非编码RNA与肿瘤免疫调控

郭乔如[1], 刘 韵[1], 苏超粤[1], 王 会[2], 张建业[1*]

(1. 广州医科大学药学院, 广东省分子标靶与临床药理学重点实验室, 广东 广州 511436;
2. 广州医科大学附属广州市妇女儿童医疗中心, 广东 广州 510623)

摘要: 非编码RNA是一类无蛋白编码功能的RNA, 在肿瘤的发生和发展过程中发挥着重要的作用。免疫系统对肿瘤的发展更有着复杂的作用, 它不仅可以抑制肿瘤的生长, 还可以为肿瘤的发展创造条件, 从而促进肿瘤的生长。肿瘤免疫治疗作为肿瘤治疗的一个重要的手段, 可以通过非编码RNA调控肿瘤免疫来实现治疗的目的。本文就非编码RNA对肿瘤免疫的调控做一综述。

关键词: 非编码RNA; 微小RNA; 长链非编码RNA; 环状RNA; 肿瘤免疫

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2019)10-1783-09

Non-coding RNA and tumor immune regulation

GUO Qiao-ru[1], LIU Yun[1], SU Chao-yue[1], WANG Hui[2], ZHANG Jian-ye[1*]

(*1. Guangdong Provincial Key Laboratory of Molecular Target and Clinical Pharmacology, School of Pharmaceutical Sciences, Guangzhou Medical University, Guangzhou 511436, China; 2. Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China*)

Abstract: non-coding RNA (ncRNA) is a kind of non-protein coding RNA, which plays a vital role in the initiation and development of tumor. The immune system also exhibits more complex function in tumor development. It can not only inhibit the development of tumor, but also create conditions for tumor growth. As an important means of tumor therapy, tumor immunotherapy can be regulated by non-coding RNA to achieve the goal of treatment. This article summarizes the regulation of tumor immunity by non-coding RNA.

Key words: non-coding RNA; miRNA; lncRNA; circRNA; tumor immunity

非编码RNA (non-coding RNA, ncRNA) 是一类无蛋白编码功能的RNA, 在细胞的发育和代谢过程中, 发挥着重要的作用[1,2]。ncRNA包括小非编码RNA (small noncoding RNA, sncRNA)、长链非编码RNA (long noncoding RNA, lncRNA) 和环状RNA (circular RNA, circRNA) 等[3]。

免疫系统与肿瘤的相互作用可以分成3个阶段: 免疫消除、免疫相持和免疫逃逸[4]。在免疫消除阶段, 机体通过基因修复、老化、细胞凋亡等方式对肿瘤细胞进行内源性的抑制; 同时, 凋亡细胞产生的危险信号和肿瘤细胞产生的抗原同时刺激免疫系统, 使得固有免疫和适应性免疫共同作用, 产生抗肿瘤效应。在免疫消除阶段过后仍残存一些变异的肿瘤细胞, 与适应性免疫细胞相互作用, 经历免疫相持阶段, 此时, 肿瘤细胞的生长被免疫机制所阻止。然而, 当肿瘤细胞和免疫系统的平衡被打破, 肿瘤细胞通过产生免疫抑制细胞因子如血管内皮生长因子 (vascular endothelial growth factor, VEGF) 和转化生长因子-β (transforming growth factor-β, TGF-β), 并募集具有免疫抑制效应的调节免疫细胞 (regulatory cells, Treg) 和骨髓来源的抑制性细胞 (myeloid-derived suppressor cells, MDSC), 产生免疫逃逸环境[5]。

收稿日期: 2019-07-17; 修回日期: 2019-09-06.
基金项目: 国家自然科学基金资助项目 (81773888, 81473320); 广州市妇女儿童医疗中心/儿科研究所科研基金 (IP-2018-012).
*通讯作者 Tel: 86-20-37103631, E-mail: jianyez@163.com
DOI: 10.16438/j.0513-4870.2019-0570

免疫逃逸作为肿瘤的生物学特征之一[6], 表现出免疫系统对肿瘤发生和发展的双重作用: 一方面, 肿瘤浸润免疫细胞可以有效地控制肿瘤的发生发展, 最终消灭肿瘤细胞; 另一方面, 可以使肿瘤逃避免疫攻击, 促进肿瘤的发展[7]; 此外, 肿瘤产生过程中, 由固有免疫细胞介导的外源性途径和肿瘤细胞介导的内源性途径共同作用, 在肿瘤微环境中产生促瘤的炎症, 促使肿瘤突破免疫防线[8]。

因此, 肿瘤免疫治疗成为肿瘤治疗中一个重要的手段, 而肿瘤免疫治疗可以通过干预表观遗传修饰来实现。表观遗传学是指不改变DNA序列而改变基因的表达, 表观遗传的改变可以破坏免疫原性和免疫识别机制, 使肿瘤细胞获得免疫逃逸的表型[9]。实现表观遗传修饰主要有3种方式: DNA甲基化、组蛋白修饰和非编码RNA调控。本文就非编码RNA对肿瘤免疫的调控做一综述。

1 miRNA与肿瘤免疫

微小RNA (microRNA, miRNA) 是sncRNA的一类, 含有19～25个单核苷酸的单链RNA, 广泛存在于真核生物中。成熟的miRNA通过进入RNA诱导的沉默复合体, 与靶RNA的3'非翻译区特异性结合, 从而抑制目的蛋白的翻译或者使转录本降解, 并可作为配体, 与Toll样受体 (Toll like receptor, TLR) 结合, 激活下游信号通路[10,11] (图1)。越来越多的研究表明, miRNA的异常表达与肿瘤的发生发展有着密切的关系[12-19]。

1.1 miRNA与固有免疫 固有免疫是机体抵御病原微生物入侵的第一道防线。执行固有免疫功能的免疫细胞主要有巨噬细胞、自然杀伤细胞 (natural killer cell, NK)、粒细胞和树突状细胞 (dendritic cell, DC), 这些固有免疫细胞可通过TLR介导的信号传导而活化, 产生非特异性免疫保护作用。

NK细胞是固有免疫系统的淋巴细胞, 不仅对肿瘤细胞具有细胞介导的细胞毒性, 而且可分泌细胞因子和趋化因子以促进或抑制其他免疫细胞的功能, 发挥调节作用[20]。有研究[21]表明, miR-30e可通过靶向调节穿孔蛋白 (perforin), 调控NK细胞的细胞毒性。miR-155也能够调控NK细胞的效应功能, 高表达的miR-155可通过靶向作用于造血细胞特异性肌醇磷酸酶1 (hematopoietic-specific inositol phosphatase 1, SHIP-1), 提高NK细胞的活性, 并使免疫刺激细胞因子γ-干扰素 (interferon-γ, IFN-γ) 分泌增加, 在肿瘤免疫反应中发挥作用[22]。

巨噬细胞在固有免疫中发挥着重要的作用, 不仅可以作为专职抗原呈递细胞 (antigen presenting cells, APC), 也可以作为溶解肿瘤细胞的效应细胞, 发挥抗肿瘤的作用。然而在肿瘤发展的过程中, 巨噬细胞可发生表型转换, 向M2表型极化, M2细胞介导抗炎和促肿瘤反应, 表现为免疫抑制、促进肿瘤血管生成和转移。肿瘤相关巨噬细胞 (tumor-associated macrophages, TAM) 一般表现为M2表型, 可促进肿瘤的发展[23]。Yin等[24]在结直肠癌细胞中发现, TAM分泌的IL-6通过激活IL-6R/STAT3/miR-204-5p通路诱导耐药, 表明miR-204-5p是调节TAM诱导的结直肠癌耐药的功能性靶标; 此外, miR-155是控制巨噬细胞表型开关的关键分子, miR-155修饰的TAMs可以被重新编程, 并恢复肿瘤杀伤能力。还有研究[25]表明, 外泌体-miR-23a-3p从发生内质网应激的肝细胞癌 (hepatocellular carcinoma, HCC) 细胞转移到巨噬细胞中, 使得肿瘤细胞逃避免疫细胞毒性, 阻断了肿瘤细胞凋亡, 表明miRNA在HCC-巨噬细胞通讯中发挥了重要的作用。

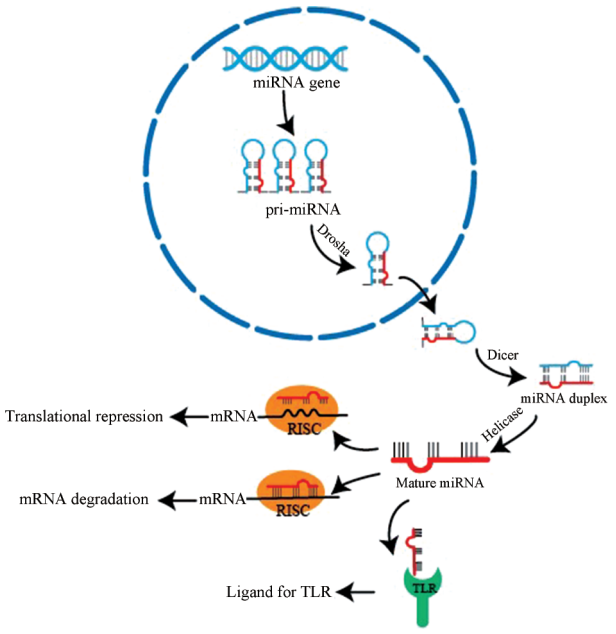

Figure 1 The mechanism of microRNA (miRNA). RISC: RNA-induced silencing complex; TLR: Toll like receptor

1.2 miRNA与适应性免疫 适应性免疫是受主要组织相容复合体调控的免疫反应, 由多种免疫细胞和免疫分子共同参与。适应性免疫具有特异性, 针对特定的抗原, 不能够遗传但是具有免疫记忆效应。适应性免疫包括细胞免疫和体液免疫两部分, 其中细胞免疫在肿瘤免疫过程中发挥着关键的作用。

T淋巴细胞在抗肿瘤免疫应答中非常重要, 其中$CD8^+$ T细胞可分化为细胞毒性T淋巴细胞 (cytotoxic lymphocyte, CTL); $CD4^+$ T细胞可在不同的细胞因子的诱导下分化成不同亚型的T细胞, 包括辅助性T细胞 (T helper cell, Th) 和调节性T细胞 (regulatory T cells,

Treg)。其中, 调节性T细胞具有免疫抑制作用, 大量的Treg细胞浸润往往与预后不良有关, 可诱导肿瘤细胞发生免疫逃逸。Anandagoda等[26]的研究表明, miR-142-5p通过控制Treg中磷酸二酯酶-3b (the cAMP-hydrolyzing enzyme phosphodiesterase-3b, PDE3B) 的表达, 对调控Treg细胞抑制功能通路起到了重要的作用, 而Treg细胞的激活可以通过增强外周对肿瘤本身的耐受或通过“免疫忽视”作用, 消除肿瘤T细胞免疫; 此外, Wan等[27]也提出, 肿瘤细胞特异miR-142-5p表达可以通过抑制磷酸酶紧张素同源物 (phosphate and tension homology deleted on chromosome ten, PTEN) 促进肿瘤免疫逃避, 限制$CD4^+$ T细胞抗肿瘤免疫。Zhou等[28]发现, 富集有miR-29a-3p和miR-21-5p的外泌体介导了TAMs和T细胞之间的相互作用, 产生一种免疫抑制微环境, 促进上皮性卵巢癌的发展和转移, 这项发现表明, 靶向这些外泌体或它们相关的miRNA可能为开发上皮性卵巢癌的新治疗方法铺平道路。

2 lncRNA与肿瘤免疫

lncRNA是一种长度大于200个核苷酸的非编码RNA。lncRNA参与了一系列的生物过程, 可促进染色质修饰, 介导基因沉默, 并可作为蛋白质的导向分子和支架, 促进细胞亚结构的形成; 控制蛋白质的合成、RNA的成熟及运输[29,30]。此外, 也有研究表明, lncRNA可以发挥“海绵”/“诱饵”作用, 通过竞争性地与miRNA结合, 降低miRNA对靶RNA的调控作用[31,32] (图2)。lncRNA的异常表达在许多癌症的发生发展中起到了重要的调控作用。

2.1 lncRNA与固有免疫 DC是免疫系统的关键调节因子, 是固有免疫和适应性免疫之间的桥梁, 它不仅可以进行抗原的呈递, 还能传递共刺激信号并产生细胞因子以调节适应性免疫[33]。在肿瘤微环境中, DCs的抗原交叉呈递功能受损, 导致抗肿瘤免疫激活反应受损, 促进肿瘤的发展, 而lncRNA在其中发挥着关键的作用: lnc-DC是DC细胞中特有的lncRNA, 在肿瘤微环境中, lnc-DC的表达下降, 导致DC刺激T细胞活化能力降低, 分化能力受损, 使得抗肿瘤免疫应答能力减弱[34]。

lncRNA也可通过调控NK细胞影响癌症的发展: Fang等[35]研究发现, lncRNA GAS5具有抑制肿瘤生长的作用, 并且GAS5的过表达可以调控miR-544/RUNX3增强NK细胞对肝癌的杀伤作用。

多项研究表明, lncRNA可调控巨噬细胞的活化与极化, 在抗肿瘤或促肿瘤反应中发挥重要的作用。Zhang等[36]发现, lncRNA Neat1在体内增强了巨噬细胞炎症小体血管内皮细胞NOD样受体蛋白3

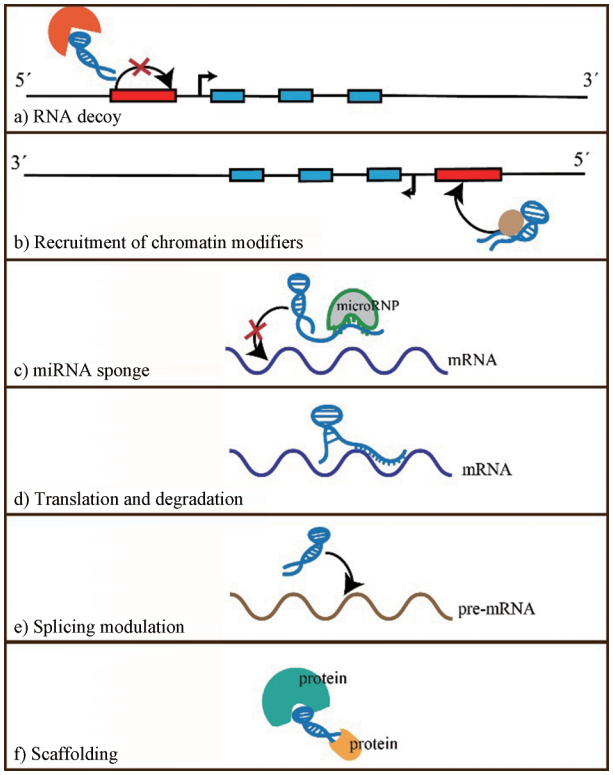

Figure 2 Mechanisms of long non-coding RNA (lncRNA) action

(NACHT、LRR and PYD domains-containing protein 3, NLRP3) 和核苷酸结合寡聚域样受体4 (NLR family, CARD domain containing 4, NLRC4) 的激活。Huang等[37]通过一系列的研究证实, TAMs中的lncRNA MALAT1可以通过介导成纤维细胞生长因子2 (fibroblast growth factor-2, FGF-2) 分泌, 抑制炎症细胞因子的释放, 促进FTC133细胞的增殖、迁移和侵袭, 促进甲状腺癌的新生血管生成。Cao等[38]研究发现, lncRNA MM2P是巨噬细胞M2极化的调节剂, MM2P的下调可以阻断细胞因子驱动的巨噬细胞M2极化, 并减弱巨噬细胞M2促进新生血管生成的特性。在上皮卵巢癌中, M2样肿瘤相关巨噬细胞分泌的表皮细胞生长因子 (epidermal growth factor, EGF) 通过表皮生长因子受体 (epidermal growth factor receptor, EGFR)-细胞外调节蛋白激酶 (extracellular regulated protein kinases, ERK) 信号通路, 抑制lncRNA LIMT的表达, 促进上皮卵巢癌的转移[39]。

2.2 lncRNA与适应性免疫 lncRNA也可以通过调控Treg细胞, 对肿瘤免疫进行调控。Pei等[40]研究发现, 通过干扰lncRNA SNHG1可提高miR-448的表达, 使吲哚胺2,3-双加氧酶 (indoleamine 2,3-dioxygenase, IDO) 表达下调, 抑制Treg细胞分化, 减轻乳腺癌细胞的免疫逃逸; EGFR是酪氨酸激酶受体家族的重要成员, lnc-EGFR通过特异性地与EGFR结合, 促进Treg

细胞分化, 促进肝癌细胞的免疫逃逸[41]。

辅助性T细胞因不同的细胞因子的诱导, 可分为不同的亚群, 包括Th1和Th2。Th1细胞产生肿瘤坏死因子 α (tumor necrosis factor alpha, TNF-α)、干扰素 γ (interferon gamma, IFN-γ)、白介素-2 (interleukin-2, IL-2) 和白介素-12 (interleukin-12, IL-12), 介导抗肿瘤作用; Th2细胞产生白介素-4 (interleukin-4, IL-4) 和白介素-10 (interleukin-10, IL-10), 可通过免疫抑制作用促进肿瘤的生长。临床资料显示, 乳腺癌患者Th1/Th2失衡, Th2释放细胞因子升高。此外, Th1占主导反应的患者生存率更高, 癌症复发率更低。因此, 调控Th1/Th2的比例可能对肿瘤的治疗产生帮助[42]。Yao等[43]研究表明, 幽门螺旋杆菌和高盐饮食均可诱导胃癌的发生, 血清和糖皮质激素诱导激酶1 (serum and glucocorticoid-inducible kinase 1, SGK1) 可在多种恶性肿瘤中被触发, 而在T细胞中, 幽门螺旋杆菌感染和高盐饮食可使得SGK1表达上调, 进而通过JunB基因上调lnc-SGK1的表达, 诱导Th2、Th17细胞分化, 降低Th1细胞分化, 诱导胃癌细胞产生肿瘤逃逸环境。Huang等[44]研究发现, T淋巴细胞激活诱导的细胞死亡 (activation-induced cell death, AICD) 可被癌细胞利用, 以逃避免疫攻击; lnc-NKILA可通过核转录因子-κB (nuclear factor-kappa B, NF-κB) 的激活, 调节各个亚型T细胞对AICD的敏感性, 从而调控肿瘤免疫反应。在肿瘤特异性细胞毒性T淋巴细胞 (cytotoxic T lymphocytes, CTL) 和Th1细胞中, NKILA的沉默可以保护它们免受AICD的侵袭; 在Treg细胞和Th2细胞中, NKILA的表达上调则增加了它们对AICD的敏感性; 将CTL细胞的*NKILA*基因敲除并增加CTL的浸润, 明显抑制了小鼠体内乳腺癌患者来源的异种移植瘤的生长。

3 circRNA与肿瘤免疫

circRNA是一类特殊的ncRNA, 是5'端帽子和3'端poly A尾通过特定的反剪接机制共价连接的RNA片段[45]。由于其缺乏游离的5'端和3'端, circRNA不易被核糖核酸内切酶和其他外切酶分解, 因此比其他ncRNA结构更加稳定[46]。cricRNA具有4种不同的来源, 并据此可分为4种不同的类型: 外显子来源的环状RNA (exonic circRNA, ecircRNA)、内含子来源的环状RNA (intronic circRNA, ciRNA)、外显子和内含子共同形成的环状RNA (exon-intron circRNA, eiciRNA) 和来自基因间区域的环状RNA (intergenic circRNA)[47] (图3)。

circRNA作为基因表达的主调控因子, 除了通过直接调节转录和干扰剪切机制等发挥作用, 主要是通过海绵样作用与miRNA竞争性结合, 抑制miRNA对靶基因的负调控作用: 程序性细胞凋亡蛋白1 (programmed cell death protein 1, PD-1) 是T淋巴细胞的一个表面因子, 当肿瘤细胞表面过度表达PD-L1时, 肿瘤细胞表面PD-L1与PD-1结合, 可抑制T细胞的活化和增殖, 产生免疫逃逸。Zhang等[48]研究发现, circRNA hsa_circ_0020397可与miR-138结合, 抑制miR-138活性, 从而导致PD-L1在结直肠癌细胞中过表达, 抑制T

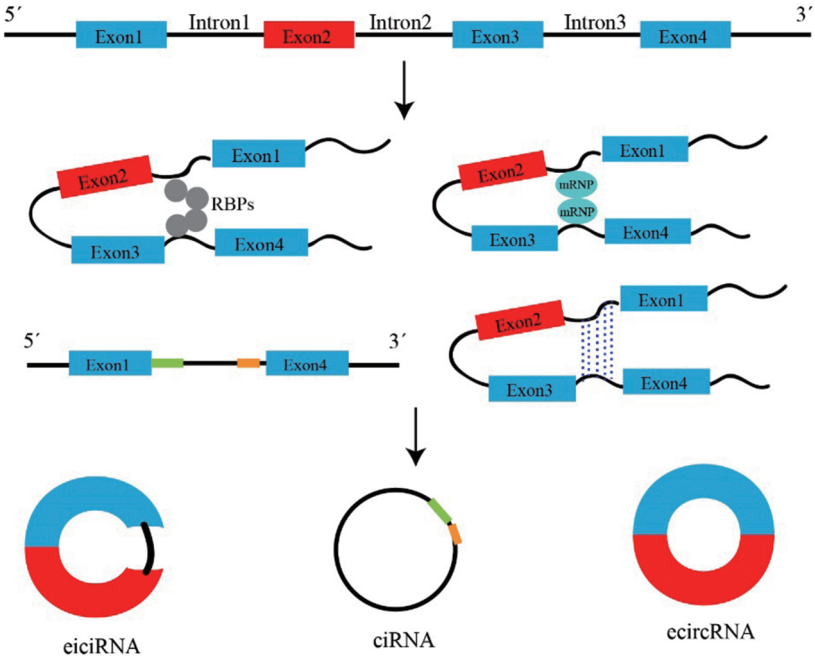

Figure 3 The formation and classification of circRNA. eiciRNA: Exon-intron circRNA; ciRNA: Intronic circRNA; ecircRNA: Exonic circRNA

细胞活化, 发生免疫逃逸。除了作为miRNA的“海绵”调控miRNA的表达外, 在癌症的发生中, 由于基因突变等原因, 肿瘤细胞产生了许多异常的circRNA, 这些新形成的异常circRNA可作为肿瘤抗原, 通过肿瘤细胞分泌的外泌体, 转运至免疫细胞, 激活抗肿瘤免疫[49]。

4 ncRNA与肿瘤炎性微环境

慢性炎症是癌症的一个特征[50], 许多因素可以触发肿瘤的炎症反应, 包括感染、组织损伤、致癌基因的激活和肿瘤抑制因子的丢失等[51]。肿瘤炎性微环境在肿瘤免疫中起到了免疫抑制的作用, 它的形成除了有上文叙述的固有免疫和适应性免疫相关细胞的参与, 许多炎症相关的细胞因子也参与其中, 如NF-κB、TGF-β和IL-6等。ncRNA可调控或者被这些细胞因子所调控, 在肿瘤微环境的发生和肿瘤的发展中起到了不可或缺的作用 (图4)。

NF-κB被认为是联系炎症与肿瘤的桥梁, 在肿瘤炎性微环境中, 持续的炎症反应引起NF-κB通路的异常激活, 促进肿瘤的发展。有研究表明, NF-κB炎性通路在肿瘤微环境中被激活, 可以促进Lin-28基因的表达, 降低miRNA let-7的产生, 从而促进IL-6的表达, 使STAT3转录因子激活。而IL-6的激活又可以促进NF-κB的表达, 在肿瘤炎性微环境中形成一个正反馈的通路, 促进癌症的发生与发展[52]。在这条通路中, miRNA let-7起到了重要的作用。当然, 介导NF-κB炎症通路的因子不仅限于let-7。Taganov等[53]最先提出miR-146是经典的NF-κB活化的负调控因子: TLR和NF-κB的共同激活诱导miR-146表达, miR-146以白介素-1受体相关激酶1 (interleukin-1 receptor-associated kinase 1, IRAK1)和肿瘤坏死因子受体相关因子6 (TNF receptor associated factor 6, TRAF6)为靶点, 可调节固有免疫, 抑制TLR信号通路并减少促炎细胞因子产生。lncRNA与circRNA在NF-κB通路的激活中也发挥着重要的作用: lncRNA Camk-A在癌症患者体内高表达, 激活Ca^{2+}/钙调素依赖激酶PNCK通路, 导致NF-κB活化, 从而导致肿瘤微环境的改变, 促进肿瘤的发展[54]。Wang等[55]发现, 在乳腺癌发展的过程中, circRNA_000911作为miR449的“海绵”, 负调控miR449a的表达。当cirRNA_000911表达下调时, 通过circRNA_000911/miR449a通路, 激活NF-κB信号通路, 使得肿瘤微环境改变, 从而促进乳腺癌的发展。在食管鳞状细胞癌 (esophageal squamous cell carcinoma, ESCC)中, circRNA ciRS-7通过激活miR-7/KLF-4及NF-κB信号通路, 触发ESCC细胞的迁移与入侵[56]。

TGF-β是一种炎症相关细胞因子, 它在肿瘤的发展中具有双重角色, 即在肿瘤发生的早期阶段发挥肿瘤抑制作用, 而在肿瘤晚期却可以促进肿瘤的转移[57]。TGF-β信号通路是介导肿瘤转移的一条必不可少的通路, 作为重要的免疫抑制性细胞因子, 介导肿瘤细胞发

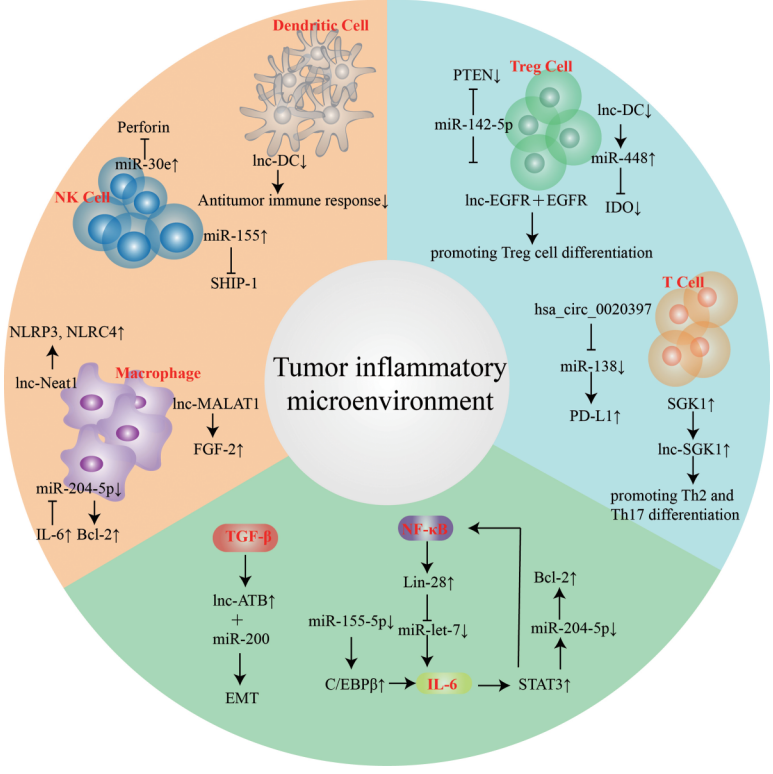

Figure 4 Components of tumor inflammatory microenvironment

生免疫逃逸, 并能促进肿瘤细胞的迁移与侵袭、血管生成、细胞增殖与凋亡[58]。在肝细胞性肝癌中, 在肿瘤微环境下 TGF-β被激活, 上调 lncRNA ATB, 并促使其与 miR-200 家族结合, 上调相关靶基因, 起到了促进上皮−间质转化和肿瘤细胞侵袭的作用[59]。Ahn 等[60]研究发现, 在卵巢癌细胞中, TGF-β可通过表观遗传机制诱导产生一种非编码 RNA nc886, nc886 可抑制卵巢癌细胞中的 miRNA 成熟, 从而抑制一系列的 miRNA 通路, 最终促进卵巢癌的发展与转移。部分 ncRNA 也可以通过干扰 TGF-β通路发挥抑癌作用: 类 Y 染色体相关高迁移率族盒蛋白 (Sry-like highmobility group box 4, SOX4) 转录蛋白由 TGF-β通路直接诱导, 在肝癌细胞中常过度表达, 而 miR-449 家族可通过干扰 TGF-β通路, 下调癌基因 SOX4 的表达, 从而起到抑癌作用[61]。

IL6/STAT3 信号通路在肿瘤微环境中是介导免疫抑制的关键通路。肿瘤免疫微环境中, TAM 细胞中 miR-155-5p 的表达常下调, 上调 TAM 细胞分泌转录因子 CCAAT 增强子结合蛋白β (CCAAT enhancer binding protein, C/EBPβ), 促使 TAM 分泌 IL-6; IL-6 转录激活信号传导转录启动因子 3 (signal transducers and acti-

Table 1 The summary of ncRNA

ncRNA	RNA type	Cancer type	Function
miR-30e	miRNA	−	miR-30e regulates NK cell cytotoxicity by targeting perforin.
miR-155	miRNA	−	miR-155 regulates IFN-gamma production in natural killer cells.
miR-204-5p	miRNA	Colorectal cancer	miR-204-5p is a functional target mediating the TAM-induced colorectal cancer chemoresistance.
miR-23a-3p	miRNA	Liver cancer	Endoplasmic reticulum stress causes liver cancer cells to release exosomal miR-23a-3p and up-regulate programmed death ligand 1 expression in macrophages.
miR-142-5p	miRNA	−	miR-142-mediated repression of phosphodiesterase 3B critically regulates peripheral immune tolerance.
miR-29a-3p, miR-21-5p	miRNA	Epithelial ovarian cancer	miR-29a-3p and miR-21-5p which are enriched in exosomes can facilitate EOC progression and metastasis.
miR-146	miRNA	−	NF-κB-dependent induction of miR-146, an inhibitor targeted to signaling proteins of innate immune responses.
miR-449	miRNA	Liver cancer	miR-449 downregulates the expression of SOX4 by interfering TGF-β signaling pathway.
nc-886	−	Ovarian cancer	nc-886 can inhibit the maturation of miRNA and ultimately promote the development and metastasis of ovarian cancer.
miR-197	miRNA	Liver cancer	miR-197 can significantly inhibit the proliferation and invasion of cancer cells by inhibiting IL-6/STAT3 signaling pathway.
lnc DC	lncRNA	−	The STAT3-binding long noncoding RNA lnc-DC controls human dendritic cell differentiation.
lnc GAS5	lncRNA	Liver cancer	lncRNA GAS5 enhances the killing effect of NK cell on liver cancer through regulating miR-544/RUNX3.
lnc Neat1	lncRNA	−	The lncRNA Neat1 promotes activation of inflammasomes in macrophages.
lnc MALAT1	lncRNA	Thyroid cancer	lncRNA-MALAT1 promotes angiogenesis of thyroid cancer by modulating tumor-associated macrophage FGF2 protein secretion.
lnc MM2P	lncRNA	−	lncRNA-MM2P identified as a modulator of macrophage M2 polarization.
lnc LIMT	lncRNA	Epithelial ovarian cancer	M2-like tumor-associated macrophages-secreted EGF promotes epithelial ovarian cancer metastasis *via* activating EGFR-ERK signaling and suppressing lncRNA LIMT expression.
lnc SNHG1	lncRNA	Breast cancer	lncRNA SNHG1 regulates the differentiation of Treg cells and affects the immune escape of breast cancer *via* regulating miR-448/IDO.
lnc EGFR	lncRNA	Liver cancer	lnc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion.
lnc SGK1	lncRNA	Gastric cancer	lnc SGK1 promotes Th2 and Th17 differentiation in human gastric cancer by SGK1/Jun B signaling.
lnc NKILA	lncRNA	Breast cancer	lnc NKILA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death.
lnc Camk-A	lncRNA	−	lncRNA CamK-A regulates Ca^{2+}-signaling mediated tumor microenvironment remodeling.
hsa_circ_0020397	circRNA	Colorectal cancer	hsa_circ_0020397 regulates colorectal cancer cell viability, apoptosis and invasion by promoting the expression of the miR-138 targets TERT and PD-L1.
circRNA_000911	circRNA	Breast cancer	circRNA_000911 negatively regulates the expression of miR-449a and activates the NF-κB pathway.
circRNA ciRS-7	circRNA	Esophageal squamous cancer; colorectal cancer	circular RNA ciRS-7 accelerates ESCC progression through acting as a miR-876-5p sponge to enhance MAGE-A family expression.

vators of transcription 3, STAT3), 使miR-204-5p的表达下降, 调控其靶基因Bcl-2的表达上调, 引起免疫逃逸作用, 引发肿瘤耐药。这项研究从一个角度说明了IL-6/STAT3通路促进了肿瘤免疫微环境和肿瘤细胞的相互交流[22]。Wang等[62]研究表明, miR-197与IL-6/STAT3通路相互调控, 影响肝细胞性肝癌的发展。miR-197通过抑制IL-6/STAT3通路, 可以显著抑制肝癌细胞的增殖与侵袭, 并促进细胞凋亡。

由此可见, 肿瘤与肿瘤相关炎性微环境之间会发生复杂的分子相互作用。肿瘤细胞可以通过分泌炎症相关细胞因子, 促进肿瘤炎性微环境的形成; 炎症也会通过调节免疫细胞、细胞因子和血管的生成, 促进肿瘤的发展, 而ncRNA在肿瘤与炎性微环境的相互作用中介导并发挥着重要的调控作用 (表1)。

5 小结与展望

综上所述, 免疫疗法在如今的肿瘤治疗中发挥着日益重要的作用, 调控非编码RNA干预表观遗传修饰成为免疫疗法的一个重要手段, 然而其临床使用仍有局限。深入探求非编码RNA对肿瘤免疫的调控作用, 不仅可以作为新兴的肿瘤标志物, 有助于肿瘤的诊断、治疗及判断预后, 也有助于今后发现新的免疫治疗靶标, 对恶性肿瘤的防治提供更有效的方法。

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