海洋来源天然成分在抗肿瘤及肿瘤免疫领域的研究进展

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摘要: 海洋是近年来极具潜力的抗肿瘤新药开发和筛选的重要来源, 每年约有56%的海洋生物活性化合物被发现具有抗肿瘤作用。本文对已发现的在抗肿瘤方面具有治疗作用的海洋来源药物进行了分类归纳, 以肿瘤免疫治疗为主要方向, 首先对免疫系统在癌症发病中的作用简短回顾并探讨了肿瘤免疫治疗当前的困境, 同时总结了海洋药物在其中的主要特点及作用机制。进一步地, 对目前已批准药物以物种来源进行了分组、归纳并概述了其被发现的历史、药物的结构特征、相关的作用通路、临床应用及治疗的特点。最后, 总结了目前海洋药物研究的不足, 展望了新药开发的未来前景及趋势。

关键词: 海洋来源药物; 抗肿瘤药物; 肿瘤免疫; 天然产物; 信号通路

中图分类号: R966　　**文献标识码**: A　　**文章编号**: 0513-4870(2022)09-2642-12

Research progress on anti-tumor and tumor immunity of marine natural products

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Abstract: In recent years, the oceans have provided an important source of highly promising new anti-tumor drugs for innovation and screening, with approximately 56% of biologically active compounds being discovered to have anti-tumor effects each year. In this study, we classified and summarized the approved drugs of marine origin in terms of anti-tumor therapy, and firstly, we briefly overviewed the role of the immune system in cancer pathogenesis and discussed the current dilemma of cancer immunotherapy and highlighted the main anti-tumor targets of marine drugs. Further, with a focus on tumor immunity, we classified and outlined the history of currently approved marine original drugs by species origin, structural features, relevant pathways, and clinical application and therapy. Lastly, the limitations of current marine drug research were discussed, as well as prospects and trends in new drug development.

Key words: drug of marine origin; anti-tumor drug; tumor immunity; natural product; signaling pathway

天然产物在药物研发中具有重要的作用, 是药物先导化合物的主要来源。近年来, 海洋来源天然产物得到研究人员的广泛关注, 已发展成为极具潜力的药物筛选资源。本综述回顾了海洋来源天然产物及其衍生物在抗肿瘤治疗及近年来发展的肿瘤免疫治疗中的应用, 以期为抗肿瘤治疗及海洋来源药物开发提供新的思路。

收稿日期: 2022-04-29;　修回日期: 2022-06-22.

基金项目: 国家自然科学基金资助项目 (81872877); 广东省普通高校特色创新类项目 (2019GKTSCX039, 2020KTSCX295); 深圳职业技术学院校级科研项目 (6021310023K).

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DOI: 10.16438/j.0513-4870.2022-0518

1 海洋抗肿瘤药物来源

海洋覆盖了地球表面的3/4, 拥有世界上最丰富的生物多样性。近年来, 随着人类对海洋天然资源的不断探索, 越来越多海洋来源的天然产物及其复合物被发现在生物医药领域极具应用前景[1]。自2008年以来, 每年有超过1 000种海洋来源的天然产物被发现, 其中约有56%的生物活性化合物具有抗肿瘤活性[1]。

由于海洋环境的特殊性, 生活在海水中的海洋生物具有特殊的代谢机制, 因此, 海洋生物活性化合物通常具有独特的化学结构和较高的生物活性。海洋天然产物 (marine natural products, MNPs) 主要包括以乳酸菌、放线菌、蓝藻菌等代表的微生物, 以海藻、红树林等为代表的植物及以海绵、海兔、海鞘等为代表的动物[2]等的组分及代谢物。表1展示了目前已批准用于临床及处于临床试验或临床前的海洋来源/衍生药物。

1.1 微生物 海洋真菌是抗癌药物的独特来源, 已鉴定出多种源自深海沉积物、藻类、红树林内生真菌及其他海洋真菌相关的抗癌化合物。例如已被美国食品药品监督管理局 (Food and Drug Administration, FDA) 批准用于治疗急性髓系白血病和肥大细胞增多症的米哚妥林 (midostaurin) 是从链霉菌发酵液中提取的星孢菌素改造而来, 通过强效抑制蛋白激酶C (protein kinase C, PKC) 发挥抗肿瘤作用。

海洋微生物的次级代谢产物是抗肿瘤新靶标和新药筛选一个新的重要方向。已发现的微生物相关代谢产物, 如discodermolide、bryostatins、sarcodictyin、eleutherobin和macrolactin-A, 均能有效抑制肿瘤生长[3,4]。此外, 还存在已鉴定的却不知具体来源的, 亦被认为是共生或寄生的微生物代谢产物, 如kahalalide F, 被发现对多种肿瘤细胞特别是实体瘤细胞具有显著抑制作用[5]。另外, 蓝藻菌在人类抗癌药物开发的历史中占有重要的一席之地, 从中提取的重要成分如wewakazole B、curacin-A、apratoxin A、GSV 224均对多种癌细胞有显著的细胞毒性和体外抑制作用[3,6-8]。

1.2 植物 以“海岸卫士”著称的红树林体系不仅对海洋生态系统的稳定有重要贡献, 更是人类抗癌药物的重要来源。相关的植物中, 木榄属的分离物brugin、老鼠簕的分离物2-benzoxazoline、红树林混合提取物granaxylocarpins A及granaxylocarpins B、海檬树种子提取物2′-*O*-acetyl cerleaside A、17*b*-neriifoline及cerberin等均发现对多种恶性肿瘤细胞有较强的抑制作用[3,9]。

Table 1 Marine-sourced/derived drugs approved for clinical use or drugs in clinical trials and preclinical. FDA: Food and Drug Administration; FLT3: Fms-related tyrosine kinase 3 ligand; PDGFR: Platelet derived growth factor receptor; VEGFR2: Vascular endothelial growth factor receptor 2; PKC: Protein kinase C. MMAF: Monomethyl auristatin F

Drug	Drug category	Drug status	Indication	Drug mechanism of action	Company
Cytarabine/ cytarabine hydrochloride	Antineoplastics	FDA approved	Acute non-lymphocytic leukemia in adults and children, meningeal leukemia, acute lymphoblastic leukemia and chronic myelogenous leukemia in blastic phase	Competitively inhibits DNA polymerase and inserts into the DNA strand to terminate the activity of DNA, so it has the greatest impact on rapidly dividing cancer cells and bone marrow cells	Jazz Pharmaceuticals
Eribulin mesylate/ Halaven	Antineoplastics	FDA approved	Breast cancer that has metastasized, liposarcoma that cannot be removed by surgery or has metastasized	Through a tubulin-based anti-mitotic mechanism, leading to G2/M cell cycle arrest, disruption of the mitotic spindle, and ultimately apoptosis	Eisai Co. Ltd.
Brentuximab vedotin/ Adcetris	Antineoplastics	FDA approved	Classic Hodgkin lymphoma and anaplastic large cell lymphoma	The drug induces tumor cell apoptosis by blocking the cell cycle progression of cytosolic microtubule channels from step G2 to M	Seagen
Trabectedin/ Yondelis	Antineoplastics	FDA approved	For patients whose cancers are advanced or cannot be removed by surgery and who have already been treated with anthracycline-based chemotherapy	Trabectedin binds to the minor groove of DNA, blocks stress-induced protein transcription, induces DNA backbone cleavage and cancer cell apoptosis	JanssenProds
Midostaurin/ Rydapt	Antineoplastics	FDA approved	For the treatment of FLT3 mutation-positive acute myeloid leukemia, aggressive systemic mastocytosis, systemic mastocytosis with associated hematologic neoplasm (SM-AHN), or mast cell leukemia in adults	Midostaurin is a multi-targeted protein kinase inhibitor that inhibits the activity of wild-type FLT3, mutant FLT, KIT (wild-type and D816V mutant), PDGFR, VEGFR2, and serine/threonine kinase PKC family members	Novartis

Continued

Drug	Drug category	Drug status	Indication	Drug mechanism of action	Company
Belantamab mafodotin/ Blenrep	Antineoplastics	FDA approved	Used to treat multiple myeloma that has returned or has not improved in adults who have received at least 4 other medications	An antibody-drug conjugate (ADC) that mediates tumor cell killing through MMAF-induced apoptosis, antibody-dependent cytotoxicity (ADCC), and antibody-dependent phagocytosis (ADCP)	GSK
Lestaurtinib/ CEP-701	Antineoplastics	Phase III	For the treatment of pancreatic cancer and acute myeloid leukemia (AML)	Multikinase inhibitor with potent activity against the Trk receptor tyrosine kinase family	Kyowa Hakko
Polatuzumab vedotin	Antineoplastics	Phase III	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma	CD79b antibody conjugated drug, which can bind to B cells expressing CD79, release monomethyl auristatin E (MMAE) under the action of lysosomal protease, and kill B cells expressing CD79	Genentech
Plinabulin	Antineoplastics	Phase III	For chemotherapy-induced severe neutropenia (CIN)	Plinabulin is a guanine nucleotide exchange factor (GEF-H1) activator, accelerates dendritic cell (DC) maturation and promotes antigen presentation, T cell activation, and prevention of neutropenia by activating the immune defense protein GEF-H1	BeyondSpring Pharmaceuticals
Marizomib (MRZ)	Antineoplastics	Phase III	For the treatment of relapsed or refractory relapsed multiple myeloma (RRMM) and glioblastoma	Irreversible, brain-penetrating ubiquitin (proteasome) inhibitor	Triphase Accelerator
Lurbinectedin	Antineoplastics	Phase III	For the treatment of adult patients with recurrent small cell lung cancer who have progressed during or after platinum-based chemotherapy	It is an inhibitor of RNA polymerase II, binds to the minor groove on the DNA double helix structure, induces tumor cell apoptosis, and ultimately reduces cell proliferation	PharmaMar
Enfortumab vedotin/Padcev	Antineoplastics	Phase II	Used to treat urothelial cancer (cancer of the lining of the bladder and other parts of the urinary tract) that has spread to nearby tissues or other parts of the body or cannot be removed by surgery, and has worsened after treatment with other chemotherapy medications or if these chemotherapy medications cannot be used for treatment	Enfortumab is an ADC that recognizes nectin-4 and delivers the anti-tubulin drug MMAE to cells, resulting in cytotoxic death	Astellas; Seagen
Tisotumab vedotin /Tivdak	Antineoplastics	Phase II	Used to treat cervical cancer (cancer that begins in the opening of the uterus) that has not improved or has come back after treatment with other medications or has spread to other parts of the body	Tisotumab vedotin is a tissue factor (TF)-targeting ADC designed to target the TF antigen on cancer cells and deliver the cytotoxic agent MMAE directly into cancer cells	Genmab; Astellas
Plocabulin/ PM060184	Antineoplastics	Phase II	Breast cancer, colorectal cancer	Binds to tubulin, thereby interfering with cell mitosis	PharmaMar
Ladiratuzumab vedotin	Antineoplastics	Phase II	Treatment of triple-negative breast cancer, hormone receptor-positive breast cancer, and other solid tumors that express LIV-1	Conjugation of a monoclonal antibody against LIV-1 *via* a cleavable linker to MMAE, a potent microtubule disruptor, kills cancer cells through a mechanism that interferes with microtubule formation	Seagen; Merck & Co.
Plitidepsin	Antineoplastics	Phase II	In combination with dexamethasone for relapsed or refractory multiple myeloma (MM) that has failed or is resistant to other therapies	Specifically binds to eukaryotic translation elongation factor 1A2 (eEF1A2) and targets the atypical effects of this protein to induce tumor cell apoptosis (programmed death)	PharmaMar

海洋植物相关的代谢物也是抗癌药物的主要来源, 其中红藻、海带、褐藻等为代表的多糖或粗提物均表现出抗肿瘤作用[3]。已分离的羽毛藻代谢物 (Chondria sp. *Condriamide-A*)、衫叶蕨藻代谢物 (Caulerpenyne sp.)、囊载藻代谢物 (*Cystophora* sp.)、马尾藻代谢物 (*Eclonia cava*) 等均表现出抗癌特性[3,10]。

1.3 动物 在海洋动物中, 海绵中分离得到的 lanesoic acid 912、isofistularin-3、urupocidin A 及 urupocidin C, 被发现对多种癌细胞系具有显著抑制作用[11-13]。海鞘中分离得到的 ET-743、aplidine, 以及海兔中分离得到的 dolastatin-10, 海天牛分离物 kahalalide F, 苔藓虫 bryostatin 1, 鲨鱼软骨提取物 AE941 均被发现有良好的抗癌作用[11,12,14-17]。

海洋来源的抗肿瘤药物种类繁多, 本文主要围绕免疫方向, 对近年来的相关研究结果进行归纳总结。

2 肿瘤免疫在临床中的应用及主要问题

宿主免疫系统在癌症发生发展过程中起着至关重要的作用[18,19]。1909 年, Paul Erlich 提出假设: 肿瘤可能由免疫系统控制[20]。随后在 1957 年, Thomas 和 Burnet 首次提出癌症免疫监视理论[21], 认为淋巴细胞充当机体的守卫角色, 发挥免疫监视作用, 及时识别、杀伤并清除突变细胞, 抑制肿瘤发生。在过去的几十年里, 以免疫系统为目标的特异性治疗手段—免疫疗法已彻底改变了癌症治疗手段。免疫疗法通过操纵免疫系统, 克服导致肿瘤逃逸的途径, 重新激活抗肿瘤免疫反应[22,23]。早期的免疫治疗主要以细胞因子作为免疫调节剂, 激活肿瘤部位的免疫效应细胞, 影响免疫细胞的功能。目前已批准上市的细胞因子药物包括白细胞介素类 [白细胞介素 (interleukin, IL)-2、IL-7、IL-12]、趋化因子类 [CCL3 (CC chemokine ligand 3)、CCL26 (eotaxin-3)、CXCL7 (neutrophil activating peptide 2)] 及其他类别如干扰素等[22,23]。近年来, 靶向免疫治疗飞速发展, 如免疫检查点抑制剂中的代表, 靶向免疫检查点细胞毒性 T 淋巴细胞相关蛋白 4 (cytotoxic T lymphocyte-associated antigen-4, CTLA4) 和程序性死亡受体 -1 (programmed cell death protein 1, PD-1) 抑制剂, 能恢复抗肿瘤免疫, 从而逆转免疫逃逸或逃避, 促进肿瘤细胞死亡, 目前已在临床治疗中取得了一定效果[24]。另一种免疫治疗方法是对患者 T 细胞进行体外改造, 以产生特定的抗肿瘤反应, 被称为嵌合抗原受体 T 细胞免疫疗法 (chimeric antigen receptor T-cell immunotherapy, CAR-T), 也在临床肿瘤治疗中取得很好效果[24]。

虽然免疫疗法打开了许多癌症的治疗困境, 但肿瘤细胞会通过多种方式逃避免疫系统监测, 如肿瘤细胞通常会过度表达免疫检查点分子, 从而限制免疫系统的作用并抑制免疫反应[25]。尽管研究人员开发出多种不同的抗体蛋白来阻断免疫检查点分子试图解除肿瘤细胞对免疫系统的抑制, 恢复免疫系统的功能使其杀伤肿瘤细胞。然而, 这种策略仅在患者肿瘤中存在抗肿瘤 T 细胞时才有效, 并不是所有肿瘤都对该免疫调节策略有反应。例如, 只有小部分黑色素瘤患者对使用抗 PD-1/程序性死亡配体 1 (PD-L1) 治疗性抗体有反应。虽然近年来开发出的 CAR-T 疗法, 可通过对 T 细胞进行基因修饰, 在 T 细胞表面稳定表达抗体结合域, 赋予与组织相容性无关的新抗原特异性, 从而能以类似于内源性 T 细胞受体的方式触发 T 细胞活化, 使得 T 细胞能识别并杀伤肿瘤细胞。但该技术的主要问题在于 CAR-T 细胞在体内的扩增有限, 在输注后会迅速消失, 因此对大多数癌症患者仍无效[26,27]。

此外, 还发现免疫疗法在临床应用中存在一些独特的不良反应, 且这些不良反应因免疫疗法的类型而异。细胞因子中以 IL-2 为例, 大剂量给药会引发 T 细胞和自然杀伤细胞 (natural killer cell, NK) 的多级下游效应, 并造成毛细血管渗漏和脓毒症样综合征, 甚至导致患者多器官衰竭, 这也是细胞因子疗法在目前临床应用中限制较多的主要原因[22-24,28]。免疫相关不良事件 (irAEs) 作为免疫检查点抑制剂的主要不良反应, 其毒性以不同的频率和严重程度可影响几乎任何器官, 主要特征是引起多种器官特异性炎症反应, 严重者甚至危及患者生命[29]。细胞因子风暴则成为 CAR-T 技术在临床应用中的另一主要障碍。这种特殊的并发症被认为是由于 CAR-T 细胞的扩增和激活导致许多免疫细胞大量或过量产生细胞因子, 从而导致全身炎症反应升高, 其临床症状可从轻微 (发烧、肌痛、疲劳和轻度低血压) 到严重症状 (如低血压、呼吸衰竭、凝血功能障碍和多器官系统衰竭)。此外, 神经毒性也是 CAR-T 技术的一大不良反应, 目前认为其主要诱因是由于细胞因子风暴产生的大量细胞因子通过血脑屏障进入中枢神经系统, 引起患者出现头痛、癫痫、谵妄、焦虑、震颤和书写能力受损、失语、意识下降甚至昏迷脑水肿等症状[22,28]。

鉴于上述免疫疗法的局限性及不良反应的存在, 因而在临床应用中必须要进行密切监测, 且控制毒性也需特殊处理, 不利于广泛应用。因此, 更广泛有效的免疫治疗策略仍待开发, 而丰富的海洋来源药物便是其中的希望之星[30-32]。

3 肿瘤免疫相关的海洋药物分类及作用机制

从海洋环境中获得的微生物、浮游植物和浮游动物的代谢产物提供了多种多样的物理和化学属性, 对作为新基因来源的海洋微生物的开发导致了更多新药

物和靶点的发现。目前发现的海洋药物针对肿瘤免疫相关的作用主要分为三大方向, 一个是以免疫系统相关的肿瘤为靶点设计开发的与单克隆抗体结合的药物偶联物, 另一个是针对 JAK/STAT (Janus kinase/signal transducers and activators of transcription) 信号通路和 cGAS/STING (cyclic GMP-AMP synthase-stimulator of interferon genes) 信号通路等固有免疫系统为基础进行免疫调节及治疗的海洋药物, 此外还有构建纳米粒抗肿瘤药物递送系统相关的壳聚糖载体。图 1 总结了肿瘤免疫相关的海洋药物分类和作用机制及其与免疫治疗的联合应用。

3.1 单克隆抗体结合药物偶联物 目前 FDA 获批和临床试验应用较多的是针对单一性某个特定免疫系统相关肿瘤细胞设计的抗体药物偶联物。该类药物的主要特点之一是药物本体细胞毒性较强, 更适合靶向药物开发和局部治疗。抗体药物偶联物中海洋来源药物主要以两种形式存在: 第一种是作为结合特异性位点的特殊靶点, 与抗肿瘤药物结合, 达到更为高效的治疗目的, 如甲磺酸艾日布林 (eribulin mesylate), 是于 2010 年便获 FDA 批准用于治疗转移性乳腺癌的微观靶向的抗肿瘤药物[33]。艾日布林是海洋天然产物软海绵素 B (halichondrin B) 结构优化得到的大环酮类似物, 可直接与微管蛋白结合, 抑制有丝分裂, 从而引起癌细胞增殖抑制和凋亡[34,35], 发挥抗肿瘤作用。另外, 艾日布林也具有强效微管解聚活性和特性, 并有别于其他微管靶向剂。第二种是作为抗肿瘤药物与靶点抗体偶联, 如 2011 年 FDA 批准抗体药物偶联剂 brentuximab vedotin (商品名 Adcetris), 可用于治疗全身间变性大细胞淋巴瘤 (ALCL) 和霍奇金淋巴瘤 (Hodgkin lymphoma)。其中, 药物中的 auristatins E 源于海兔毒素及其衍生物, 但因其严重的不良反应不能单独用于临床治疗, 通过与 CD30 抗体偶联, 可特异性结合 CD30 阳性淋巴瘤细胞并干扰微管形成, 从而导致细胞周期阻滞和诱导凋亡[36,37]。此外, 还有 polatuzumab vedotin (商品名 Polivy), 来源于软体动物和蓝藻菌, 与 B 细胞抗原受体蛋白 CD79b 偶联结合, 用于治疗非霍奇金淋巴瘤 (NHL)、慢性淋巴细胞白血病 (CLL)、淋巴瘤、B 细胞淋巴瘤和滤泡淋巴瘤 (FL)[38]。其他类似药物还有 enfortumab vedotin, 可特异性靶向 nectin-4, 于 2019 年 12 月获 FDA 批准用于治疗转移性尿路上皮癌[39]。此外还

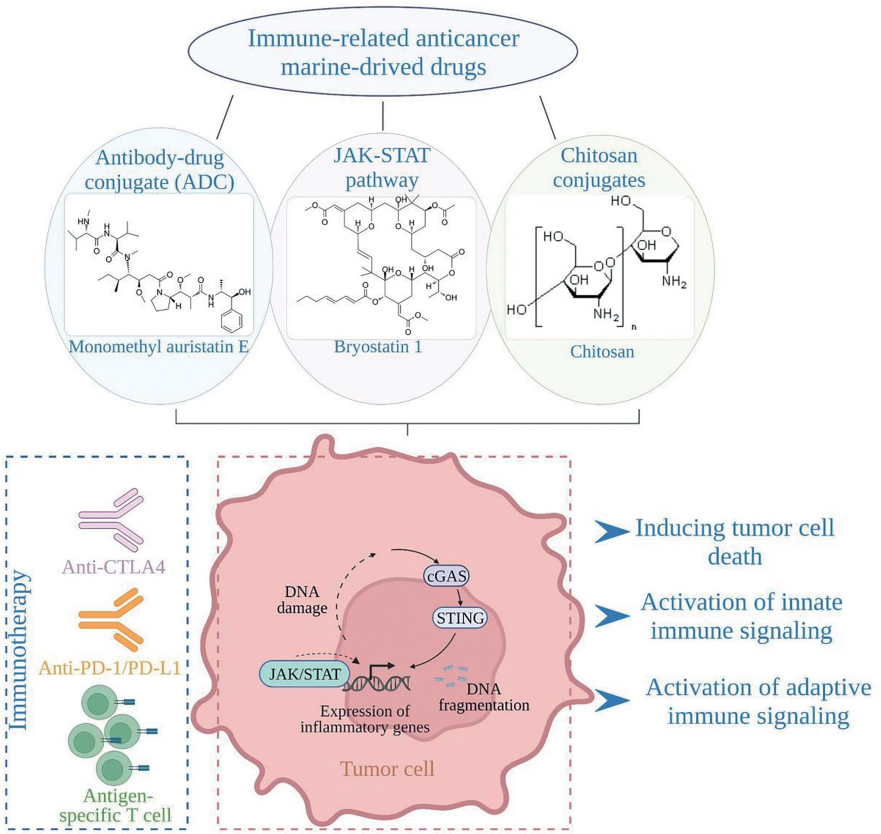

Figure 1 Classification and mechanism of immune-related anticancer marine-derived drugs and their combined application with immunotherapy. JAK-STAT: Janus kinase/signal transducers and activators of transcription; CTLA4: Cytotoxic T-lymphocyte-associated antigen 4; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1; cGAS: Cyclic GMP-AMP synthase; STING: Stimulator of interferon genes

有 belantamab mafodotin, 可特异性靶向 B 淋巴细胞刺激因子, 于 2020 年 8 月获 FDA 批准用于治疗复发/难治性多发性骨髓瘤 (RRMM)[40]。

3.2 JAK/STAT 信号通路相关的海洋来源药物 目前大量研究虽然揭示了海洋来源的抗癌药物在免疫途径上的一些重要作用, 然而, 其在细胞中所作用的具体信号通路目前仍待进一步探讨。不过, 通过介导固有免疫相关通路发挥抗肿瘤作用, 如 JAK/STAT 信号通路, 则是目前抗肿瘤免疫调节的基本策略。

JAK/STAT 信号通路由 3 个部分组成, 分别是接收信号的酪氨酸激酶相关受体、传递信号的酪氨酸激酶 JAK 和产生效应的转录激活因子 STAT 家族成员。信号转导和转录激活因子在细胞因子信号转导中具有特殊作用[41,42]。细胞因子如干扰素 (IFNs) 和白介素 (ILs) 等通过其特异性受体结合在细胞表面, 细胞因子受体与 JAK 家族成员相互作用[43], 介导受体酪氨酸磷酸化, 募集 STATs 使其发生磷酸化, 磷酸化的 STATs 进一步二聚化并转位至细胞核, 介导下游特定基因表达[43,44]。JAK/STAT 通路是一个高度保守的信号转导通路, 参与细胞增殖和分化、器官发育及免疫稳态调控[41,42], 其失调被认为可导致多种疾病, 尤其是恶性肿瘤和自身免疫性疾病。

许多研究发现干扰素/抗病毒免疫在海洋生物中也存在类似作用。例如, 在鱼类中 (硬骨鱼、鲶鱼、河豚鱼、斑马鱼和大西洋鲑鱼) 存在与哺乳动物相似的 IFNs, 且其作用及结构基本一致[45]。Santos 等[46]的相关研究描述了鱼类新型 I 型细胞因子受体及胞质 JAK 和 STAT3 结合基元, 并测定了日本比目鱼糖蛋白 130 同源物 (JfGPH) 的免疫功能。Zhang 等[47]的研究表明, JAK/STAT 通路的负反馈抑制因子细胞因子信号转导抑制因子 2 (suppressor of cytokine signaling 2, SOCS2) 参与中华绒毛蟹的免疫防御反应。而 Mu 等[48]认为在大黄鱼 (*Pseudosciaena crocea*) 嗜水气单胞菌感染过程中, JAK/STAT 信号通路和 Toll 信号及 MAPK 信号共同参与先天免疫反应抵抗感染。此外, 在少数无脊椎动物中, 如珍珠贝 *Pinctada fucata* 中的 SOCS-2、岩鲷中的 RbSTAT4、凡纳滨对虾中的 LvJAK 均与 JAK/STAT 信号通路相关[49-51]。

苔藓抑素 1 (bryostatin 1) 是一种海洋来源的抗肿瘤药物, 用于 CLL 的治疗。Battle 等[52]研究表明苔藓抑素 1 通过诱导干扰素 γ (IFNγ) 自分泌环以 PKC 依赖性方式激活 STAT1, 这对苔藓抑素 1 诱导的 CLL 细胞分化至关重要。Hong 等[53,54]发现海洋软珊瑚 cembrenolide 二萜类化合物 LS-1 可通过活性氧 (ROS) 依赖机制诱导细胞凋亡, 对结肠癌细胞具有抗增殖和细胞毒性潜能。该化合物还能诱导 c-Jun N 末端激酶 (JNK) 的磷酸化和 STAT-3 的去磷酸化。Apratoxin A 是一种细胞毒性海洋天然产物, 可快速抑制 STAT3 磷酸化。Liu 等[55]表明 apratoxin A 抑制 IL-6 诱导的 JAK/STAT 信号的激活, 并阻止触发蛋白酶体降解的受体酪氨酸激酶的 *N*-糖基化。两种来源于海洋红藻 *Gracilaria verrucosa* 的烯酮脂肪酸 GV-c9 和 GV-c10 通过阻断 NF-κB 核转位和 JAK/STAT (p-STAT1) 信号通路抑制炎性介质, 包括 NO (nitric oxide)、TNF-α (tumor necrosis factor-alpha)、IL-6 产生[56]。

3.3 壳聚糖载体 壳聚糖是从虾、蟹等贝类外骨骼中提取的甲壳素经脱乙酰作用得到的化学高分子生物材料, 被认为是一种无毒、可生物降解、生物相容性强的聚阳离子生物聚合物。由于其可生物降解的特性, 壳聚糖在医药、食品、化工等诸多领域具有重要作用。壳聚糖可被用作药物转运体, 能显著提高药物保存期和药物生物利用度[57]。已有研究表明壳聚糖具有体内外抗肿瘤作用, 可作为抗肿瘤的辅助剂和载体。壳聚糖已被广泛用作生物大分子和低分子质量药物的非病毒递送载体[58]。此外, 壳聚糖具有黏膜黏附性, 其阳离子性质可增强对黏膜的亲和力, 从而有助于跨黏膜给药, 因此壳聚糖的这些特性有助于递送鼻咽癌和肺组织癌症的化学治疗剂[59]。

壳聚糖纳米粒可用于递送亲水性药物和疏水性药物, 在最近一项研究中, 水溶性药物多柔比星 (DOX) 可通过与琥珀酸酐反应后与壳聚糖自组装形成纳米粒, 然后将该纳米粒与曲妥珠单抗缀合, 实现主动靶向药物递送, 从而克服与大多数抗肿瘤药物相关的全身不良反应[60]。在另一项研究中, Rajan 等[58]使用离子凝胶技术制备了一种载有透明质酸酶-5-氟尿嘧啶 (5-FU) 的壳聚糖−PEG−明胶聚合物纳米复合材料, 作为靶向和受控的药物递送载体, 能特异性靶向癌细胞, 从而提高 5-FU 的生物利用度并减轻不良反应。而 Cavalli 等[61]制备的用于递送 5-FU 的新型壳聚糖纳米球不仅能以时间和浓度依赖性方式减少 HT29 (人结肠直肠癌) 和 PC-3 (人前列腺癌-3) 肿瘤细胞的增殖, 而且还抑制其与人脐静脉内皮细胞 (HUVEC) 的黏附。这些研究都表明, 基于壳聚糖的纳米粒有可能开发多种具有不同物理化学性质的药物。

除了在药物递送中的重要作用, 壳聚糖由于其安全性、生物相容性、阳离子性等特征, 有可能成为理想的疫苗佐剂。壳聚糖可增强体液和细胞介导的免疫反应, 显示出与不完全弗氏佐剂相当的效力, 并优于传统免疫佐剂氢氧化铝 (Imject Alum) 的免疫活性。重要的是, 壳聚糖可将肽抗原保留在给药部位的时间更长,

从而使抗原呈递以实现有效的免疫活性。壳聚糖还可通过吞噬细胞中的NLRP3 (NOD-like receptor protein 3) 炎症小体诱导免疫活性, 并促进IL-1β分泌[62]。另据报道, 壳聚糖诱导线粒体DNA介导的cGAS-STING途径激活, 导致I型IFN的分泌。I型IFN反过来刺激树突状细胞, 导致抗原呈递及随后的Th1 (1型T辅助细胞) 免疫反应[63,64]。

4 已获批的海洋来源药物

目前已获批准上市的海洋来源抗肿瘤药物较少。截至2021年底, 已批准12种海洋来源抗肿瘤药物, 主要来源于藻类、被囊动物、软体动物及其共生的蓝细菌, 还有海绵。

4.1 Plitidepsin Plitidepsin是一种细胞毒性肽, 最初在海鞘*Aplidium albicans*中发现。研究表明, plitidepsin显示出体外和体内抗肿瘤活性[65,66]。由于获取*Aplidium albicans*极为困难, 且缺乏可能的水产养殖替代的自然捕捞的方法, plitidepsin目前均通过多步全合成法合成, 将与Thr和piruvir-l-pro连接的3个氨基酸 (*R*)-*N*-Me-Leu和6个氨基酸亚基组成的主链连接在一起[67]。Plitidepsin被批准用于治疗多发性骨髓瘤 (商品名Aplidin)。有研究显示plitidepsin的抗肿瘤活性似乎与真核延伸因子1A2 (eEF1A2) 蛋白的相互作用有关[68], 可诱导早期氧化应激, 激活Rac1 GTPase和抑制蛋白磷酸酶, 这有助于JNK和p38丝裂原活化蛋白激酶 (p38/MAPK) 的快速和持续激活, 以及诱导凋亡[69]。此外, 还证实了蛋白激酶C delta (PKC-delta) 介导plitidepsin的细胞毒性作用, 并参与caspase级联激活和凋亡的执行。事实上, 在药物治疗后, PKC-delta缺失的细胞比野生型细胞的存活率更高[69]。

4.2 Trabectedin及其类似物lurbinectedin Trabectedin是一种四氢异喹啉生物碱, 从加勒比海海囊藻*Ecteinascidia turbinata*中分离得到[70], 后来被鉴定为细菌共生*Candidatus Endoecteinascidia frumentensis*的产物[71]。它是ecteinascidin家族中一个非常有效的生物活性化合物, 含有2、3个四氢异喹啉 (THIQ) 亚基和1个活性的氨基喹啉官能团。Trabectedin已被批准用于不能手术切除或特定的晚期软组织肉瘤的治疗药物。研究发现, trabectedin的作用是通过与DNA修复机制的相互作用来介导的, 其可沿DNA螺旋的小沟与富含GC区的DNA序列结合, 使双链螺旋朝向大沟侧弯曲, 其中部分可向DNA螺旋的外侧伸出, 与蛋白质加合物的特定部位, 如XPG (xeroderma pigmentosum group G) 或RNA聚合酶II相互作用, 导致双链DNA的断裂, 阻断细胞周期, 诱导细胞凋亡[72]。另外, 修复双链DNA断裂的同源重组 (HR) 途径也被认为在trabectedin的作用机制中起作用。近来有研究显示, trabectedin在杀死肿瘤细胞的同时还能影响肿瘤微环境[72,73], 特别是对单核吞噬细胞系统 (肿瘤相关巨噬细胞) 及血管的影响。Trabectedin对单核吞噬细胞具有毒性作用, 其机制在于trabectedin会迅速触发caspase依赖性细胞凋亡, 由于单核细胞高表达caspase-8上游受体TRAIL-R1/R2 (TNF-related apoptosis-inducing ligand receptor 1/2), caspase-8被迅速激活, 诱导细胞发生凋亡[74]。

Lurbinectedin是一种人工合成的四氢吡啶 [4,3,2-de] 喹啉-8(1*H*), 最初是从被囊动物*E. turbinata*中分离的海洋化合物ET-736的一个类似物。2020年6月, lurbinectedin获FDA批准用于在铂基化疗期间或之后病情进展的转移性小细胞肺癌成人患者[75]。然而, 在CORAIL III期试验中, lurbinectedin在铂耐药卵巢癌患者中的疗效并不优于聚乙二醇化脂体多柔比星或拓扑替康[76]。Lurbinectedin具有多种作用机制, 其结合于蛋白质编码基因启动子、相互作用的转录因子或DNA修复分子上的少量富含CG的沟槽序列, 诱导细胞周期扰动和细胞死亡[74,77,78]。作为trabectedin的类似物, lurbinectedin同样也能减少肿瘤相关巨噬细胞的数量, 从而调节肿瘤微环境。

4.3 Midostaurin Midostaurin是一种吲哚卡唑生物碱staurosporine的类似物, 最初从被囊动物*Toealensis*中分离出来[79-81]。Midostaurin于2017年获得FDA批准, 可用于治疗新诊断的FMS样酪氨酸激酶3 (FLT3) 突变阳性急性髓系白血病合并标准阿糖胞苷 (cytarabine) 和柔红霉素诱导、阿糖胞苷巩固或侵袭性系统性肥大细胞增多症的成人患者[79-81]。Midostaurin可靶向多种蛋白激酶, 如FLT3、PKC和血管内皮生长因子受体 (VEGFRs)。Midostaurin与staurosporine的结构相比, 酚基的加入增加了分子的吸附能力, 降低了分子毒性。来自海洋化合物的其他激酶抑制剂有吲哚卡唑莱司替尼 [对FLT3、JAK-2、TRK (receptor tyrosine kinase)-A、TRK-B、TRK-C具有活性的多激酶抑制剂]、enzastaurin [PKCβ和GSK-3β (glycogen synthase kinase-3 beta) 抑制剂] 和CEP-2563 (TRK-A/B/C抑制剂)[79-81]。

4.4 抗体−药物偶联物 该类药物均为抗肿瘤活性肽, 且最终均用于抗体−药物偶联物 (ADC)。其中, brentuximab vedotin是首个商业化使用的ADC, 其有效载荷来自海洋的天然化合物: 平均4个MMAE (monomethyl auristatin E) 分子通过间隔物对氨基苯氨基甲酸酯、组织蛋白酶可切割连接物 (缬氨酸−瓜氨酸) 和1个由己酸和马来酰亚胺组成的附着基团与抗CD30抗体连接。MMAE与dolastatin保持相同的结构, 除了C端dolaphenine残基被 (1*S*,2*R*)-(+)-去甲麻黄碱取代[82]。

MMAE的高毒性使其无法单独使用[83], 因此, 与抗体结合是其对抗癌细胞的基础, 一旦被网格蛋白介导的内吞作用内化, 溶酶体蛋白酶就会裂解连接器并将MMAE释放到胞质中。MMAE作为其原始分子多拉司他汀, 与微管结合, 有效抑制微管聚合, 诱导G2/M期细胞周期阻滞, 进而诱导细胞凋亡。与其他用于治疗淋巴瘤的抗有丝分裂药 (如长春碱) 相比, 该配方的效力可达200倍。Brentuximab vedotin被FDA批准用于霍奇金淋巴瘤、全身间变性大细胞淋巴瘤、皮肤和外周T细胞淋巴瘤的不同适应症[84-86]。

Polatuzumab vedotin是另一种以MMAE为有效成分的上市ADC, 于2019年获FDA批准, 与苯达莫司汀和利妥昔单抗联合用于治疗至少两种既往治疗后复发或难治的弥漫性大B细胞淋巴瘤[87,88]。平均3.5个MMAE分子与人源化的抗CD79b IgG1抗体偶联[89]。该抗体的靶点在淋巴瘤患者的B细胞中高度表达, 使得治疗具有高度特异性。该批准是基于一项针对复发或难治性弥漫性大B细胞淋巴瘤患者的多中心Ib/II期研究, 该研究对象为既往有ASCT (autologous stem cell transplant) 经历治疗失败且被认为不适合移植的患者[89]。

MMAE也是enfortumab vedotin的有效载体, 基于一项使用enfortumab vedotin作为单药疗法的II期临床试验结果[90,91], 该药物于2019年获FDA批准, 用于治疗先前接受PD-1或PD-L1抑制剂和含铂化疗方案的局部晚期或转移性尿路上皮癌患者[92]。在这里, 抗体靶向nectin-4, 一种在尿路上皮癌细胞中表达的细胞表面蛋白, 参与Ca^{2+}不依赖的细胞黏附。

另一种合成的用于有效载荷的auristatin衍生物是单甲基auristatin F (MMAF), 它不同于MMAE, 在其C端有1个苯丙氨酸。这部分降低了细胞毒活性, 并有助于膜的不透性[93]。MMAF被纳入抗BCMA (B cell maturation antigen) 药物belantamab mafodotin中, 并于2020年8月获得FDA批准, 用于治疗复发或难治性多发性骨髓瘤患者[94,95]。

4.5 阿糖胞苷及其衍生物 核苷类药物在海洋源性药物的历史中发挥了关键作用。20世纪50年代早期, Cimino等[96]发表了对海洋和海洋衍生的生物活性化合物作为药物的先驱研究, 描述了阿拉伯核苷海绵胸腺嘧啶 (arabinonucleoside spongothymidine, Ara-T) 的化学结构, 以及其他海绵衍生的核苷海绵苷和海绵尿苷, 启发了两种来自海洋的上市药物的合成, 阿糖胞苷和阿糖腺苷 (vidarabine, Ara-A), 其分别于1969年和1976年获得FDA的批准[96]。值得注意的是, 阿糖胞苷和阿糖腺苷是在从天然来源的*Streptomyces griseus*链霉菌、金齿柳菌*Eunicella cavolini*和抗生素链霉菌菌株的发酵液中提取之后在实验室合成的[96,97]。阿糖腺苷之后进一步发展出新药磷酸氟达拉滨 (fludarabine phosphate) 和奈拉滨 (nelarabine), 并在2005年被FDA批准应用于临床。

阿糖胞苷是一种前药, 在细胞内被脱氧胞苷和嘧啶激酶转化为相应的三磷酸激活代谢物, 进而抑制DNA多聚酶的活性而影响DNA合成; 也可掺入DNA中干扰其复制, 使细胞死亡[97]。因此, 快速分裂的细胞 (需更多的DNA复制) 受影响最大[98-100]。阿糖胞苷作为第一种用于治疗白血病的海洋衍生药物, 自1969年以来已被广泛用于血液癌。此外, 阿糖胞苷脂质体制剂还可改善阿糖胞苷的稳定性和快速脱氨, 增加半衰期, 从而延长药物暴露于中枢神经系统肿瘤细胞的时间[101-103]。

磷酸氟达拉滨是嘌呤阿拉伯核苷的磷酸盐, 其碱基为2-氟腺嘌呤。与上文类似物一样, 它是一种必须在细胞内转化为活性形式的前药。它最初在血浆中被去磷酸化为2-fluoro-Ara-A, 然后运输到细胞, 在那里被脱氧胞苷激酶磷酸化为2-fluoro-Ara-ATP。后者一旦被整合到DNA中, 就成为DNA链终止子[104-106]。它在临床上与环磷酰胺和利妥昔单抗联合使用治疗成人慢性淋巴细胞白血病[107]。

奈拉滨是一种具有细胞毒性的脱氧鸟嘌呤类似物9-*β*-*D*-阿拉伯呋喃鸟嘌呤 (Ara-G) 的水溶性前体药物, 与阿糖胞苷的作用机制相同。奈拉滨最初被内源性腺苷脱氨酶去甲氧基化为Ara-G, 其被脱氧鸟苷和脱氧胞苷激酶磷酸化为阿拉伯糖基鸟嘌呤核苷酸三磷酸 (Ara-GTP) 产生细胞毒性代谢物, 负责阻断DNA合成。2005年, FDA批准该药用于至少接受过两次化疗的复发或难治性T细胞淋巴母细胞白血病和T细胞淋巴母细胞淋巴瘤患者的治疗[107]。

甲磺酸艾日布林eribulin mesylate是源于海绵的聚醚大环内酯halichondrin B的类似物, 于2010年被批准用于转移性乳腺癌的治疗[108]。之后, FDA批准eribulin也可用于不可切除和转移性脂肪肉瘤的治疗[109,110]。

5 海洋药物开发的现状与限制因素

目前, 关于开发海洋药物仍有诸多挑战。首先, 许多海洋来源代谢物是对海洋环境变化的一个反馈调节。在瞬息万变的海洋环境中, 可能导致同一生物每次产生的代谢物都不一样, 使得研究很易陷入困境。此外, 许多海洋来源的生物活性化合物是由寄生或共生在水生动物体内的微生物形成的, 而此类微生物一般不能单独在纯群落中培养。通常, 它们所分泌的代谢物是直接基于宿主的行为进行的调控, 体外培养较难模拟实际生存环境而难以获得相应的化合物。所以, 对该类化合物的微生物分离培养存在较大困难, 在

进一步探索这些物种的代谢能力方面存在严重障碍。组学的兴起可允许将此类不可培养的微生物和微生物群落直接应用于组学分析中, 可直接进行初期化合物的筛选。此外, 规模化提取和合成海洋来源药物也往往是一个挑战。先导化合物只能在有限浓度下获得, 并且分离此类化合物在技术上相当具有挑战性。因此, 如何提高海洋来源化合物的规模化分离和提取是未来解决临床应用的一个关键问题。

海洋来源的生物材料的多样性几乎等同于海洋生物多样性本身, 海洋环境是一种宝贵而又被低估的抗癌化合物来源。阿糖胞苷在1969年获FDA批准后, 在过去的数十年中, 海洋衍生化合物的商业开发效率达到高潮, 一批其他海洋衍生药物也被批准用于癌症治疗。然而, 从海洋资源开发药物是一个耗时、高风险的过程, 需大量投资, 需要科研机构和制药企业之间进行更紧密的合作。目前药物开发的初始阶段原材料获得方式仍比较原始, 应加强多学科交流合作, 建立一套化学或生物全合成的开发体系, 从而降低原始采样难度, 加快合成效率, 为海洋药物开发的快速通道搭建基础平台。另外, 还需在医学、法律及伦理专家共同努力下, 有效推进临床试验, 在证明其效力、效率、安全性和投资回报的情况下, 最终完成开发并进入市场。目前, 纳米粒包裹海洋药物, 作为一种非常成功的方法, 被用作ADC的有效载荷, 为其他类型海洋来源药物提供了一个重要示范。此外, 随着多组学策略如转录组、蛋白组、代谢组、表观组等的渗透, 以及合成生物学迅速崛起, 可预见海洋天然产物的发现和药物开发将进入新的快车道。

作者贡献: 欧阳紫君负责全文撰写; 孙晓凡负责图表绘制及全文格式修改; 孙海燕负责完善文章思路并修改文章; 孙洋负责文章的选题与审阅。

利益冲突: 所有作者均声明本文无相关利益冲突。

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