miR-21在类风湿性关节炎中的作用机制及研究进展

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摘要 类风湿性关节炎(rheumatoid arthritis, RA)是一种病因未明的慢性自身免疫性疾病, 以手、足小关节的多关节和对称性损害为特征。RA的发病机制复杂、病程较长且致残率比较高, 严重损害了患者的健康和生活质量。miRNA是近年来研究最多的非编码RNA, 在机体的生理和病理过程中发挥重要作用。诸多研究表明, miR-21与RA的发生发展密切相关。因此该文就miR-21在RA中的作用机制及进展进行综述, 作用机制主要是miR-21通过与lncRNA的相互作用, 靶向SNF5、TET1及调节相关信号通路(Wnt、PI3K/AKT、JAK/STAT和NF-κB)来调控RA, 旨在为miR-21与RA的相关研究提供参考及为RA的诊疗提供新策略。

关键词 类风湿性关节炎; miR-21; 信号通路; 靶向; lncRNA

The Mechanism and Research Progress of miR-21 in Rheumatoid Arthritis

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Abstract RA (rheumatoid arthritis) is a chronic autoimmune disease of unknown etiology, which is characterized by multiple joints and symmetrical damage to the small joints of the hands and feet. The pathogenesis of RA is complex, the course of disease is long and the morbidity rate is relatively high, which seriously damages the health and quality of life of patients. miRNA is the most studied non-coding RNA in recent years, which plays an important role in the physiological and pathological processes of the body. Many studies have shown that miR-21 is closely related to the occurrence and development of RA. Therefore, this paper reviews the mechanism and progress of miR-21 in RA, miR-21 mainly through the interaction with lncRNA, targeting SNF5, TET1 and regulating related signaling pathways (Wnt, PI3K/AKT, JAK/STAT and NF-κB) to regulate RA, aiming to provide a reference for the related research of miR-21 and RA and provide a new strategy for the diagnosis and treatment of RA.

Keywords rheumatoid arthritis; miR-21; signaling pathway; targeting; lncRNA

类风湿性关节炎(rheumatoid arthritis, RA)是一种受免疫、遗传、性别、年龄、感染和吸烟等多种因素影响, 以滑膜炎为基本病理改变的慢性自身免疫性疾病[1-2]。RA患者通常表现为对称性的多个关节疼痛、肿胀和僵硬, 最常累及双手的近端指间关节、掌指关节和腕关节等, 晚期可出现关节畸形[2]。RA的发病机制复杂、病程较长且致残率比较高, 给患者健康和生活质量带来了严重影响, 同时也给社

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会卫生系统带来了巨大的经济损失[3]。目前针对RA的治疗主要是抗风湿药物治疗, 但它们有诸多副作用且需要高昂的价格[4]。此外, RA的早期诊断较为复杂。因此, 迫切需要进一步深入研究及阐明RA的发病机制, 寻找特异度及灵敏度高的早期诊断标志物和潜在的治疗靶点。

miRNA在机体的多种生理和病理过程中起着关键作用[5], 尤其是在自身免疫性疾病中[6]。近来研究表明, miRNA与RA的发生发展密切相关, 参与调控成纤维细胞样滑膜细胞的增殖分化和滑膜炎等生理病理过程[7-9]。因此, 相关miRNA很有可能成为RA的有效早期诊断分子标志物或潜在的治疗靶点。研究发现, miR-21是细胞凋亡的重要调节因子, 可以调控T细胞的存活[10-11]。一项研究发现, 调节性T细胞(regulatory T cells, Treg)在RA患者中的积累较多, 且具有巨大的抗凋亡作用, 而Treg在RA中的作用主要与Bcl-2和miR-21的高表达有关[12]。另一项研究发现, miR-21在RA患者中的表达水平显著降低, 而促炎细胞因子IL-17、IL-6、IL-1β、TNF-α和IL-22表达水平升高[13]。由此推测miR-21在RA的发生发展过程中充当重要角色, 其或许可以为RA的早期精确诊断及有效治疗带来新的希望。因此, 本文就近年来miR-21在RA中的作用机制及进展进行综述, 旨在为miR-21与RA的相关研究提供参考及为RA的诊疗提供新策略。

1 miR-21简介

miRNA是一种内源性的具有调控功能的非编码RNA, 其大小为18~24个核苷酸, 主要通过碱基互补配对的方式识别相应靶信使RNA(mRNA), 并根据互补程度的不同指导沉默复合体降解靶mRNA或者阻遏靶mRNA的翻译, 从而调控mRNA的稳定性和翻译来介导基因表达的转录后调控[14-15]。miRNA可以与多种miRNA、mRNA和lncRNA等相互作用形成复杂的基因调控网络, 而且这种复杂的基因调控网络与诸多生理病理过程密切相关。miR-21由位于重叠蛋白编码基因内含子中的保守启动子转录而来, 位于人类17号染色体上, 且高度保守[16]。研究表明, miR-21参与了细胞增殖、细胞分化、细胞凋亡、机体感染以及免疫应答等生理或病理过程的调控, 与恶性肿瘤、心血管系统疾病、神经系统疾病和免疫性疾病等的发生发展有着密切关系[17-20]。miR-21与大部分的蛋白质编码mRNA类似, 其表达受到复杂信号通路的动态调节, 并且可以在免疫细胞发育过程中被细胞外信号增强。单核细胞可以根据接收到的细胞外信号不同分化成各种成熟细胞, 在激活过程中显示miR-21的表达量增加[21-22]。在免疫体系中, miR-21广泛表达于B细胞、T细胞、巨噬细胞、中性粒细胞、单核细胞及树突状细胞等中, 与相关炎症反应密切相关[23]。据报道, miR-21在巨噬细胞中的表达量增加, 而使用miR模拟物单独提高miR-21水平会导致LPS诱导的TNF-α表达和核因子κB(nuclear factor κB, NF-κB)活化受到抑制[24]。这表明, miR-21的表达与促炎反应减弱和炎症消退有关。此外, 在腹膜炎小鼠模型中用促进炎症消退的脂质介质Resolvin D1治疗后, miR-21的表达水平进一步增加[25]。因此, miR-21在自身免疫性疾病中起着关键作用, 可成为相关免疫性疾病新的治疗靶点。

2 miR-21在RA中的作用

miR-21在恶性肿瘤、心血管系统疾病、神经系统疾病和免疫性疾病等的发生发展中起着至关重要的作用, 参与了细胞增殖、细胞分化、细胞凋亡、机体感染以及免疫应答等生理或病理过程的调控[17-20]。近来研究表明, miR-21与RA的发生发展密切相关, 且其在RA中呈低表达。YANG等[26]通过逆转录定量聚合酶链反应检测RA患者和健康者中miR-21的表达量, 与健康组相比, RA患者的miR-21表达量显著降低。一项RA动物实验表明, miR-21过表达可以抑制IL-6和IL-8的表达, 从而缓解RA的炎症反应[27]。另一项RA动物实验也表明, 上调的miR-21可以抑制滑膜增生并减少相关炎性细胞因子分泌, 从而减缓RA的进展[28]。GONG等[29]使用miR-21抑制剂和miRNA模拟物分别处理从RA中分离的成纤维细胞样滑膜细胞, 然后通过蛋白质印迹分析相关蛋白的表达情况, 结果抑制剂组中的TNF-α、IL-6和IL-1的表达量显著增加, 而模拟组中的TNF-α、IL-6和IL-1的表达量显著降低。这些研究表明, 过表达的miR-21可以抑制相关炎症因子的释放, 从而缓解RA的炎症反应。此外, 相关临床实验表明miR-21的表达与RA患者的红细胞沉降率和C反应蛋白呈负相关[26]。总而言之, miR-21在RA中呈高表达, 而且过表达的miR-21可以抑制RA的炎症反应及减缓RA的进程。

3 miR-21调控RA的作用机制

miRNA主要通过与相关mRNA特异结合, 从而抑制转录后基因表达, 对基因表达、细胞周期和生物体发育等起着至关重要的作用[14-15]。作为miRNA的一员, miR-21在RA的发生发展过程中起着不可替代的作用, 其主要通过与相关lncRNA相互作用、靶向相关重要蛋白及调节相关信号通路[Wnt、PI3K/AKT、Janus激酶信号转导及转录激活因子(JAK/STAT)和NF-κB]来调控RA。

3.1 相关lncRNA通过靶向miR-21调控RA

lncRNA是一类长度超过200个核苷酸且不编码蛋白质的RNA分子, 与细胞生长、细胞周期、细胞分化、细胞凋亡和炎症反应等生理病理过程有关[30]。研究表明, lncRNA与miRNA之间存在负性调控关系, 即lncRNA可以通过靶向相应的miRNA, 减少miRNA与靶mRNA的结合, 进而促进mRNA的表达与翻译, 从而影响细胞的生物学行为[31]。

lnc-NEAT1在系统性红斑狼疮(systemic lupus erythematosus, SLE)患者中表达失调[32], 而且通过靶向miR-204-5p促进RA中成纤维样滑膜细胞的增殖和炎性细胞因子的产生[33]; 此外lnc-NEAT1通过调节外泌体介导的巨噬细胞极化介导炎症性肠病的炎症反应[34]; 同时miR-21和miR-125a是RA的潜在诊断生物标志物[12,35]。因此, lnc-NEAT1在调节炎症和自身免疫中发挥重要作用, 或许主要通过靶向miR-21和miR-125a以调节炎症[36]。YANG等[26]为了研究lnc-NEAT1与RA炎症反应、疾病活动、治疗结果及其靶标miR-21和miR-125a之间的关系, 通过逆转录定量聚合酶链反应检测130名RA患者和60名健康者中的lnc-NEAT1、miR-21和miR-125a的表达水平, 与健康组相比, RA患者的lnc-NEAT1水平升高, 同时miR-21和miR-125a水平下降(均P<0.001), 而且lnc-NEAT1水平与miR-21和miR-125a呈负相关(均P<0.05); 此外, 升高的lnc-NEAT1与RA患者的红细胞沉降率、C反应蛋白以及关节疾病活动度评分相关(均P<0.05); 在RA患者治疗过程中, lnc-NEAT1在病情得到缓解的患者中明显下降。这表明, lnc-NEAT1可以靶向miR-21和miR-125a来调控炎症细胞因子和免疫反应, 从而控制RA患者的炎症反应, 而且下降的lnc-NEAT1在一定程度上与RA患者的治疗效果相关。lncRNA GAS5在多种炎症反应和免疫性疾病中充当重要角色[37], 而且已经发现其通过靶向miR-21调控骨关节炎[38]。研究表明, lncRNA GAS5在RA患者的血清样本和成纤维样滑膜细胞中的表达显著下调, 而GAS5的过表达抑制滑膜细胞增殖、炎症反应以及促进细胞凋亡[39]。DONG等[13]发现, miR-21表达水平在RA患者中显著降低, 而促炎细胞因子IL-17、IL-6、IL-1β、TNF-α和IL-22水平升高。此外, miR-21是lncRNA GAS5的直接靶标[38,40]。由此可以进一步推测lncRNA GAS5可能通过靶向miR-21调控RA的发生发展, 这或许是接下来相关研究者的研究方向。

3.2 miR-21调控RA的关键蛋白

SNF5是SWI/SNF染色质重塑复合物的核心组分之一, 高度保守, 其表达水平在细胞分化过程中保持不变[41]。SNF5被称为真正的肿瘤抑制因子, 其失调与肿瘤发生之间的联系已在广泛的癌症相关靶通路中得到证明[42-43]。目前SNF5在有关肿瘤疾病方面的研究较多, 但在自身免疫性疾病中的研究相对匮乏。XIE等[44]研究发现, SNF5促进巨噬细胞中IL-1β的表达和分泌; 同时miR-21已经被证明在RA中起着重要作用[13]。WU等[45]为了探讨miR-21在脂多糖(lipopolysaccharide, LPS)诱导的RA滑膜成纤维细胞(MH7A)炎症中的作用和潜在机制, 通过荧光素酶报告基因测定确定miR-21与SNF5的相互作用, 而MH7A用LPS和miR-21模拟物及抑制剂分别处理, 同时也进行SNF5的转染实验; 然后用ELISA和Western blot检测相关促炎因子和SNF5的蛋白表达水平; 结果发现IL-1β和IL-6的蛋白表达水平与LPS呈正相关, 而miR-21与SNF5的蛋白表达水平呈负相关; miR-21的上调显著抑制SNF5的表达, 过表达的SNF5消除了miR-21模拟物对细胞活力和促炎介质的影响。这表明, miR-21通过抑制MH7A细胞系中的SNF5激活来调控LPS诱导的炎症反应, 其可以成为RA治疗的潜在靶点。

TET1蛋白是一种5-甲基胞嘧啶羟化酶, 属于人α-酮戊二酸加氧酶的TET蛋白家族[46]。TET1主要通过识别并结合基因组5'-CpG-3'二核苷酸密度高的区域, 从而启动DNA去甲基化程序, 进而维持基因组甲基化稳态并实现表观遗传调控[47]。有研究发现, TET1在RA中的表达上调[48]。此外, 胃癌中*KLF4*启动子的DNA甲基化与TET1表达的显著下调有关[49], 骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs)通过分泌细胞外囊泡来减轻关节炎的严重程度并减少胶原蛋白诱导的关节损伤[50]。LI

等[28]为了探究BMSCs衍生的外泌体中miR-21对滑膜细胞增殖和炎症因子表达的影响, 敲低了BMSCs中miR-21的表达, 结果滑膜细胞中的炎症细胞因子TNF-α和IL-1β显著上调; qPCR和蛋白质印迹分析检测发现TET1在RA小鼠关节组织中高度表达, 双荧光素酶测定发现miR-21的过表达显著抑制TET1-WT荧光素酶活性; 功能测定显示miR-21过表达促进滑膜细胞增殖, 而TET1的过表达则会抵消miR-21过表达的作用; 蛋白质印迹分析检测正常小鼠和RA小鼠骨关节组织中KLF4的表达情况, 同样显示KLF4在RA小鼠骨关节组织中的表达升高; 此外, 下调TET1导致KLF4蛋白表达量显著下降, 而KLF4的过表达逆转了miR-21过表达的作用[28]。这些表明, BMSCs衍生的外泌体中miR-21通过靶向TET1以抑制KLF4的表达, 从而缓解RA。

3.3 miR-21调控RA的主要信号通路

Wnt信号通路包括经典Wnt/β连环蛋白(β-catenin)通路、Wnt/PCP通路和Wnt/Ca^{2+}通路[51], 与多种生长相关的生理和病理过程密切相关[52]。其中研究较多的是Wnt/β-catenin信号通路。Wnt是一种分泌型糖蛋白, 与细胞膜上的7次跨膜卷曲蛋白(frizzled, Fzd)和低密度脂蛋白受体相关蛋白(LRP5/6)相结合之后活化的Fzd和LRP5/6通过募集DVL(disheveled)蛋白到 质膜干扰了胞质降解复合物AXIN1-GSK3β的合成, 从而使不再被降解的β-catenin蛋白从细胞质稳定地转移到细胞核激活相关靶基因的表达[53]。研究发现, Wnt信号通路在RA的发生和发展中充当重要角色[54], 同时miR-21已经被证明在RA中起着重要作用[13]。LIU等[27]为了探究miR-21是否通过Wnt信号通路调控RA的发生发展, 将30只大鼠分为对照组(健康大鼠, n=10)、模型组(RA大鼠模型, n=10)和MiR组(RA大鼠模型注射miR-21慢病毒, n=10), 然后采用爪体积和关节炎指数测定、逆转录聚合酶链反应(RT-PCR)法和荧光蛋白印迹等方法来分析各组小鼠爪体积、关节炎指标和蛋白表达水平的变化。结果发现, MiR组炎症因子TNF-α和IL-1β表达水平较模型组显著下降, 而模型组的炎症因子高于对照组和MiR组; 与对照组比较, 模型组从第7天起的爪体积和炎症反应明显增加, 而MiR组爪体积和关节炎指标明显小于模型组, 而且MiR组爪体积随着转染时间的延长明显减小; 此外, MiR组的*IL-6*、*IL-8*和*Wnt*的mRNA表达水平高于对照组, 低于模型组。这表明, 过表达的miR-21可能通过下调Wnt信号通路来抑制IL-6和IL-8的表达, 从而缓解RA的炎症症状。

磷脂酰肌醇-3-激酶(phosphatidylinositol-3-kinase, PI3K)是脂激酶家族的成员之一, 由一个调节亚基(p85)和一个催化亚基(p110)组成。当配体与膜受体结合后, 受体激活p85并招募p110, 进而催化膜内表面的磷脂酰肌醇-4,5二磷酸(phosphatidylinositol diphosphate, PIP2)生成磷脂酰肌醇-3,4,5三磷酸(PIP3), PIP3进一步激活AKT磷酸化, p-AKT可通过磷酸化多种酶和转录因子, 从而调控细胞的生物学行为[55-56]。FENG等[57]研究发现, 青蒿琥酯(Art)通过抑制PI3K/AKT信号通路来缓解RA大鼠炎症反应并加速细胞凋亡和自噬。诸多研究表明, PI3K/AKT信号通路与RA的发生和发展密切相关[54,57]。同样, miR-21已经被证明在RA中起着重要作用[13,58]。GONG等[29]为了探究miR-21是否通过PI3K/AKT信号通路来调控RA的发生发展, 从RA中分离成纤维细胞样滑膜细胞(fibroblast-like synoviocytes, FLS), 使用抑制剂抑制miR-21的表达(抑制剂组)和使用miRNA模拟物(模拟组)模拟miR-21的过表达, 然后通过蛋白质印迹分析相关蛋白的表达情况; 结果抑制剂组中的TNF-α、IL-6和IL-1的表达水平显著增加, 而模拟组中的TNF-α、IL-6和IL-1的表达水平显著降低, 同时Bcl-2、PI3K和AKT的表达水平于模拟组中明显增加, 而在抑制剂组中则相反。这表明, miR-21可以通过激活PI3K/AKT信号通路影响RA发病和细胞凋亡。另一项研究也表明, miR-21通过激活PI3K/AKT信号通路参与RA的发生发展[59]。

Janus激酶信号转导及转录激活因子(JAK/STAT)信号通路是多种细胞因子进行细胞内信号转导的关键通路, 参与细胞的增殖、分化、凋亡以及免疫调节等许多重要的生物学过程[60]。当细胞因子与相应的受体结合后会引起受体二聚化, 使得与受体偶联的JAK激酶通过交互的酪氨酸磷酸化作用而被活化, 活化后的JAK与STAT的SH2结构域相结合激活STAT, 被激活的STAT蛋白以二聚体的形式进入细胞核内与靶基因结合而调控基因的转录, 从而调控细胞的生物学行为[61]。研究表明, JAK/STAT信号通路对RA的发生和发展起着至关重要的作用[54,61], 同时miR-21亦在RA中起着重要作用[13,58]。YANG等[62]为了探究miR-21是否通过JAK/STAT信号通路来调控RA的发生发展, 通过蛋白质印迹和实时PCR评估

STAT3活化、miR-21和Bax/Bcl-2表达, 与健康对照组相比, RA患者血清中的IL-34水平较高, 且IL-34水平与miR-21表达呈显著正相关; 同时IL-34显著降低了FLS的细胞凋亡, 蛋白质印迹显示p-STAT3的表达在IL-34上以剂量依赖性方式明显增加, 并且FLS中的miR-21表达也升高; 而STA21(一种STAT3抑制剂)抑制了IL-34诱导的p-STAT3活化和miR-21表达。这表明, IL-34通过激活JAK/STAT信号通路来促进miR-21表达, 从而缓解RA的炎症反应。另一项研究表明, 低表达的miR-21可以通过抑制STAT3的表达和STAT3的磷酸化来影响JAK/STAT信号通路激活, 从而缓解幼年特发性关节炎的炎症反应[63]。

NF-κB是真核细胞转录因子Rel家族成员之一, 由p50和p65两个亚单位组成。当其受到TNF-α信号、炎症因子以及紫外线等外界刺激时, IκB随即从p50/p65/IκB异源三聚体中解离出来, 从而NF-κB得以暴露其核定位序列, 然后迅速从细胞质进入细胞核内, 与核内DNA上的特异序列相结合, 从而启动或增强相关基因的转录。近年研究表明, NF-κB信号通路与RA的发生密切相关[54,64-65], 同时miR-21亦在RA中起着重要作用[13,58]。CHEN等[66]为了探究miR-21对RA的FLS增殖的影响及其机制, RA-FLS和正常FLS分别用慢病毒(抗miR-21或pro-miR-21)感染, 用于miR-21的过表达或下调, 通过蛋白质印迹和MTT测定评估过表达或抑制miR-21对NF-κB水平和FLS细胞增殖的影响; 与对照组相比, miR-21和NF-κB在RA-FLS中显著增加; 与抗阴性对照组相比, RA-FLS中miR-21的下调导致核蛋白NF-κB水平和细胞增殖率显著降低, 而正常的FLS中的miR-21过表达导致核蛋白NF-κB水平和细胞增殖率显著增加。这表明, 过表达的miR-21可以通过促进NF-κB信号通路的激活来调控RA。此外, 低表达miR-21通过抑制MH7A细胞系中由SNF5激活的NF-κB信号通路, 从而增强LPS诱导的炎症反应[45]。

4 总结与展望

综上所述, miR-21在RA的发生和转归中发挥了重要作用, 尤其是大量研究证实了miR-21的过表达可以缓解RA的炎症反应, 从而缓解RA的病情。目前已得到证明的是, miR-21主要通过与少数lncRNA的相互作用、靶向SNF5及调节相关信号通路(Wnt、PI3K/AKT、JAK/STAT和NF-κB)来调控RA(图1)。然而目前miR-21在RA中的作用机制还相对缺乏, 通过调节相关信号通路及相关靶标来调控RA仍需要大量实验来验证, RA中各种miRNA之间的相互作用仍然需要不断深入研究。

目前已知用于治疗RA的抗风湿药物有诸多不良影响, 而且价格昂贵。迫切需要针对RA患者的新药物或治疗靶点。miR-21在RA的发生和发展中发挥了重要作用, 已经显示出重要的靶向治疗潜力, 但是目前相关研究相对匮乏。因此深入地研究miR-21在RA中的作用机制, 可以精确阐明RA的发病机制, 为RA的预防和诊治寻找依据, 并对最终改善RA患者病情意义重大。总之, miR-21可作为RA病理过程的重要调控因素, 为RA的诊断、治疗和预后带来新的希望。

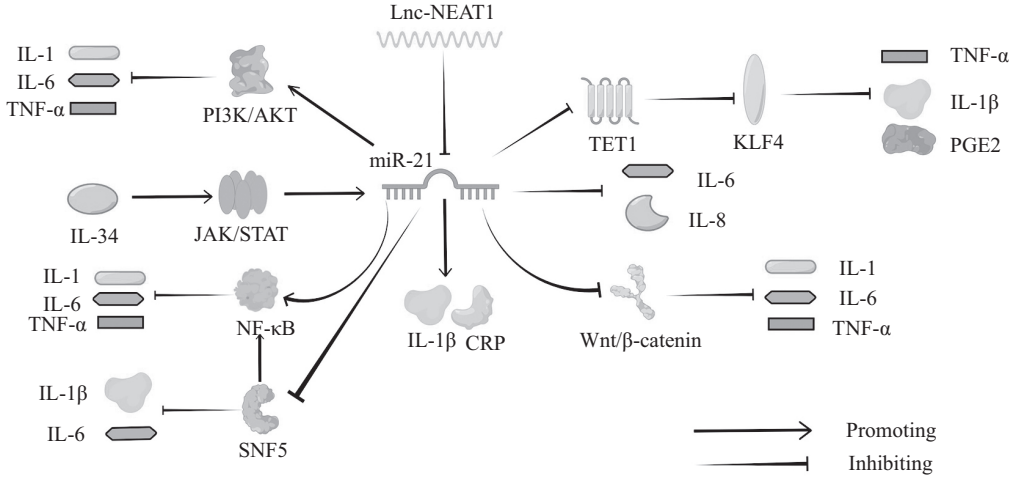

图1 miR-21调控类风湿性关节炎的机制示意图

Fig.1 Schematic diagram of the regulatory mechanism of miR-21 in RA

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