miRNA对固有免疫信号通路调控的研究进展

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摘要 小RNA (miRNA)作为一种小分子非编码RNA, 通过抑制表达或降解靶基因mRNA的方式对目标基因进行调控, 参与多种生理和病理过程. 随着对miRNA的深入研究发现, miRNA可通过调控免疫通路及通路中的免疫因子影响免疫进程. Toll样受体(TLR)、维甲酸诱导基因 I 样受体(RLRs)和核苷酸结合寡聚化结构域样受体(NLRs)作为固有免疫模式识别受体(PRR)重要成员, 在识别病原及诱导下游免疫因子抵抗病原入侵方面有重要作用. 本文将就miRNA对TLR, RLRs, NLRs固有免疫信号调控方式及结果的最新研究进行总结, 为深入研究miRNA对固有免疫调控作用提供参考.

关键词 miRNA, 固有免疫通路, 免疫调控

固有免疫作为抵抗病原入侵的第一道防线, 主要发挥抗感染作用. 固有免疫通过模式识别受体(pattern recognition receptor, PRR)作用并依赖固有免疫细胞对入侵病原微生物的识别和信号转导启动自然免疫进程^[1]. PRR能识别病毒进化中保守的抗原——病原相关分子模式, 从而有效检测病原入侵及触发免疫应答反应^[2]. 近年来, 三类宿主PRRs被广泛研究: Toll样受体(Toll-like receptor, TLRs)、维甲酸诱导基因 I 样受体(retinoic acid-inducible gene I (RIG-I)-like receptor, RLRs)和核苷酸结合寡聚化结构域样受体(pucleotide-binding oligomerization domain (NOD)-like receptors, NLRs)^[1,3]. TLRs自Toll基因首次在*Drosophila melanogaster*发现以来^[4], 13种鼠TLR及11种人TLR被发

现^[5,6], 参与细菌、病毒、真菌和寄生虫的识别及免疫应答, 在固有免疫中有重要作用, 随后RLRs和NLRs也被发现具有与TLR一样重要的识别作用^[7]. RLR家族有3个重要成员: RIG-I, MDA5 (melanoma differentiation-associated gene 5) 和LGP2 (laboratory of genetics and physiology 2)^[8], 其中RIG-I和MDA5能识别细胞内RNA病毒并诱发产生I型干扰素和各种免疫因子^[9], 参与抗病毒进程. NLRs是一个大家族, 其中NOD1, NOD2和NALP3最具代表性, NOD1和NOD2能识别细胞内细菌产物, 而NALP3则可产生NALP3炎症因子促进IL-1炎症因子释放.

microRNA是只含有12~23个核苷酸的小RNA, 参与转录后基因的表达调控^[10], 近年来发现其对调控固

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有免疫通路有重要意义。此外, miRNA还参与多种生物进程, 包括早期细胞分化、增殖和凋亡, 免疫应答和维持病毒感染机体后内环境平衡^[11]。miRNA基因存在于许多不同基因编码位置上, 如细胞内或细胞外编码蛋白质基因上和未编码RNAs上^[12], 能有效抑制相关蛋白质合成、降解靶基因mRNA或以其他调节机制抑制靶基因表达产生基因沉默作用。介于固有免疫在抵抗病原中发挥重要作用和miRNA在调控固有免疫进程中的重要性和作用的特殊性, 本文将就miRNA对固有免疫通路的调控机制及研究进展进行综述, 为研究免疫疾病预防方法及治疗药物提供新的研究方向和参考。

1 miRNA对TLR通路的调控

根据是否需要接头蛋白髓样分化因子88 (myeloid differentiation factor 88, MyD88)介导, TLR信号通路主要分为MyD88依赖信号通路和MyD88非依赖信号通路(或TRIF依赖通路)。研究表明, 除TLR3外, 所有TLRs都通过触发MyD88依赖信号通路进行免疫调节^[5]。但TLR4较特殊, 可通过与易位关联膜蛋白(translocation associated membrane protein, TRAM)结合, 间接激活TRIF依赖通路^[13]。在MyD88依赖信号通路中, MyD88通过招募激活酶如IRAK4, TRAF6和TAK1启动NF- κ B和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)炎性通路, 产生炎性因子。在TRIF依赖通路中, TRIF通过招募下游激活酶TRAF3, TRAF6和TAK1激活NF- κ B, MAPK炎性通路和干扰素调节因子3 (interferon regulatory factor 3, IRF3)通路, 促进干扰素等相关细胞因子的表达^[5], 介导抗病毒反应(图1)。

miRNA可通过直接结合TLRmRNA的3' UTR区调节TLRs表达, 对TLR通路进行调控。TLRs作为自然免疫进程的重要成员, 抑制其表达可在不同程度上减弱机体对病原的抵抗能力, 但个别TLR在特定环境中被抑制后将提高机体防御能力。人结直肠癌(colorectal carcinoma, CRC)细胞和CRC组织中的miR-143可抑制TLR2表达进而减弱大肠癌细胞入侵和迁移能力^[14]。多数miRNAs抑制TLRs表达, 将普遍造成机体免疫能力下降。THP-1人早幼粒细胞受细菌脂蛋白刺激后表达的miR-146a和人口腔角质细胞介导产生的miR-105^[15,16]均可抑制TLR2表达。此外miR-146a还可抑制TLR4 mRNA

表达, 减弱TLR4通路的效率; 降低氧化的低密度脂蛋白聚集防止动脉粥样硬化发生^[17]; 抑制角质细胞IRAK-1和TRAF6表达从而阻止NF- κ B激活和IL-8活化^[18]; 激活巨噬细胞IRAK1, IRAK2和TRAF6进而抑制I型干扰素、IL-1 β 和IL-6表达^[19-21]。同时miR-146a还可抑制许多炎症因子如IL-6, TNF- α , IL-8, CCL3, CCL2, CCL7和CXCL10表达^[22]。miR-146家族中另一成员miR-146b可被脂多糖刺激后的单核细胞通过IL-10介导的STAT3依赖循环通路激活, 通过与TLR4通路上的许多细胞因子如MyD88, IRAK1和TRAF6直接结合而抑制炎症因子和炎症趋化因子的产生^[22]。

其他TLR成员同样可受miRNA直接调控。miR-26a可负向调节小鼠(*Mus musculus*)巨噬细胞TLR3^[23]同时抑制IFN- β 表达^[24]。miR-21、人胰癌细胞分泌的miR-203^[25]、阻塞性肺疾病的病人体内的miR-149-3p^[26]均可直接与TLR43' UTR区结合, 负向调节TLR4蛋白表达^[27]减少炎性细胞因子产生。此外miR-21还可通过抑制NF- κ B活化减弱炎性过程^[28]; 调控MyD88, 增强I型干扰素等抗病毒因子表达^[29]; 抑制IL-12p35, IFN- γ 表达^[30], 减弱抗病毒效果。另一些miRNA只调控TLR4在mRNA水平上表达, 如Let-7 miRNA家族(let-7e和let-7i)。Let-7e和let-7i均可抑制TLR4 mRNA表达, 但他们分别作用于鼠腹膜巨噬细胞和人胆管上皮细胞, 对于这种同一家族miRNA对不同细胞上TLR进行调控的现象可能与不同细胞分泌的miRNA及环境细胞因子有关^[31]。miRNA除对单一特定的TLR进行直接调控外, 还可同时对多种TLR进行调控, miRNA-223能同时调控粒细胞上TLR3和TLR4表达^[32]。miRNA也可正向调控TLR通路。MiR-19a/b是目前唯一能直接正向调控TLR的miRNA, 对TLR2有双重调控作用。通常情况下miR-19a/b上调TLR2表达, 但过量表达miR-19a/b后TLR2在蛋白表达水平上降低, 进而降低TLR2下游细胞因子和激酶表达量减弱免疫反应^[33], 这暗示miR-19a/b对TLR2的表达调控或呈剂量依赖性。

除直接与TLR结合, miRNA还可通过直接调节MyD88和TRIF通路中的接头分子和相关激酶调控TLR通路。MiR-155可与MyD88^[10], IKK α 和IKK β ^[34]直接结合, 通过抑制MyD88表达负向调控TLR通路, 相反, 其与IKK α 和IKK β 的结合则可促进TNF- α 的转录正向调控TLR通路。此外, miR-155还可抑制p38MAPK通路、TLR介导的IL-1炎性通路和炎性因子产生, 减弱机体

图1 MyD88依赖通路与TRIF通路

抗病能力^[35]。可影响MyD88通路效率的miRNA还有miR-628^[36], miR-200成员(miR-200a, miR-200b)^[37]、miR-21^[29], miR-628^[36]和miR-149^[38], 其中miR-628通过抑制NF-κB和IKKα表达而负向调控MyD88依赖信号通路^[36]; miR-200成员通过下调人肾脏细胞上MyD88表达而降低TLR4通路效率^[37]; miR-21则上调MyD88表达而增强TLR4通路效率。此外miR-346, miR-223, miR-199a, miR-92a, miR-12, THP-1单核细胞产生的miR-132和miR-212, 可分别与TLR免疫通路中的Bruton2a抗蛋白激酶(Bruton's tyrosine kinase, BTK)、IKKα, IKKβ、促细胞分化酶、TNFR6和IRAK4进行结合, 减少自然免疫中各免疫分子、细胞因子和炎症因子的产生对MyD88通路进行负向调控^[39-44]。miR-194, miR-146a-5p和miR-29均可减弱TRIF通路效率从而降低机体抗病

毒能力, 其中miR-194可抑制TRAF6和TNF-α表达^[45]; miR-146a-5p在H3N1患者体内可正向调控炎症因子表达, 但过量表达miR-146a-5p可抑制TRAF6活化而减少了炎症因子分泌^[46]; miR-29则通过对TRAF4负向调节减弱机体免疫能力^[45]。

通过调节TLR通路中的信号分子、转录因子、调节因子可影响TLR相关通路效率以调控TLR免疫进程。NF-κB在巨噬细胞成熟及招募过程中有不可取代的作用, 在分化炎症和趋化因子、细胞生存、增殖分化和凋亡等方面也发挥重要作用, 参与免疫细胞的增殖、分化和引起免疫应答^[47]。NF-κB作为TLR通路中的炎症介导因子, 下调NF-κB的表达, 在一定程度上可防止过度炎症。miR-329, miR-21和miR-200b/c均可通过负向调控NF-κB而减弱炎症过程, 其中miR-329激活NF-κBp65

从而抑制IL-6表达^[48], miR-21和miR-200b/c则与NF- κ B的3' UTR区作用, 抑制NF- κ B活化^[28,37]. 一些miRNA可增强NF- κ B表达, 小鼠巨噬细胞产生的miR-210可激活NF- κ B1表达, 加强炎症反应进程^[49]; miR-29a可通过TLR7和TLR8与树突状细胞结合激活NF- κ B并加强NF- κ B下游炎性因子TNF- α 和IL-6表达, 提高机体抗病能力^[50]. miRNA既可调控转录因子同时又可被其他细胞因子调控, 一方面miR-9可负向调控NF- κ B炎性通路, 另一方面miR-9受细胞因子TLR2, TLR4, TLR7/8, 促炎性因子TNF- α 和IL-1 β 的调控^[51].

转录信号传导和活化因子(signal transduction and activator of transcription, STAT)可介导细胞的恶性转化, 参与肿瘤的增殖、分化、血管生成、侵袭转移和免疫逃避等生理功能的调控^[52]. 此外STAT还在TLR3及MAPK通路中有重要作用^[53]. 据报道, 在骨髓抑制细胞上的miR-17-5p和miR-20a均可激活STAT, 减弱骨髓抑制性细胞功能从而增强机体抵抗力^[54]; miR-223可通过激活STAT3减少巨噬细胞对IL-6和IL-1 β 的分泌^[55]. TNF- α 在抗肿瘤进程中有重要作用, 一些miRNA可抑制此过程. miR-1224与TNF- α 3' UTR区结合通过抑制sp1表达, 减少TNF- α 生成减弱抗肿瘤作用^[56]; miR-125b和miR-187可直接结合TNF- α 3' UTR区, 抑制TNF- α 在mRNA水平上表达, 其中miR-187在抑制TNF- α 表达的同时, 间接减少IL-6和IL-12p40表达^[34,57]; miR-181, miR-17和miR-92可抑制上皮细胞上TNF- α 产生下游细胞因子, 但具体机制还未清楚^[58,59]. 巨噬细胞或单核细胞共激活因子P300 (EP300)在激活抗病毒基因过程中有重要作用, 但miR-132可通过结合EP300 3' UTR区抑制其表达, 使抗病毒相关基因表达下调, 细胞因子生成减少, 减弱抗病毒作用^[60]. miR-27b可直接激活NF- κ B依赖通路中的过氧化物酶增殖物激活受体(peroxisome proliferators-activated receptors, PPARs)或抑制LPS分泌TNF- α 减弱炎症过程(表1)^[61].

激活TLR通路后会产生一系列促炎性因子、趋化因子和共刺激分子. 这些细胞因子在消除病原和招募炎性因子抵抗病原体入侵的过程中有重要作用. 一些由TLR介导的细胞因子如I型干扰素、IL-6, IL-8, IL-10, IL-1 β 和IFN- γ 等已经被证实可被miRNA调控. 一方面, miRNA可通过调控TLR介导的细胞因子抑制免疫进程. miR-4661通过与IFN- α 的3'-UTR直接结合, 抑制IFN- α 表达减弱抗水疱性口炎病毒能力, 此外其

在乙脑病中也发挥相同作用^[62]. miR-34a, miR-145和let-7b都对IFN- β 有抑制作用, 其作用机制与miR-4611对IFN- α 作用机制一致^[24,63]. miR-181a和miR-181b均可负向调控IL-8, 但miR-181a对IL-8的抑制作用明显强于miR-181b, 对IL-8起主要调控作用, 而在人牙髓成纤维细胞中, 本应对IL-8有同样抑制作用的miR-302a却未表现出与miR-181a相同的调控功能, 这或许与不同环境中的细胞因子有关^[64]. miR-155可抑制IL-6表达, 同时减少粒细胞集落刺激因子表达^[65,66], 受miR-29a调控的胸腺上皮细胞, 可使IFN- α 受体表达量降低, 减弱抗病毒能力^[67]. 其他细胞因子如IL-10可被miR-106a和miR-106b负向调控; IL-12p35和IFN- γ 可被miR-21负向调控^[30,68-70]; 干扰素可被miR-132负向调控促进病毒的复制^[60]; IFN- γ 可被miR-29抑制表达, 但具体机制还未明确^[71]. 虽研究人员在IL-6上发现了let-7的结合位点, 暗示着let-7可能与IL-6的表达有关^[72], 但其相互作用机理还未明确. 另一方面, miRNA对免疫进程也有促进作用. miR-16, miR-365和miR-142-3p均可上调IL-6表达, 还可通过反馈机制减少内毒素产生^[63,73,74]. IFN- α 可抑制miR-378和miR-30e的表达, 最终使自然杀伤细胞表达上调^[75].

近年来, 一些看似与TLR通路无关的细胞因子被发现可与TLR调节通路发生间接联系. 乙酰胆碱酯酶(acetylcholinesterase, ACHE)作为神经调节的重要因子, 可通过减少细胞因子产生而抑制炎症反应, 近年来发现, ACHE在TLR通路中也扮演重要角色. ACHE可阻止NF- κ B核转移作用抑制NF- κ B激活, 减弱TLR通路中NF- κ B炎性通路的效率, 但当miR-132与ACHE结合并抑制其表达后, TLR通路上与ACHE相关的基因活化水平降低, 正向调控TLR-NF- κ B通路^[76]. 钙调素依赖性蛋白激酶II α (calcium/calmodulin-dependent protein kinase II α , CaMK II α)作为钙通路中的重要一员参与受精、繁殖、记忆等诸多生物进程^[77], 最近发现, CaMK II α 还可参与TLR通路产生促炎性因子和I型干扰素的过程, 对TLR信号通路施行正向调节. 但miR-148/152可结合CaMKII α 3' UTR区抑制其表达, 下调TLR通路中IL-12, IL-6, TNF- α 和IFN- β 表达量, 减弱TLR通路介导的炎性作用^[78]. 细胞凋亡相关基因程序性细胞死亡因子4 (programmed cell death 4, PDCD4)可通过抑制蛋白转录和翻译过程抑制肿瘤细胞生长^[79,80], 活化NF- κ B同时抑制IL-10表达完成促炎性进程^[28]. 但miR-21可结合

表 1 miRNA对固有免疫通路的调控

miRNA 名称	调控因子	调控结果
miR-143	TLR2	抑制大肠癌细胞的入侵和迁移
miR-146a	TLR2	减弱自然免疫进程
	TLR4	减弱TLR4免疫通路作用
	IRAK1	防止炎性介质的发生
	TRAF6	
	MyD88	减少炎症因子产生
	IL-6	抑制IL-6表达
	IFN- β	抑制IFN- β 的表达
	IL-1 β	抑制IL-1 β 表达
miR-146b	IFN- α	抑制IFN- α 的表达
	IRAK1	防止炎性介质的发生
	TRAF6	
miR-146a-5p	MyD88	减少炎症因子产生
	MyD88	上调MyD88表达
	IRF7	上调IRF7表达
miR-105	IFN- β	上调IFN- β 表达
	TLR2	减弱自然免疫进程
miR-21	TLR4	下调TLR4蛋白表达
	MyD88	提高 I 型干扰素等抗病毒因子表达
	IFN- γ	抑制IFN- γ 表达
	IL-12p35	抑制IL-12p35表达
	PDCD4	抑制PDCD4表达, 减弱NF- κ B活性, 负向调节TLR4通路
miR-203	TLR4	下调TLR4蛋白表达
	MyD88	抑制MyD88表达
miR-149-3p	TLR4	抑制TLR4的蛋白表达
Let-7e/i	TLR4	抑制TLR4表达
let-7	SOCS4	直接激活SOCS4表达
miRNA-223	TLR3	抑制TLR3表达
	TLR4	抑制TLR4表达
	IKK α	减少炎性因子, 细胞因子产生
	STAT	减少巨噬细胞分泌IL-6和IL-1 β
miR-26a	IFN- β	抑制IFN- β 的表达
	TLR3	负向调节TLR3表达
miR-19a/b	TLR2	少量时上调TLR2表达, 过量时抑制TLR2表达
miR-155	IKK α	减少炎症因子产生
	IKK β	
	TNFR	
	p38MAPK	减少细胞因子及炎性因子的产生, 降低机体抵抗微生物的能力
	IL-6	抑制IL-6和细胞集落因子表达
	SHIP1	抑制SHIP1表达, 减弱NF- κ B活性, 负向调节TLR4通路
	SOCS1	正向调节TLR3, TLR4通路, 促进 I 型干扰素的表达以抵抗病毒

续表1

miRNA 名称	调控因子	调控结果
miR-628	TRAF6	减弱MyD88依赖信号通路作用
	MyD88	抑制MyD88表达
	IKK α	减弱MyD88依赖信号通路作用
miR-200a	MyD88	降低TLR4 通路的效率
miR-200b/c	NF- κ B	抑制NF- κ B活化
miR-149	MyD88	抑制MyD88表达
miR-132	IRAK4	调节炎症因子
	P300	下调抗病毒相关基因表达, 减少细胞因子生成
	Ache	抑制Ache表达, 使TLR通路上与ACHE相关基因活化水平降低, 负向调节对TLR反应通路
miR-212	IRAK4	调节炎症因子
miR-194	TRAF6	抑制TRAF6表达
miR-29	IFN- γ	抑制IFN- γ 表达
	IRAK4	肿瘤抑制调控
miR-29a	NF- κ B	加强TNF- α 和IL-6表达
	IFN- α	抑制IFN- α 的表达
miR-124	MyD88	上调炎症因子的表达
	TNFR6	激活NF- κ B通路产生炎症因子促进免疫应答
miR-346	BTK	减少炎症因子, 细胞因子产生
miR-199a	IKK β	
miR-92a	促细胞分化酶	减少免疫分子, 细胞因子, 炎症因子的产生
miR-329	NF- κ B	减弱炎症过程
miR-210	NF- κ B1	加强炎症反应
miR-9	—	负向调控NF- κ B炎症通路
miR-17-5p/20a	STAT	减弱骨髓抑制细胞的功能
miR-181/ 17/92	TNF- α	抑制在上皮细胞上的TNF- α 产生下游细胞因子
miR-1224	TNF- α	减少TNF- α 的生成, 减弱抗肿瘤作用
miR-125b/187	TNF- α	抑制TNF- α 表达
miR-16/365/142-3p	IL-6	激活IL-6表达, 减少内毒素产生
miR-181a/b	IL-8	抑制IL-8表达
miR-106a /b	IL-10	抑制IL-10表达
miR-34a/145/7b	IFN- β	抑制IFN- β 的表达
miR-148/152	CaMKII α	抑制CaMKII α 表达, 减弱促炎性作用
miR-187	IL-6	减少IL-6和IL-12p40的表达
miR-466l	IFN- α	抑制IFN- α 的表达
miR-98	CIS	直接激活CIS表达
miR-101	MAPK phosphatase 1	正向调节TLR通路

PDCD4 3' UTR区而抑制其表达. miR-155同时对SHIP1 (Src homology 2 domain-containing inositol-5'-phosphatase, SHIP1)和SOCS1 (cytokine signalling 1, SOCS1)

有负向调控作用, 抑制SOCS1表达后, 提高了TLR3和TLR4通路效率同时促进 I 型干扰素表达^[10].

除以上miRNA外, 能调控TLR信号通路中调节因子

的miRNA还有miR-98, let-7和miR-101, 其中miR-98和let-7都可与cytokineinducible Src同源蛋白2 (cytokineinducible Src homology 2 protein, CIS2)和细胞因子信号转导抑制因子4 (suppressors of cytokine signaling 4, SOCS4)作用. CIS和SOCS4作为细胞因子信号转导抑制蛋白家族的成员之一, 在感染隐孢子虫或受LPS刺激后被激活, 可抑制IkappaBalpha表达调控NF- κ B活化, miR-98和let-7通过与CIS和SOCS4的mRNA直接结合抑制其转录, 其中抑制CIS转录可间接调控IkappaBalpha和NF- κ B表达而加强免疫作用, 这一过程与TLR调节通路相关^[81-83]. 丝裂原活化蛋白激酶磷酸酶-1 (mitogen-activated protein kinases, MKP-1)是负向调控MAPK的重要因子之一, 参与细胞内信号传导, 调节细胞增殖和分化等进程^[84]. 由于MKP-1未编码区mRNA序列还未明确, 研究人员通过软件分析推测, miR-101或可靶向结合MKP-1而抑制炎症因子表达. 此外, miR-101的表达由多个TLR配体诱导, 即miR-101通过调控MKP-1可间接对TLR进行正反馈调节^[85].

2 miRNA对RLRs信号通路的调控

RLRs定位于胞浆内, 可识别细胞内RNA病毒并诱发产生I型干扰素和各种免疫因子^[9]. MDA5, RIG-I和LGP2作为RLRs主要成员, 在抗病毒进程中行使不同功能, 其中MDA5和RIG-I可诱导产生I型干扰素, 而LGP2则抑制MDA5和RIG-I介导表达I型干扰素, 在抗病毒进程中起负向调控作用^[86]. MDA5和RIG-I均可识别病毒, 但有不同的病毒识别范围, MDA5对新城疫病毒(newcastle disease virus, NDV)、仙台病毒(dendai virus, SeV)、疱疹性口炎病毒(vesicular stomatitis virus, VSV)、甲型流感病毒和日本脑炎病毒(Japanese encephalitis virus, JEV)识别, 而RIG-I对脑心肌炎病毒(encephalomyocarditis virus, EMCV)、脑脊髓炎病毒(Theiler's encephalitis virus)、门戈病毒(Mengo virus)识别^[87]. 最近有报道发现, miR-4661能直接与IFN- α 3' UTR区结合抑制感染SeV和VSV的巨噬细胞和树突细胞的抗病毒反应^[63].

此外miR-146a能通过结合TRAF6, IRAK1和IRAK2减弱RIG-I信号, 干扰VSV诱导产生I型干扰素^[20]; miR-122可减弱IFN- α 作用而加强HCV复制; miR-29a

则抑制IFN- α 受体而避免机体发生过度免疫反应^[68]; 最近研究还发现, miR-145可与MDA5结合, 下调MDA5 mRNA的表达量以调节RLRs信号通路^[88].

3 miRNA对NLRs信号通路的调控

NLR参与组装和活化炎性小体、caspase-1活化和IL-1 β 及IL-18分泌^[89]. 许多NLRs在肿瘤发生及发展的过程中发挥重要作用. 其中, NLRP3, NLRP4, NLRP9和NAIP的表达量在膀胱癌病人体内不同程度升高, 同时可靶向这些NLRs的miRNA (miR-146a-5p, miR-106a-5p, miR-17-5p, miR-223-3p, miR-141-3p, miR-19a-3p, miR-145-5p, miR-185-5p)的表达也随之变化, 暗示这些miRNA在膀胱癌发生中可通过对NLRs的调控影响病程发展^[90]. miR106a-5p, miR17-5p和miR19a-5p的升高伴随NLR mRNA表达量降低, 减弱炎症进程; miR-223-3p可靶向NLRP3, 抑制IL-1 β 分泌^[91]; miR-19a-3p被预测可与NLRP9结合^[91]且在弱恶性肿瘤患者体内表达升高^[92]; miR-146a-5p抑制胃癌细胞的增殖、迁移和入侵^[93], 此过程或与NLRs信号通路相关但具体机制还未明确; miR-17可破坏硫氧还原蛋白, 抑制NLRP3介导的炎症过程、caspase-1活化和IL-1 β 分泌^[94].

4 展望

除miRNA对固有免疫调控有重要意义外, 长链非编码RNA (lncRNA)在调控固有免疫方面也有重要作用, 且可与miRNA共同作用参与调控各种生理病理过程. 目前关于miRNA和lncRNA调控生理病理过程的研究很多, 但还有许多问题未能解决, 为解决这些问题需深入探究miRNA和lncRNA间的相互作用对固有免疫及疾病的影响. 虽然研究证实lncRNA与miRNA相互调控与许多疾病的发生发展密切相关, 但由于lncRNA与miRNA作用的复杂性, 疾病发生发展的不确定性, 研究手段的单一性, 导致lncRNA与miRNA相互调控对疾病的影响的研究甚少, 即使有探究, 也未能说明其具体的调控机制. 因此, 需要开发更有效的软件和方法应用于探究lncRNA与miRNA相互调控与固有免疫的关系, 这不仅为深入了解机体免疫作用奠定了基础, 同时为研究新的药物和治疗方法提供了新的研究方向.

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Research progress of miRNA regulation of innate immune pathway

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MicroRNAs (miRNAs) are small non-coding RNAs that are involved in various physiological and pathological processes and which can regulate target genes by inhibiting their expression or degrading their respective mRNAs. Research has shown that miRNAs can affect the immune process by regulating the immune pathway or immune factors. Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are three important pattern recognition receptors (PRRs) that play crucial roles in recognizing pathogens and regulating downstream immune factors to resist the invasion of pathogens. In this paper, we summarize the newest research developments regarding the miRNA regulation of TLRs, RLRs, and NLRs pathways. This summary provides a significant reference for further research on the miRNA regulation of innate immune pathways.

miRNAs, innate immune pathway, immune regulation

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