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# 单克隆抗体的肿瘤免疫治疗进展

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**摘要** 单克隆抗体是由单个B细胞克隆产生的抗体, 这些抗体都与特定的抗原特异性结合, 具有亲和力高、特异性好的特性, 被广泛应用于疾病的诊断和治疗。肿瘤是机体易感细胞在各种致癌因子长期相互作用和多种基因突变过程中导致的过度增生, 具有致命性和难治性, 严重影响了人类生命和生活, 加重了国家医疗卫生负担。单克隆抗体能够通过抑制细胞信号转导、直接细胞毒性作用、免疫效应作用、免疫检查点阻断、药物载体作用等一系列机制来抑制肿瘤的生长, 表现出了令人鼓舞的肿瘤治疗效果。随着抗体发现技术的不断发展和升级, 以及各种形式的抗体如片段抗体、双特异性抗体、TCR模拟抗体、糖基化抗体的出现和深入研究, 在未来, 单克隆抗体必将在肿瘤免疫治疗领域大放异彩。

**关键词** 单克隆抗体; 肿瘤; 肿瘤免疫; 肿瘤免疫治疗

# Progress in Tumor Immunotherapy with Monoclonal Antibodies

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**Abstract** mAbs (monoclonal antibodies) are immunoglobulins generated from a single B cell clone. These antibodies exhibit high affinity and specificity by binding selectively to distinct antigens, which have been broadly applicated in disease diagnosis and therapeutic interventions. Tumorigenesis ensues from prolonged interactions of susceptible cells with various oncogenic factors and the occurrence of multiple genetic mutations. Tumors, characterized by their lethality and refractory nature, significantly impact human life and well-being, exacerbating the overall national healthcare burden. Monoclonal antibodies excute their anti-tumor effects through variety

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of mechanisms, including the modulation of cell signaling pathways, direct cytotoxicity, engagement of immune effector functions, immune checkpoint blockade, and functioning as carriers for delivery of chemotherapeutic drugs, which display great efficacy in controlling tumor growth. With the evolvement of antibody discovery technologies, coupled with the emergence and in-depth exploration of diverse antibody formats such as antibody fragments, bispecific antibodies, TCR-mimic antibodies, and glycosylated antibodies, the future holds substantial promise for monoclonal antibodies to make significant strides in the realm of cancer immunotherapy.

**Keywords** monoclonal antibodies; tumor; tumor immunity; tumor immunotherapy

1890年, BEHRING和KITASATO[1]首次在白喉动物模型研究中发现了一种存在于血液中的中和物质并将之描述为抗体(antibody)。在接下来的一个世纪里, 一些重要的科学进展为使用抗体治疗癌症奠定了重要基础。HEIDELBERGER和AVERY[2]鉴定抗体为能够识别特定抗原的蛋白质。在1947年, FAGRAEUS[3]证明抗体是由适应性免疫系统中的浆细胞产生的。随后, NOSSAL等[4]证明了克隆选择学说, 即单个B细胞克隆产生单一种特异性的抗体, 被定义为单克隆抗体(monoclonal antibodies, mAbs)。随着杂交瘤等各种技术的建立, 人们开始研究利用单克隆抗体治疗肿瘤, 如抗黑色素瘤单克隆抗体被证明可以抑制裸鼠身上的人黑色素瘤的生长[5], 并在1980年进行了第一例单克隆抗体治疗淋巴瘤的人体试验[6]。随着抗体技术的发展, 科学家们利用转基因小鼠或体外酵母、噬菌体等展示技术克服免疫原性等问题可生产出接近全人源的单抗[7-8]。从1997年第一个批准的抗肿瘤抗体药物利妥昔单抗(Rituximab)至今, 已有超过30种单克隆抗体药物被用于临床抗肿瘤治疗(表1)。全球抗体类抗肿瘤药物的市场已激增至4 600亿美金, 且预计2026年将会继续增加800亿美金。为了更好地了解单克隆抗体在肿瘤免疫治疗中的进展, 我们综述了它们的结构、作用机制、发现技术、临床应用以及未来的发展趋势。

## 1 人源抗体的分子特性

抗体是免疫系统响应抗原刺激而产生的浆细胞分泌的一种蛋白质, 具有针对抗原高特异性的特点。人源的抗体主要由5个不同的亚型组成, 包括: IgG、IgA、IgM、IgD和IgE[9]。其中, 人源的IgG1和IgG4亚型抗体常被用于临床治疗。在结构上, 抗体由两条相同的重(high, H)链和两条相同的轻(light, L)链(κ链或λ链)构成, 每条链包含一个可变区域(variable area, V)和一个恒定区域(constant area, C), C区通过二硫键结合在一起, L链和H链均由可变的N末端和恒定的C末端组成。在每个V区中都有3个超变区[即免疫球蛋白互补性决定区(complementarity-determining region, CDR)], 它们是抗体特异性的分子基础, 3个补体区(CDR1、CDR2和CDR3)与可变区(VH和VL)相对应, 分别位于两条L链和两条H链的N末端。单克隆抗体表现出相对缓慢的组织穿透和长血清半衰期(范围在几天到几周)。这是它们巨大的分子大小超过肾小球滤过截止值和通过新生儿Fc受体(FcRn)由血管内皮进行回收的结果, 这两者共同作用使得其在患者中维持滴度数周的时间, 而无需重新给药[10-11]。用于优化单克隆抗体药物的分子工程策略包括延长它们的血清半衰期、增强靶标亲和力(亲和力成熟)、增强效应功能、减少免疫原性以及改善其聚合物的生成情况[12-15]。

## 2 单克隆抗体的作用机制

单克隆抗体能够通过一系列机制执行其治疗作用, 它在肿瘤治疗中的主要机制如图1所示。

### 2.1 抑制细胞信号转导

单克隆抗体可以通过多种机制抑制细胞信号转导途径, 包括中和信号转导因子[例如血管内皮生长因子(vascular endothelial growth factor, VEGF)、肝细胞生长因子(hepatocyte growth factor, HGF)], 结合并阻断细胞表面受体表达(即防止受体与信号转导因子结合), 以及减少细胞表面受体的表达水平[16]。配体阻断是贝伐珠单抗(Avastin)的主要作用机制, 可防止VEGF与其同源受体(VEGFR1和VEGFR2)结合, 从而抑制血管生成[17]。在多数情况下, 细胞信号转导的阻断不需要单克隆抗体的Fc结构域的参与, 而是通过Fab结构域来实现的, 例如曲妥珠单抗(Bevacizumab)和西妥昔单抗(Cetuximab)与表皮生长因子受体(epidermal growth factor receptor, EGFR)和人上皮生长因子受体(human epidermal

**表1 被美国FDA批准用于肿瘤治疗的单克隆抗体(截至2023年6月)**

**Table 1 The FDA approved monoclonal antibodies for tumor therapy (until June 2023)**

| 国际非专利药名<br>INN | 药品名称<br>Drug name | 公司<br>Company | 靶点/类型<br>Target/form | 适应症<br>Indications | 获批时间<br>Year of approval |
|---|---|---|---|---|---|
| Rituximab | Mabthera | Genentech (Roche) | CD20/chimeric IgG1 | Follicular lymphoma, diffuse large B cell lymphoma, leukemia | 1997 |
| Trastuzumab | Herceptin | Genentech (Roche) | HER2/humanized IgG1 | $HER2^+$ breast cancer | 1998 |
| Alemtuzumab | Campath | Genzyme (Sanofi) | CD52/humanized IgG1 | Chronic myeloid leukemia | 2001 |
| Ibritnmomab | Zevalin | Biogen, Acrotech | CD20/radioactive labeling mouse IgG1 | Non-Hodgkin's lymphoma | 2002 |
| Tositumaomab-131 | Bexxar | Corixa (GSK) | CD20/mouse IgG2a | Non-Hodgkin's lymphoma | 2003 |
| Cetuximab | Erbitux | ImClone (Eli Lilly) | EGFR/chimeric IgG1 | Colorectal cancer, head and neck cancer | 2004 |
| Bevacizumab | Avastin | Genentech (Roche) | VEGF/humanized IgG1 | Colorectal cancer, non-small-cell lung carcinoma, $HER2^-$ breast cancer | 2004 |
| Panitumumab | Vectibix | Amgen | Amgen/human IgG1 | Colorectal cancer | 2006 |
| Ofatumumab | Arzerra | Genmab, Novartis | CD20/human IgG1 | Leukemia | 2009 |
| Denosumab | Xgeva | Amgen | RANKL/human IgG2 | Bone metastasis, giant cell tumor of bone | 2010 |
| Ipilimumab | Yervoy | Medarex (BMS) | CTLA-4/human IgG1 | Melanoma, renal-cell carcinoma, colorectal cancer | 2011 |
| Pertuzumab | Perjeta | Genentech (Roche) | HER2/humanized IgG1 | $HER2^+$ breast cancer | 2012 |
| Obinutuzumab | Gazyva | Genentech (Roche) | CD20/glycosylated humanized IgG1 | Leukemia, follicular lymphoma | 2013 |
| Ramucirumab | Lapatinib | Dyax, Eli Lilly | VEGFR2/human IgG1 | Gastric carcinoma, non-small-cell lung carcinoma, colorectal cancer | 2014 |
| Nivolumab | Opdivo | Medarex (BMS) | PD-1/human IgG1 | Melanoma, non-small-cell lung carcinoma, renal-cell carcinoma | 2014 |
| Pembrolizumab | Keytruda | Merck & Co. | PD-1/humanized IgG4 | Melanoma, non-small-cell lung carcinoma, Hodgkin's lymphoma | 2014 |
| Blinatumomab | Blincyto | Micromet (Amgen) | CD19, CD3/bi-specific mouse scFv | Philadelphia chromosome-negative precursor B-cell acute lymphocyte leukemia | 2014 |
| Necitumumab | Portrazza | ImClone (Eli Lilly) | EGFR/human IgG1 | Non-small-cell lung carcinoma | 2015 |
| Cetuximab | Unituxin | United Therapeutics | GD2/chimeric IgG1 | Neuroblastoma | 2015 |
| Darzalexb | Dasabuvir | Genmab, Janssen (J&J) | CD38/human IgG1 | Multiple myeloma | 2015 |
| Eculizumab | Empliciti | Abbvie, BMS | SLAMF/humanized IgG1 | Multiple myeloma | 2015 |
| Ollamumab | Lartruvo | ImClone (Eli Lilly) | PDGRFa/human IgG1 | Soft tissue sarcoma | 2016 |
| Atezolizumab | Tecentriq | Genentech (Roche) | PD-L1/humanized IgG1 | Bladder cancer, non-small-cell lung carcinoma, triple negative breast cancer | 2016 |
| Avelumab | Bavencio | EMD Serono, Pfizer | PD-L1/humanized IgG1 | Merkel cell carcinoma, urothelial carcinoma, renal-cell carcinoma | 2017 |
| Durvalumab | IMFINZI | MedImmune (AstraZeneca) | PD-L1/human IgG1 | Non-small-cell lung carcinoma, small-cell lung carcinoma | 2017 |

续表1

| 国际非专利药名<br>INN | 药品名称<br>Drug name | 公司<br>Company | 靶点/类型<br>Target/form | 适应症<br>Indications | 获批时间<br>Year of approval |
|---|---|---|---|---|---|
| Mogamulizumab | Poteligeo | Kyowa Kirin | CCR4/humanized IgG1 | Mycosis fungoides, Sézary syndrome | 2018 |
| Cemiplimab | Libtayo | Regeneron. Sanofi | PD-1/human IgG4 | Skin squamous cell carcinoma, basal-cell carcinoma, non-small-cell lung carcinoma | 2018 |
| Moxetumomab pasudotox | Lumoxiti | Innate Pharma, AstraZeneca | CD22/mouse IgG1 dsFvPE38 cytotoxin conjugates | Hairy cell leukemia | 2018 |
| Isatuximab | Sarclissa | ImmunoGen, Sanofi | CD38/chimeric IgG1 | Multiple myeloma | 2020 |
| Tafasitamab | Monjuvi, Minjuvi | MorphoSys, Incyte | CD19/humanized IgG1 | Humanized IgG1 | 2020 |
| Naxitamab | Danyelza | Y-mAbs | GD2/humanized IgG1 | Neuroblastoma | 2020 |
| Dostarlimab | Jemperli | GSK | PD-1/humanized IgG4 | dMMR-endometrial cancer, dMMR-advanced solid tumor | 2021 |
| Amivantamab | Rybrevant | Genmab, Janssen (J&J) | EGFR, cMET/bi-specific human IgG1 | *EGFR* exon 20 insertions non-small cell lung cancer | 2021 |
| Tebentafusp | Kimmtrak | Immunocore | Gp100, CD3/bi-specific conjugated antibody | Metastatic uveal melanoma | 2022 |
| Teclistamab | TECVAYLI | Jannsen (J&J) | CD3, BCMA/bi-specific mouse-human IgG4 | Multiple myeloma | 2022 |
| Tremelimumab | Imjudo | MedImmune (AstraZeneca) | CTLA-4/human IgG2 | Hepatoma | 2022 |
| Retifanlimab | Zynyz | Incyte | PD-1/humanized IgG4 | Merkel cell carcinoma | 2023 |
| Epcoritamab | Epkinly | Abbvie | CD20, CD3/bi-specific humanized IgG1 | Diffuse large B cell lymphom, B cell lymphoma | 2023 |
| Glofitamab | Columvi | Genentech (Roche) | CD20, CD3/bi-specific humanized IgG1 | Diffuse large B cell lymphom, follicular lymphoma | 2023 |

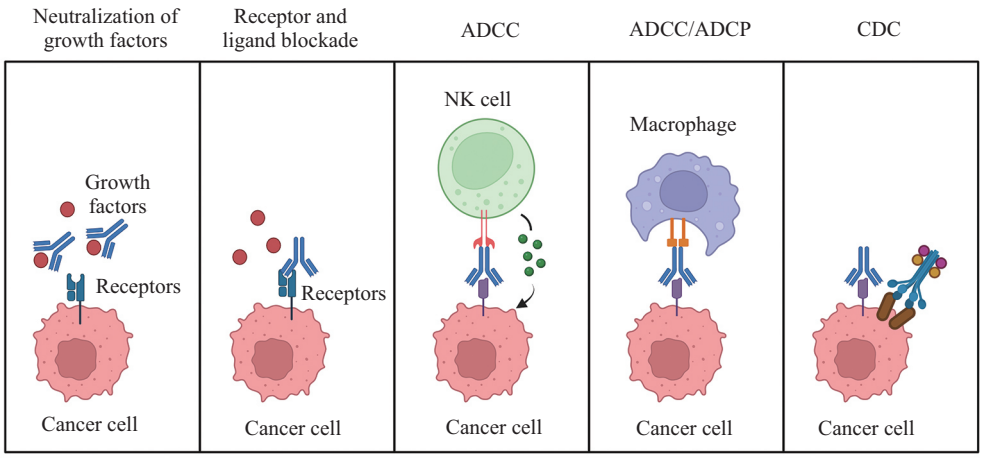


**图1 单抗的作用机制**

**Fig.1 Antibody effector mechanism**

growth factor receptor, hEGFR)的结合。HER1、HER2、HER3和HER4受体酪氨酸激酶之间的活性研究表明, Fab片段能够在异种移植模型中减少依赖性的肿瘤生长[18]。减少受体表达量的作用是通过从细胞表面“剥离”受体或加速受体的内化和分解代谢来实现的。

### 2.2 细胞毒性作用

靶细胞的直接细胞毒性是B细胞恶性肿瘤中靶向CD20的II型单抗的主要作用机制, 例如奥比妥珠单抗(Obinutuzumab), 它不介导靶细胞表面CD20分子的聚集, 而通过caspase的活化诱导恶性B细胞的程序性细胞死亡。这与典型的坏死样程序性细胞死亡过程相反, 其依赖于肌动蛋白重组、溶酶体膜渗透和随后释放的活性氧和组织蛋白酶B[19-21]。然而, 靶向CD52、CD47、HLA-DR、CD74和CD99的单抗则通过非caspase依赖性机制诱导肌动蛋白重组, 对靶细胞产生直接细胞毒性作用, 其中靶向CD52的阿仑单抗(Alemtuzumab)机制比较明确[22-23]。

抗体依赖性细胞毒性(antibody-dependent cellular cytotoxicity, ADCC), 是由抗体的Fc结构域与免疫细胞表面的FcγRIIIa之间的相互作用介导的。单克隆抗体可以通过其Fab结构域结合细胞表面靶标, 然后通过Fc结构域与表达FcγRIIIa的白细胞结合, 引起细胞杀伤作用[24]。一组利妥昔单抗(Rituximab)对淋巴瘤患者的疗效研究表明, 表达FcγRIIIa低亲和力变体(在第158位含有苯丙氨酸残基)的患者经利妥昔单抗治疗后的生存时间比有第158位缬氨酸的受体高亲和力变体的患者短, 其他的研究也出现类似的现象, 这表明ADCC对单抗体内疗效具有重要作用[25-26]。

早期研究表明, 抗APO-1单抗在体外和体内以不同于ADCC和补体依赖的细胞毒性作用(complement-dependent cytotoxicity, CDC)的方式诱导肿瘤细胞凋亡。在无补体和无血清的条件下, 抗APO-1单抗也会引起细胞死亡, 这种细胞死亡的模式与细胞凋亡一致, 表明单抗与靶标的相互作用可以直接诱导细胞凋亡[27]。这一类单抗可以通过激活死亡受体介导癌细胞的直接细胞毒性, 例如肿瘤坏死因子(tumor necrosis factor, TNF)相关凋亡诱导配体的受体DR4和DR5作为抗体靶点, 导致FAS相关蛋白的募集, 随后形成死亡诱导信号复合物, 启动依赖caspase的凋亡性细胞死亡[28-29]。虽然候选药物的临床数据至今仍然有限, 但基于IgM或工程化六聚体IgG可能提供更有效的靶细胞凋亡, 这些药物最近已进入临床开发[28,30-31]。

### 2.3 免疫效应作用

虽然单抗在肿瘤治疗中的理论基础最初集中在直接抑制细胞信号和受体多聚化等上, 但研究表明免疫效应功能在许多治疗肿瘤的药物中起着至关重要的作用[32]。利用IgG Fc受体(*FcγR*)基因敲除小鼠研究表明, Fc介导的免疫效应功能在曲妥珠单抗和利妥昔单抗的抗肿瘤活性中具有重要作用, 这些功能是通过抗体分子的Fc区、免疫细胞上的Fcγ受体(FcγRI、FcγRIIa、FcγRIIb、FcγRIIIa和FcγRIIb)以及补体的补体C1q(complement 1 q)蛋白之间的相互作用来介导的[33]。不同的lgG亚型对不同的FcγR和补体具有不同的亲和力和结合模式, 特别是人IgG4亚型无法招募Clq[34]。特异性的Fcγ受体如FcγRIIa和FcγRIIb, 分别对效应细胞本身发挥刺激或抑制作用, 因此可以根据不同类型单抗的作用来选择定制不同的功能效应[35-36]。广泛的体外研究表明, ADCC和抗体依赖性细胞吞噬作用(antibody-dependent cellular phagocytosis, ADCP)是通过抗体Fc/FcγR相互作用介导的。同样, 输注利妥昔单抗后患者血清补体成分C2的快速消耗为CDC作用提供了间接证据[37]。

机体通过自然杀伤(natural killer, NK)细胞表面的FcγRIIIa参与抗体靶向细胞的ADCC是一个特别有效的机制, 它允许通过释放含有穿孔素和颗粒酶的细胞毒性颗粒靶向破坏肿瘤细胞[38]。然而, NK细胞在抗体介导的肿瘤清除中作用不明确且缺乏确凿的体内证据[39]。使用*FcγR*基因敲除小鼠的多个体内研究反而强调了FcγR表达的髓系亚群发挥重要作用, 特别是单核细胞/巨噬细胞和中性粒细胞促进了抗体驱动的抗肿瘤反应[40]。例如小鼠动物模型实验表明, 单抗介导的抗肿瘤活性完全依赖于表达活化性受体FcγRIV的单核细胞/巨噬细胞和中性粒细胞, 而与NK细胞无关[34]。过往研究证明, 在针对CD19、CD20和模型鼠抗原gp75的单抗的抗肿瘤治疗中单核细胞/巨噬细胞发挥主要作用[40]。

细胞靶点的调理作用和细胞毒性介质的释放是单核/巨噬细胞作用的基础。例如M1巨噬细胞(经典的活性巨噬细胞)表达低水平的FcγR, 容易产生一氧化氮和活性氧, 比M2巨噬细胞(可选择的活化巨噬细胞)更有效地介导ADCC, 在体外表达更高水平

的FcγR并介导更高水平的ADCP[41]。虽然释放细胞毒性颗粒是中性粒细胞抗细菌、病毒和真菌活性的一种公认机制, 但中性粒细胞也可通过ADCC依赖的吞噬作用诱导目标细胞坏死性死亡[42-44]。

除了ADCC和ADCP以及补体机制外, 直接通过CDC或间接通过补体依赖性细胞毒性(complement-dependent cellular cytotoxicity, CDCC)和补体依赖性细胞吞噬机制, 也与抗体如抗CD20的利妥昔单抗和奥法木单抗(Ofatumumab)[45]等介导的抗肿瘤作用有关。

## 3 单克隆抗体在肿瘤治疗中的应用

### 3.1 免疫检查点阻断

除了通过抗体免疫效应功能直接杀伤肿瘤细胞外, T细胞通过抗体阻断免疫检查点受体介导的免疫激活已经改变了肿瘤治疗的方法[46]。细胞毒性T淋巴细胞相关蛋白4(cytotoxic T-lymphocyte-associated protein 4, CTLA-4)是一种免疫检查点分子, 在细胞毒性T淋巴细胞上高表达, CTLA-4通过一系列受体–配体相互作用和对B7配体的高亲和力驱动免疫抑制和肿瘤逃避免疫监视[47], 并竞争性抑制与辅助受体CD28的相互作用, 从而阻断激活信号转导, 下调T细胞活性[48-50]。易普利姆玛(Ipilimumab)是一种抗CTLA-4的高亲和力全人的单抗, 于2011年获得美国食品药品监督管理局(Food and Drug Administration, FDA)批准上市, 通过破坏CTLA-4/B7的相互作用并通过CD28信号恢复T细胞的激活。程序性细胞死亡蛋白1(programmed cell death protein 1, PD-1)及其配体(programmed cell death 1 ligand 1, PD-L1)也是相关单抗的靶标, 包括靶向PD-1的派姆单抗(Pembrolizumab)、纳武利尤单抗(Nivolumab)、西米普利单抗(Cemiplimab)和多塔利单抗(Dostarlimab)以及靶向PD-L1的阿特珠单抗(Atezolizumab)、阿维单抗(Avelumab)和德瓦鲁单抗(Durvalumab)[51]。其他免疫检查点包括淋巴细胞激活基因-3(lymphocyte activation gene-3, *LAG-3*)、T细胞免疫球蛋白和含黏蛋白结构域蛋白3(T cell immuno-globulin and mucin domain-containing protein 3, *TIM-3*)和T细胞免疫球蛋白和ITIM结构域(T cell immunoreceptor with Ig and ITIM domain, *TIGIT*)等基因也受到了相当大的关注, 它们的共同点是通过阻断受配体结合后抑制信号的传递, 且可与PD-1和PD-L1阻断剂协同作用进一步提升抗肿瘤作用[52-54]。针对以上免疫检查点的单抗药物正在进行多项临床试验评估, 其中大部分是检测其与抗PD-1或抗PD-L1单抗的联合应用。目前, 针对LAG-3的瑞拉利单抗(Relatlimab)与纳武利尤单抗联合治疗不可切除或未经治疗的转移性II/III期黑色素瘤和针对TIGIT的替瑞利尤单抗(Tiragolumab)与阿特珠单抗联合治疗广泛期III期小细胞肺癌的临床试验均已取得巨大进展[55-56]。最近的结果显示, 在无病进展生存期方面, Relatlimab加Nivolumab联合治疗取得了显著的改善(10.2个月对比4.6个月), 但在19.3个月的中位随访期间总体生存期没有统计学显著差异(NCT03470922)[57]。这些数据导致了FDA最近批准了Relatlimab加Nivolumab联合治疗Opdualag用于治疗转移性黑色素瘤, 因此代表了第三种进入市场的免疫检查点抑制剂。在Tiragolumab的情况下, 与单独使用Atezolizumab相比, 无病进展生存期和总体生存期在13.9个月的中位随访期间没有改善(NCT04256421)[58]。尽管延长的随访可能会揭示治疗效益, 但这些数据凸显了将新的免疫检查点抑制剂的临床前研究结果转化为临床实践的挑战, 以及需要更准确地识别它们与该领域已经建立的药物的协同效应的临床前模型。

另一种通过免疫检查点阻断来诱导T细胞活化以促进抗肿瘤反应的方法是使用激动性抗体[59]。尽管在小鼠中的临床前研究强调这是一种有前途的策略, 但激动性抗体的开发具有挑战性。从蛋白质工程的角度来看, 与开发阻断性抗体相比, 需要额外考虑能够触发激动性信号的单克隆抗体。例如抗CD28的单抗TGN-1412, 已被证明能够在没有T细胞(抗原)受体(T cell receptor, TCR)参与的情况下刺激T细胞增殖, 从而为单抗增加免疫介导的肿瘤清除提供了一种可能的机制[60-61]。然而, 激动性单抗可能会带来重大风险, TGN-1412的首次临床试验就证明了这一点, 6名健康志愿者在使用TGN-1412后不久都经历了细胞因子风暴, 导致所有受试者出现了严重的副作用[62]。目前处于临床开发中的激动性单抗的靶点包括41BB、OX40、糖皮质激素诱导的肿瘤坏死因子受体相关蛋白(glucocorticoid-induced tumor necrosis factor receptor-related protein, GITR)、ICOS(induced T cell costimulator)和CD27等, 剂量高于1 mg/kg的靶向41BB的乌瑞芦单抗(Urelumab, IgG4)治疗会引起严重肝毒性。相比之下, 另一种具

有较弱激动活性的靶向41BB的乌托鲁单抗(Utomilumab, IgG2)在剂量增高至10 mg/kg时其在人体中仍具有良好的耐受性[63-64]。FcγR阳性细胞表面的Fc交联可增强激动性抗体的活性, 以反式呈递至T细胞, 特别是通过高表达抑制性受体FcγRIIb的B细胞。因此, 开发以Fc交联为条件诱导T细胞活化的较弱激动性抗体可能会产生更安全的T细胞激动剂[65]。免疫受体激动性单抗除了能激活T细胞外, 也可通过促进调节T(regulatory T cells, Treg)细胞的失能和耗竭, 进一步增强抗肿瘤反应。这种双重作用机制在评估靶向GITR、OX40、ICOS以及CTLA-4的单克隆抗体活性的临床前研究中已被广泛报道, 并且在白细胞介素-2(interleukin-2, IL-2)-Fc融合蛋白中也发现类似的效果[66-71]。

### 3.2 抗体–药物偶联

抗体药物复合物(antibody-drug conjugates, ADC)由三个主要组成部分组成: 单克隆抗体(mAb)、细胞毒负荷(cytotoxic payload)和连接物(linker)。当ADC与肿瘤细胞上的目标抗原结合时, ADC可以通过受体介导的内吞作用将细胞毒素负荷传递到靶向细胞的细胞质, 随后在溶酶体降解期间释放ADC中的细胞毒药物, 从而破坏DNA或以其他方式抑制细胞分裂, 并最终杀死肿瘤细胞。目前, 已有50多种抗原被用作ADC的临床前或临床开发的靶点; 这些抗原包括HER2、滋养层细胞表面抗原-2(trophoblast cell-surface antigen 2, Trop-2)和B细胞成熟抗原(B cell maturation antigen, BCMA)[72-74]。截至目前, 已有14种ADC被美国食品和药物管理局(FDA)批准用于癌症治疗。目前处于第III期临床试验的ADCs总结在表2中。

CD19在B细胞发育和分化的各个阶段, 从前B细胞到浆细胞, 都广泛表达, 是治疗B细胞恶性肿瘤的一个理想靶点[75]。Loncastuximab tesirine-lpyl是一种新型的ADC药物, 由人源化的抗CD19抗体、烷化剂吡咯苯并二氮卓二聚体SG3199和可被卡特普辛酶剪切的缬氨酸–丙氨酸连接剂组成[76]。2021年FDA授予了Loncastuximab tesirine-lpyl作为单药治疗复发性或难治性弥漫性大B细胞淋巴瘤成年患者的加速批准, 这些患者至少接受过两种先前的全身治疗[77]。BCMA在多发性骨髓瘤(multiple myeloma, MM)的体内发病机制中起着中心作用, 并在MM细胞中过表达[78]。因此, BCMA已被证明是一种有前途的细胞表面抗原, 可用于靶向治疗, 如CAR-T疗法、双特异性抗体(BsAbs)和抗体药物复合物(ADCs), 改善复发性或难治性多发性骨髓瘤(relapsed and refractory MM, RRMM)患者的治疗格局。Belantamab mafodotin是一种首创的抗-BCMA ADC, 于2020年8月被FDA加速批准, 作为成人RRMM患者的单药治疗[79]。在这项随机开放标签II期试验中, 97名患者每3周一次静脉注射建议的2.5 mg/kg Belantamab mafodotin。总体反应率为31%, 73%的应答者显示了持续6个月或更长时间的改善[80]。然而, Belantamab mafodotin可能导致严重的眼睛问题, 包括角膜变化、视力降低和/或视觉模糊。目前正在进行以Belantamab mafodotin为单一疗法和与化疗联合应用的临床试验, 用于治疗多发性骨髓瘤患者。

HER2在大约20%的乳腺癌患者中过表达[81]。在2013年, Ado-Trastuzumab emtansine(T-DM1)一个以抗-HER2抗体Trastuzumab为基础, 通过稳定的硫醚连接剂与微管抑制剂DM1(一种美登木素生物碱)结合的HER2靶向ADC, 获得了治疗HER2阳性转移性乳腺癌患者的批准[82]。在临床III期试验中, 患者被随机分配接受T-DM1($n$=495)或拉帕替尼加卡培他滨($n$=496)。中位无进展生存期和中位总生存期在接受T-DM1的患者中明显优于接受拉帕替尼加卡培他滨的患者[83]。三阴性乳腺癌(triple negative breast cancer, TNBC)细胞缺乏雌激素受体、孕激素受体或HER2表达, 从而限制了它们对激素治疗或HER2靶向疗法的响应[84]。患有TNBC的患者通常治疗选择有限。Sacituzumab govitecan是一种经FDA批准的ADC, 包括人源化的抗Trop-2单克隆抗体(hRS7)、可切割的连接剂和拓扑异构酶1抑制剂SN-38作为荷载[85]。与其他FDA批准的ADC(在单分子水平)相比, SN-38荷载的效力是适度的。由于其新颖的连接剂技术(极性PEG基连接剂), Sacituzumab govitecan在药物对抗体比(drug to antibody ratio, DAR)方面达到了相对较高的水平, 约为7.6, 而目前正在使用的ADC的DAR约为4。Sacituzumab govitecan于2020年4月基于涉及108名TNBC患者的临床试验(NCT01631552)中的积极结果, 获得了加速的FDA批准, 用于难治性转移性TNBC[86]。在这项试验中, 响应率为33.3%, 响应的中位持续时间为7.7个月。Sacituzumab govitecan代表了患者治疗方面

表2 被美国FDA批准和在三期临床试验的用于肿瘤治疗的ADC单克隆抗体(截至2023年6月)

Fig.2 The FDA approved and at phase III clinical trial antibody-drug conjugates for tumor therapy (until 2023 June)

| 国际非专利药名 INN | 药品名称 Name | 公司 Company | 靶点/类型 Target/form | 适应症 Indications | 获批时间 Year of approval |
|---|---|---|---|---|---|
| Bentuximab | Adcetris | Seagen | CD30/chimeric IgG1 ADC | Hodgkin's lymphoma, anaplastic large cell lymphoma | 2011 |
| Ado-trastuzumab emtansine | Kadcycla | Genentech (Roche) | HER2/humanized IgG1 ADC | $HER2^+$ breast cancer | 2013 |
| Nitoxizumab-Ozagremycin | BESPONSA | Wyeth (Pfizer) | CD22/humanized IgG4 ADC | B-acute lymphoblastic leukemia | 2017 |
| Rituximab-Hyaluronidase | Rituxan Hycela | Genentech (Roche) | CD20/chimeric IgG1 ADC | Follicular lymphoma, diffuse large B cell lymphoma, leukemia | 2017 |
| Gemtuzumabozogamicin-Ozawa gamin | Mylotarg | Wyeth (Pfizer) | CD33/human IgG4 ADC | Acute myeloid leukemia | 2017 |
| Polatuzumab vedotin | Polivy | Genentech (Roche) | CD79b/humanized IgG1 ADC | Diffuse large B cell lymphoma | 2019 |
| Darzalex Wien | Padcev | Astellas, Seagen | Nectin-4/human IgG1 ADC | Urothelial carcinoma | 2019 |
| Trastuzumab deruxtecan | Enhertu | AstraZeneca, Daiichi Sankyo | HER2/humanized IgG1 ADC | $HER2^+$ breast cancer, gastric carcinoma | 2019 |
| Daratumumab-hyaluronan-FIHJ | Darzalex Faspro | Genmab, Janssen (J&J) | CD38/human IgG1 ADC | Multiple myeloma | 2020 |
| Belantamab | BLENREP | GSK | BCMA/humanized IgG1 ADC | Multiple myeloma | 2020 |
| Sacituzumab govitecan | TRODELVY | Immunomedics (Gilead) | TROP-2/humanized IgG1 ADC | Triple negative breast cancer | 2020 |
| Loncastuximab | Zynlonta | ADC Therapeutics | CD19/humanized IgG1 ADC | Diffuse large B cell lymphoma | 2021 |
| Tisotumab-Vedotin | Tivdak | Genmab, Seagen | CD142/human IgG1 ADC | Cervical cancer | 2021 |
| Mirvetuximab-Soravtansine | ELAHERE | ImmunoGen | FRα/chimeric IgG1 ADC | Platinum-resistant ovarian cancer | 2022 |
| Trastuzumab-Dukangmycin | SYD985 | Byondis | HER2/humanized IgG1 ADC | Metastasis breast cancer | Phase III |
| Depatuxizumab-Mafodotin | ABT-414 | Abbvie | EGFR/chimeric IgG1 ADC | Glioblastoma multiforme, gliosarcoma | Phase III |
| Disitamab-Vedotin | Iicction (RC48) | RemeGen | HER2/humanized IgG1 ADC | Locally advanced or metastatic breast cancer with low expression of HER2 | Phase III |

的重大进展, 因为它是专门针对转移性TNBC的首个获批ADC。

## 4 单抗肿瘤免疫治疗的发展趋势

### 4.1 抗体片段、双特异性T细胞接合器(bi-specific T-cell engagers, BiTEs)和TCR模拟抗体(TCR mimics, TCRm)

抗体片段与全长IgG抗体的不同之处在于其缩小的尺寸和较短的血清半衰期, 同时保留了其大多数特异性结合的特性[87]。虽然它们缩小的尺寸最初促进了其在组织中的分布, 但也导致了其在血清持续时间缩短和组织之间的低浓度梯度, 因此, 它们非常适合用于介导短期药理作用, 特别是对于治疗窗口期小且不良事件风险高的适应症或靶点。在这种情况下, 较短的半衰期作为一个安全网, 保证了治疗的快速失效, 并在发生不良事件时得到一定程度的控制。

按照这个逻辑, 抗体片段的关键应用是作为细胞毒性或放射性药物的载体和BiTEs。BiTEs通过靶向TCR复合物和肿瘤抗原的激动性抗体片段, 通过

第二个遗传融合抗体片段与T细胞结合，从而形成人工免疫突触，促进T细胞介导的靶细胞杀伤，从而架起T细胞与癌症靶细胞之间相互作用的桥梁[88]。小尺寸的单链Fv抗体片段(single-chain fragment variable, scFv)与两个结合域之间的柔性连接体最初目的是为了镜像复制T细胞和靶细胞之间免疫突触的几何结构，然而由于T细胞激活可导致广泛的免疫激活，发生细胞因子风暴和神经毒性，如免疫效应细胞相关神经毒性综合征(immune effector cell-associated neurotoxicity syndrome, ICANS), BiTEs会导致治疗相关的不良事件发生[89-90]。随着新一代药物进入临床，对不良事件的管理将是至关重要的，例如用地塞米松等皮质类固醇以及抗IL-6受体和抗TNF-α抗体对患者进行预处理。尽管存在这些挑战，但与许多CAR-T细胞疗法不同，BiTEs不需要个性化定制，具有相当大的治疗前景[91]。

近年来，利用TCRm作为靶向片段的BiTEs和CAR-T细胞模式受到了相当大的关注，这些抗体被设计为可识别主要组织相容性复合体(major histocompatibility complex, MHC)-抗原结合物，从而增加了可靶向抗原的范围，包括由MHC加工和呈递的细胞内蛋白。由于与其他多肽的交叉反应性、与呈递HLA等位基因的反应性以及与其他HLA等位基因的同种反应性，TCRm的开发变得复杂。尽管存在个别例子，但TCRm抗体的工程仍然是一个挑战[92]。

### 4.2 糖基化的或活化的抗体

虽然天然人IgG单克隆抗体在肿瘤治疗中发挥了出色效果，但可控地改变抗体结构可以扩大其临床适用性，最常见的工程改变是Fc的糖基化。早在2002年就有研究表明，非岩藻糖基化Fc可以促进其与NK细胞FcγRIIIa的结合，可以增加IgG1抗体的ADCC[93]。非岩藻糖基化抗体主要针对循环淋巴细胞的特定亚群，如肿瘤中表达CD20(如Obinutuzumab)、C-C趋化因子受体4(如Mogamulizumab)、自身免疫中表达CD19(如Inebilizumab)或IL-5Rα(如Benralizumab)的抗体，已被证明在非常低的临床剂量下就能有效地清除靶细胞。值得注意的是，糖基化不会影响单克隆抗体的生物物理特性和更广泛的化学、制造等特性。相较于半乳糖基化和唾液基化Fc作为替代修饰，非岩藻糖基化显示产生的抗体IgG具有优越的药理学特性，并已转化为临床应用[38]。

增强激活FcgRIIa和FcgRIIIa亲和力的突变已应用于多种单克隆抗体，包括靶向CD19治疗弥漫性大B细胞淋巴瘤的他法西单抗(Tafasitamab)和靶向HER2治疗晚期乳腺癌的玛格妥昔单抗(Margetuximab)[94-95]。增强对抑制性FcgRIIb受体亲和力的突变已被用于激动抗体的激动活性，包括那些与DR5结合的抗体，如OX40、41BB和CD40，因为它们促进FcgRIIb阳性细胞表面的有效聚集，从而使巨噬细胞有助于T细胞的多价呈递[96-97]。据推测，这种策略可以通过靶向OX40、41BB和ICOS的激动性单克隆抗体来预防或减少Treg细胞的ADCC，从而消除了潜在的有利特征。此外，pH<6.5可增强IgG对FcRn亲和力的突变，此现象已被鉴定并应用于免疫调节和抗CD20单克隆抗体中，以促进FcRn循环并延长半衰期[98]。促进IgG六聚化以增强C1q沉积和CDC的突变已被应用于IgG同型序列，典型出现在巨噬细胞表面表达的增强补体受体相互作用的突变已被应用于阿仑单抗，以促进补体依赖性细胞吞噬作用[99]。最后，减少或消除IgG1效应功能的Fc沉默突变已被批准用于抗PD-L1单克隆药物德瓦鲁单抗和阿特珠单抗，作为使用低效应功能IgG4的替代方案，或完全消除IgG4与FcgRs的相互作用，如用于治疗食管鳞状细胞癌的抗PD-1的替雷利珠单抗(Tislelizumab)[100-101]。

### 4.3 非IgG的其他亚型抗体

除了IgG单克隆抗体外，用于治疗目的的非IgG同型抗体的开发也取得了进展。例如，以五聚体或六聚体形式天然存在的IgM单克隆抗体已被开发用于对抗糖脂和聚糖等具有挑战性的靶标，或对抗诸如死亡受体这类受益于多价结合的靶标。一个潜在的缺点是，虽然它们是CDC的有效介质，但它们不参与FcγRs通路，因此不介导ADCC或ADCP[102]。IgA和IgE提供了参与其他效应细胞组合的可能性，因为它们与和IgG不同的Fc受体相互作用，即FcαRI(在单核细胞、嗜酸性粒细胞和中性粒细胞上表达)和FcRεI/FcγRεII(在单核细胞、嗜碱性粒细胞、肥大细胞和嗜酸性粒细胞上表达)[103]。由于IgA、IgM和IgE类抗体不与FcRn相互作用，因此与IgG相比，血清半衰期较短[104-105]。尽管非IgG抗体在某些应用上很有前景，但其在临床和商业上需进一步工程化或确定特定适应症，需证明在这些适应症中其优于已开发的IgG类抗体。

作为通过单克隆抗体固有的免疫激活特性来增强CDC或ADCC的替代方案，它的作用是免疫抑

制还是免疫刺激, 取决于干扰素-α、TNF-α以及常见的γ链受体细胞因子家族, 特别是IL-2和IL-15, 与不同同源受体的相互作用[106]。一些抗体–细胞因子融合疗法现已进入临床试验阶段[107]。

### 4.4 联合治疗

虽然单克隆抗体作为一种单一疗法在一些患者中取得了成功, 但治疗模式正趋向于将其与化疗、放疗、分子靶向药物、针对同一靶点的其他抗体、免疫检查点抑制剂、疫苗和/或细胞疗法联合使用[108]。目前已广泛认识到单克隆抗体的作用机制包括免疫效应细胞成分, 特别是西妥昔单抗的有效性部分归因于ADCC, 它可以将先天和适应性抗肿瘤免疫反应联系起来, 通过NK细胞介导的ADCC破坏肿瘤细胞释放肿瘤细胞特异性蛋白, 当抗原呈递细胞将其呈递给细胞毒性T细胞时, 可导致更有效的抗肿瘤反应[109]。免疫检查点抑制剂的兴起, 可以进一步增强这种免疫反应, 越来越多的研究支持抗PD-1/PD-L1单抗联合西妥昔单抗治疗的方案[110]。此外, 派姆单抗或阿维单抗联合西妥昔单抗目前正在临床试验中(NCT03082534和NCT03082534)。同样, 在乳腺癌中使用免疫检查点抑制剂以增强抗HER2单抗治疗是一种很有前途的策略。临床前证据表明, 联合免疫检查点抑制剂治疗可有效抑制曲妥珠单抗单药耐药带来的临床问题的发生[111]。

虽然T细胞活化有许多免疫检查点, 但每个检查点都有不同的机制。因此, 靶向多个检查点的组合将以协同方式增强T细胞反应。靶向CTLA-4和PD-1的单克隆抗体联合使用在临床前小鼠模型中的表现明显优于单独使用任一抗体[112]。同样, 在转移性黑色素瘤患者中, 易普利姆玛和纳武利尤单抗联合治疗被发现比单独使用任何一种治疗更有效。此后, FDA批准了易普利姆玛和纳武利尤单抗联合治疗黑色素瘤[113]。作为首个获得FDA批准的免疫检查点阻断联合疗法, 目前正在进行临床试验继续评估在其他癌症类型中的疗效。免疫检查点LAG3和TIM3通常与PD-1在衰竭T细胞上共表达, LAG3联合抗PD-1的免疫检查点阻断正在进行胶质母细胞瘤(NCT02658981)和其他癌症(NCT02460224)的临床试验。在肝癌(NCT03680508)和其他几种实体瘤(NCT03744468)中, 也有类似的抗TIM3和抗PD-1抗体联合治疗的临床试验。

另一种有希望的联合策略是将免疫检查点阻断与激活刺激受体的激动抗体联合起来, 4-1BB是一种存在于T细胞和NK细胞上的共刺激受体, 目前正在进行评估4-1BB激动剂抗体与抗PD-1单抗联合治疗的临床试验(NCT02253992和NCT02179918)。一种针对GITR的激动剂抗体, 可促进T细胞活化, 与纳武单抗联合使用也被证明是成功的[114]。其他单抗组合包括仅在活化的T细胞上表达的OX40激动剂抗体, 也应用于多个临床试验(NCT01714739和NCT01750580)。

## 5 总结

癌症仍然是全球范围内人类死亡的一个主要原因, 也是医疗卫生系统的一个重大负担。自首个用于肿瘤治疗的单克隆抗体——利妥昔单抗获批以来的25年里, 用于肿瘤治疗的抗体疗法已经比较成熟, 可以说单克隆抗体用于肿瘤治疗是过去10年中最伟大的成功策略之一。随着从实验室研究和临床试验中吸取教训, 应用创新方法, 如抗体工程、靶标等, 单克隆抗体的肿瘤免疫治疗必将为肿瘤患者带来更多的临床效益。然而, 由于疗程延长, 患者对单克隆抗体产生耐药性, 耐药的机制多种多样, 包括肿瘤细胞的突变、肿瘤细胞生长的替代信号通路的出现以及效应细胞的功能受损, 解决耐药性仍然是一项重大挑战。因此, 尽管单克隆抗体在肿瘤治疗方面取得了显著的成功, 但该领域的研究仍在与日俱增。

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