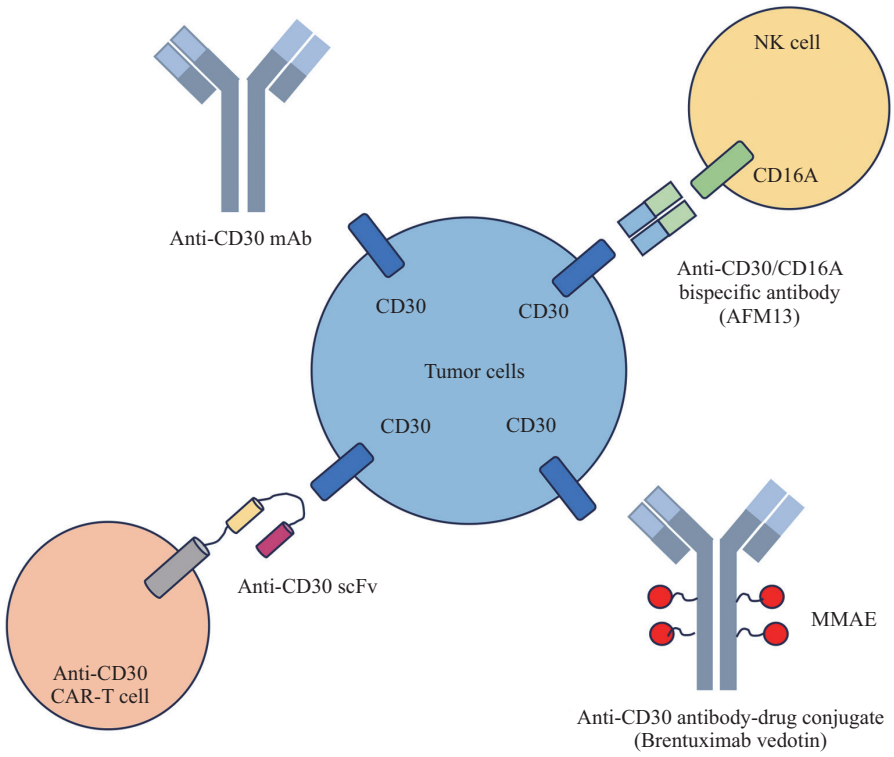

图3 靶向CD30治疗经典霍奇金淋巴瘤的示意图

Fig.3 Schematic diagram of targeting CD30 for the treatment of cHL

患者达到完全缓解(complete response, CR)或部分缓解(partial remission, PR)[45]。MDX-060的I期和II期临床试验共招募72例HL患者, 其中25例患者达到SD, 2例PR, 4例CR, 各组中位病情缓解持续时间均小于6个月。人们分析CD30单抗治疗效果不佳的原因可能与肿瘤抗原结合性能差, 可溶性CD30中和以及抗体依赖的细胞杀伤能力在免疫抑制的HL患者中受限有关[46]。人们也测试了SGN-30联合化疗的临床治疗效果, 在一项II期临床试验中使用SGN-30联合吉西他滨、长春瑞滨和聚乙二醇化脂质体阿霉素(gemcitabine, vinorelbine, polyethylene glycol liposome doxorubicin, GVD)治疗30例复发的cHL患者, 由于5名患者在治疗过程中出现肺炎导致临床试验过早结束。除了明显的肺部毒性外, 与单独使用GVD相比, SGN-30联合使用组的预后无明显改善[47]。

3.2 维布妥昔单抗

虽然CD30单克隆抗体没有达到预期疗效, 但是CD30相关的抗体偶联药物BV在cHL的临床治疗中获得了巨大的成功。BV的主要结构是通过一个蛋白酶体可切割的连接器将CD30单克隆抗体与细胞毒性小分子药物单甲基澳瑞他汀E(Monomethylauristatin E, MMAE)偶联在一起[48]。BV发挥抗肿瘤作用的机制如下: (1) BV中的CD30抗体识别cHL细胞上的CD30; (2) 细胞通过内吞作用将BV内化至溶酶体; (3) BV在溶酶体内水解释放MMAE; (4) MMAE抑制微管聚合, 通过阻滞G_2/M期诱导细胞凋亡。此外, MMAE在细胞死亡后还可以释放到肿瘤微环境中杀伤周围肿瘤细胞[20]。

BV在cHL中的疗效及安全性已经在临床试验和临床治疗中得到验证。BV最早的临床研究是追溯到2010年由YOUNES等[49]发表的I期临床试验数据(NCT00430846), 该研究初步探索了BV在复发难治性CD30阳性淋巴瘤治疗中的使用剂量以及安全性。接着在一项招募了102例HL患者的I期临床试验中首次证实了BV的疗效, 客观缓解率(objective response rate, ORR)为75%, 其中34%的患者达到CR[50]。2011年美国食品药品监督管理局(Food and Drug Administration, FDA)批准BV可用于治疗自体造血干细胞移植失败或不适合自体造血干细胞移植、接受过至少2种化疗方案无效的cHL患者。此后BV的适应症不断扩大, 先后获批用于复发或进展高风险cHL患者接受造血干细胞移植后的巩固治疗, 也可联合化疗方案用于复发难治性cHL的初治[51]。

2020年中国国家药品监督管理局正式批准BV用于治疗成人CD30阳性的复发或难治性cHL。真实世界临床治疗的回顾性研究同样证实了BV单用或联用对复发难治性HL的疗效[52-54]。研究显示, BV疗效与CD30表达水平无相关性[55]。BV安全性较好, 常见的不良反应包括中性粒细胞减少、血小板减少、贫血、周围神经病、疲劳、上呼吸道感染等, 可通过减量或停药使症状缓解[56]。

3.3 CD30 CAR-T细胞

CAR-T在血液肿瘤的治疗中取得了巨大的成功, 它的原理是将抗体的可变区与T细胞受体恒定区结合, 在共刺激分子的协同作用下, 使T细胞同时具有肿瘤特异性识别和杀伤功能[57]。HOMBACH等[58]首次对CD30 CAR-T细胞的安全性和有效性进行研究。在小鼠模型中CD30 CAR-T细胞不能靶向CD30/CD34阳性的正常造血细胞和活化淋巴细胞, 安全性较好, 但由于当时设计的CAR分子缺乏共刺激信号, 因此细胞杀伤效果一般。第二代和第三代(携带共刺激信号)的CD30 CAR-T细胞在cHL体外及小鼠体内模型中展现了强大的肿瘤杀伤能力[59]。一项临床试验募集了6例复发或难治性cHL患者接受CD30 CAR-T治疗, 尽管患者对CAR-T细胞有良好的耐受性, 但临床效果有限, ORR为33%[60]。2014年解放军总医院招募了18例复发难治性霍奇金淋巴瘤患者进行CD30 CAR-T细胞输注治疗, 临床试验结果表明CD30 CAR-T细胞耐受性较好, 客观缓解率为39%(7/18), 疾病控制率为72%(13/18), 无疾病进展时间平均为9.5个月[61]。在随后的临床研究中, 人们发现CD30 CAR-T细胞联合清除淋巴细胞的化疗可以显著改善CAR-T细胞的疗效[8]。一项临床试验招募了32例复发难治性cHL患者接受CD30 CAR-T细胞联合清除淋巴细胞化疗, 其中ORR为72%, 19例病人(59%)达到CR。此外, 双靶点的CAR-T细胞(CD30/CD19)在cHL中也有较好的疗效[62]。上述研究表明CD30 CAR-T细胞可能是复发/难治性cHL的一种新的治疗选择。

3.4 其他疗法

双特异性细胞衔接器由两种scFv抗体片段融合而成, 分别结合免疫细胞和肿瘤细胞表面分子, 在肿瘤细胞周围招募并活化免疫细胞, 诱导免疫细胞对肿瘤细胞的杀伤。20世纪90年代研究人员开发了一种靶向CD30和CD64(巨噬细胞和单核细胞上的fc-γ受体)的双特异性抗体H22xKi-4, 该抗体通过抗体依赖性细胞介导的细胞毒作用对CD30阳性肿瘤细胞进行杀伤, 10名难治性cHL患者接受了该抗体治疗, 有4例达到SD, 1例病人CR, 3例PR[63]。接着人们开发了同时靶向cHL肿瘤细胞表面CD30和NK细胞表面CD16A的双特异性细胞衔接器AFM13, 它可以招募NK细胞杀伤CD30阳性的肿瘤细胞, 在细胞和动物水平展示出很好的抑瘤效果[64]。临床研究发现, 虽然AFM13单独使用对cHL治疗效果有限, 但AFM13与Pembrolizumab联合治疗cHL的ORR高达83%[7-65]。临床前研究结果显示, AFM13与成人血液或脐带血自然杀伤细胞(natural killer cell, NK)联合使用也有比较好的效果[66]。

H-RS细胞同时表达两种肿瘤坏死因子受体家族成员CD30和CD137。因此, 研究人员开发了一种可以同时结合CD30和CD137的双特异性抗体。该抗体对肿瘤细胞的特异性较高, 可以诱导抗体依赖和细胞介导的细胞毒性, 有望成为一种新型HL治疗药物[67]。

除了BV外, 人们还开发了其他抗体偶联药物。在一项早期研究中, 人们利用Ber-H2抗体偶联皂草素。虽然4名接受该药物治疗的患者肿瘤进展受到抑制, 但治疗反应持续时间有限[68]。Ki-4/dgA是CD30单抗和去糖基化蓖麻毒素a链的偶联物, Ki-4/dgA可以使cHL小鼠模型的平均生存时间从42天(未治疗组)延长到132天(治疗组)以上[69]。15例HL患者接受Ki-4/dgA治疗, 其中1例病人PR, 1例轻度缓解[70]。SCHNELL等[71]开发了一种放射免疫偶联物, 使用碘-131标记CD30小鼠单克隆抗体Ki-4。22例cHL患者接受了^{131}I-Ki-4的治疗, 尽管有6例反应(1例CR和5例PR), 但7例患者在治疗后出现严重血液学毒性, 导致该研究停止。

4 总结与展望

本文综述了CD30在cHL中的表达、肿瘤生物学功能、分子机制以及靶向CD30治疗cHL的最新进展。CD30高表达是cHL肿瘤细胞的重要分子特征, 临床上可根据CD30表达差异区分cHL和一些其他类型淋巴瘤。CD30可通过配体–受体结合激活下游信号通路、调控肿瘤微环境等分子机制促进cHL肿瘤细胞的增殖和存活。深入研究CD30在cHL中的表达调控和促癌机制, 可为cHL的治疗提供新的靶点, 具有重要的理论及转化价值。作为一个在cHL细胞

特异性高表达并发挥促癌作用的膜蛋白, CD30被认为是一个理想的肿瘤治疗靶点。研究人员开发了多种靶向CD30治疗cHL的策略, 其中抗体偶联药物BV在cHL的治疗中取得了巨大的成功, 显著改善了cHL病人的预后(表1)。

尽管关于CD30与cHL相关的基础及临床研究

表1 部分靶向CD30治疗cHL的临床前及临床研究

Table 1 Some preclinical studies and clinical trials using CD30 as a therapeutic target

治疗方式 Intervention	药物名称 Drug	治疗阶段 Study type	治疗效果 Efficacy results	参考文献 References
CD30 monoclonal antibody	SGN-30	cHL cell lines (preclinical studies)	Inhibited tumor cells growth	[72]
		38 R/R cHL patients (clinical trials)	11 patients achieved SD, no patients achieved CR or PR	[45]
	SGN-30 and GVD	30 R/R cHL patients (clinical trials)	5 patients developed pneumonia and the clinical trial was terminated	[47]
	MDX-060	72 lymphoma patients (clinical trials)	25 patients achieved SD, 2 patients achieved PR and 4 patients achieved CR	[46]
BV	BV	42 R/R cHL patients (clinical trials)	ORR was 36%, CR was 21% and PR was 14%. Median duration of response was 9.7 months	[49]
	BV	102 R/R cHL patients (clinical trials)	ORR was 75% and CR was 34%. Median PFS was 5.6 months	[50]
	BV	182 R/R cHL patients (retrospective study)	1-year OS was 83% in BV group. Potential adverse effects included peripheral sensory neuropathy, neutropenia and lymphocytopenia	[53]
CD30 CAR-T cells	The first generation of CD30 CAR-T cells	cHL cell lines (preclinical studies)	The CAR-T cells could not kill tumor cells effectively	[58]
	The third generation of CD30 CAR-T cells	cHL cell lines and mouse models (preclinical studies)	The CAR-T cells could kill tumor cells and inhibited tumor growth	[59]
	The second generation of CD30 CAR-T cells	6 R/R cHL patients (clinical trials)	The CAR-T cells were well-tolerated in patients. ORR was 33%	[60]
	The second generation of CD30 CAR-T cells	18 R/R cHL patients (clinical trials)	The CAR-T cells were well-tolerated in patients. ORR was 39% and PFS was 9.5 months	[61]
Immunoconjugates	Ki-4.dgA	cHL cell lines and mouse models (preclinical studies)	Ki-4.dgA inhibited tumor growth and prolonged the survival of mice	[69]
		15 R/R cHL patients (clinical trials)	6% patients achieved PR and 12% patients achieved SD	[70]
	^{131}I-Ki-4	22 R/R cHL patients (clinical trials)	1 patient achieved CR and 5 patient achieves PR. Severe hematological toxicity occurred in 7 patients	[71]
Bispecific tandab antibody	H22 x Ki-4	10 R/R cHL patients (clinical trials)	4 patients achieved SD, 1 patient achieved CR, 3 patients achieved PR	[63]
	AFM13	cHL cell lines (preclinical studies)	AFM13 could kill tumor cells effectively	[64]
	AFM13 and pembrolizumab	30 R/R cHL patients (clinical trials)	ORR was 88%, 37% CMR and 47% PMR	[7]

R/R cHL: 复发/难治经典型霍奇金淋巴瘤; ORR: 客观缓解率; PR: 部分缓解; CR: 完全缓解; CMR: 完全代谢缓解; PMR: 部分代谢缓解; OS: 总生存; PFS: 无进展生存。

R/R cHL: recurrent/refractory classic Hodgkin lymphoma; ORR: objective response rate; PR: partial response; CR: complete response; CMR: complete metabolic response; PMR: partial metabolic response; OS: overall survival; PFS: progression free survival.

取得了一些进展, 但目前还有许多问题有待研究推进。首先, 目前有效的CD30靶向治疗策略主要是将CD30作为一个肿瘤识别标志物, 例如抗体偶联药物以及CD30 CAR-T等。而直接靶向抑制CD30通路对cHL的治疗效果有限, 其中的机制需要进一步研究。其次, 尽管早在上世纪90年代就开展了CD30在cHL中的研究, 但我们对CD30在cHL中的调控机制、肿瘤生物学作用及分子机制仍然了解不多, 尤其是缺乏多组学研究。还有, CD30除了在细胞膜上表达, 还能够以sCD30和外泌体的形式分泌至胞外, 这类形式的CD30在cHL的靶向治疗中的作用仍然不是很清楚。最后, 尽管抗体偶联药物BV在cHL的治疗中取得了很大的进展, 但其临床适应症还需进一步拓展, 其他靶向CD30的治疗策略也需推进临床转化。

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