NLRs的免疫调控作用研究进展

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摘要 核苷酸结合寡聚化结构域样受体(nucleotide-binding oligomerization domain like receptors, NLRs)在机体的固有免疫和适应性免疫过程中均发挥着独特的调控作用, 其成员不仅可作为适配器介导NF-κB通路、MAPK通路及I型IFN信号通路, 又可作为调节器与信号通路关键蛋白互作, 继而通过细胞凋亡和细胞自噬等方式调控细胞免疫应答反应, 维持宿主细胞内环境的稳态。鉴于近年来NLRs在机体免疫防御及肿瘤发生中的作用备受关注, 该文就NLRs在抗感染免疫及肿瘤免疫过程中的调控作用进行简要论述, 以期为由病原微生物引起的疾病及癌症的治疗提供新思路。

关键词 核苷酸结合寡聚化结构域样受体; 抗感染免疫; 肿瘤免疫

Research Advances in the Immunoregulation of NLRs

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Abstract NLRs (nucleotide-binding oligomerization domain like receptors) play a unique regulatory role in the innate immunity and adaptive immunity. Its members not only act as adapters to mediate the NF-κB pathway, MAPK pathway and type I IFN signaling pathway, but also act as regulators to interact with key moleculars in the signaling pathways. Then, they regulate the cellular immune response through apoptosis and autophagy to maintain the homeostasis of host cells. In recent years, the roles of NLRs in the immune defense and tumorigenesis have attracted much attention. In this paper, the regulatory roles of NLRs in the process of anti-infective immunity and tumor immunity are briefly discussed in order to provide new ideas for the treatment of diseases and cancers caused by pathogenic microorganisms.

Keywords NLRs; anti-infective immunity; tumor immunity

核苷酸结合寡聚化结构域样受体(nucleotide-binding oligomerization domain like receptors, NLRs)是一类细胞质内模式识别受体(pattern recognition receptors, PRRs), 可通过调控一系列信号级联反应参与机

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体获得性免疫和固有免疫应答过程[1]。它与C型植物血凝素受体(C-type lectin receptors, CLRs)、Toll样受体家族(Toll-like receptors, TLRs)和视黄酸诱导型基因样受体(retinoic acid inducible gene-I-like receptors, RLRs)一样, 可与病原相关分子模式(pathogen-associated molecular patterns, PAMPs)和损伤相关分子模式(damage-associated molecular patterns, DAMPs)直接结合, 启动天然免疫反应[2]。NLRs家族成员主要通过参与炎症反应或与免疫信号通路的关键蛋白互作调控多种疾病的发生和发展, 其重要成员含热蛋白结构域的nod样受体蛋白1(nod-like receptor pyrin domain-containing protein 1, NLRP1)、NLRP3、NLR家族CARD包含结构域蛋白4(NLR family CARD domain containing 4, NLRC4)、神经元凋亡抑制剂蛋白(neuronal apoptosis inhibitor protein, NAIP)等作为炎性小体传感器, 通过与其同源配体结合诱导白介素-1(interleukin-1, IL-1)和IL-18的分泌和炎性形式的细胞焦亡参与机体免疫调节过程[3]。NLRs家族成员NOD1、NOD2和NLRP3等可通过激活NF-κB信号通路、I型IFN信号通路和促分裂素原活化蛋白激酶(mitogen-activated protein kinase, MAPK)通路参与机体抗感染免疫过程。在某些病理条件下, NLRs家族成员还可通过与NF-κB信号通路关键分子、自噬相关蛋白、半胱天冬蛋白酶(caspase, CASP)、应激酶、干扰素调节因子互作从而参与机体的免疫调节过程, 进而调控微生物感染相关疾病及肿瘤的发生和发展[4-6]。因此, 深入探究NLRs的活化条件及免疫调控机制, 可为靶向NLRs蛋白家族成员的药物研发和相关疾病的治疗提供新思路。

1 NLRs的结构与功能

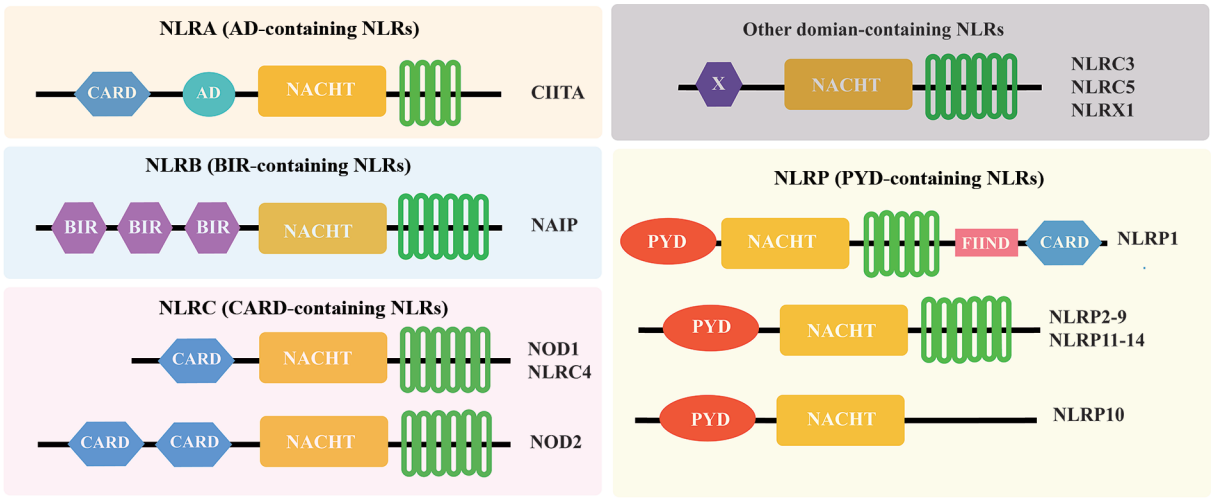
研究发现, 人类基因组包括22个NLRs家族成员, 这些蛋白均由N末端效应结构域、中央的核苷酸结合寡聚化结构域(nucleotide-binding oligomerization domain, NBD)和C末端的亮氨酸富集结构域(leucine-rich repeat domain, LRR)构成[7-8]。其中N末端效应结构域包括pyrin结构域(pyrin domain, PYD)、CASP活化募集结构域(caspase activating and recruitment domain, CARD)及杆状病毒抑制剂重复结构域(baculovirus inhibitor of apoptosis protein repeat domain, BIR), 它们主要负责适配器分子与下游效应器的识别; NBD结构域介导自身的寡聚化, 其与NLRs家族成员存在的ATP酶活性有关[9]; LRR结构域主要负责识别并结合PAMPs和DAMPs, 进而介导NLRs与下游接头蛋白互作激活免疫级联反应[3,10]。

基于N末端结构域的不同, NLRs可被分为5个亚家族, 即含酸性反式激活结构域(acidic transactivation domain, AD)的NLRA、含BIR结构域的NLRB、含半胱天冬氨酸蛋白酶募集结构域的NLRC、含pyrin结构域的NLRP和含未知结构域的NLRX[4]。NLRA亚家族只有一个成员, 即II类主要组织相容性复合物反式激活因子(class II major histocompatibility complex transactivator, CIITA), 它由AD结构域、LRR结构域和GTP结合结构域构成, GTP结合结构域是MHC II类分子转录的正向调节剂, 负责将蛋白质转运至细胞核[11]。NLRB亚家族唯一成员NAIP是一种抗凋亡蛋白, 主要通过抑制CASP3、CASP7和CASP9的活性阻止细胞凋亡[4,12](图1)。在多种病理条件下, NAIP是神经元存活的介质, 抑制多种信号诱导的细胞凋亡[13-14]。NLRC亚家族由NOD1、NOD2、NLRC4 3个成员组成, 它们是微生物入侵及免疫系统的监测器, 主要通过激活或抑制信号通路影响细胞因子的分泌。NLRP亚家族由14个成员组成, 其特征是N末端存在PYD效应器结构域, 而该结构域含多种人类蛋白的保守序列基序, 介导凋亡和炎症信号传导[3,15]。NLRX亚家族成员NLRC3、NLRC5和NLRX1的N末端是一个未知结构域, 参与自噬的起始, 并调节炎症反应和I型IFN信号通路的传导[16]。NLRs家族成员的具体结构与功能如图1和表1。

2 NLRs在机体抗感染过程中的免疫调节作用

2.1 NLRs在细菌感染过程中的免疫调控作用

在细菌感染过程中, NLRs不仅可作为模式识别受体识别细菌细胞壁成分, 而且还可作为调节器与自噬相关蛋白及信号通路关键因子互作, 调节细胞自噬及细胞因子的分泌, 从而发挥免疫调节作用。研究发现, 结核分枝杆菌可通过早起分泌抗原靶蛋白-6(early secreted antigenic target-6, ESAT-6)家族蛋白EsxL促进巨噬细胞中CIITA的甲基化来抑制MHC II类分子的表达, 从而抑制$CD4^+$ T细胞呈递抗原的功能[39]。鼠伤寒沙门氏菌感染时, NAIP可通过结合鞭毛蛋白和革兰氏阴性细菌的III型分泌系统(type 3 secretion system, T3SS)成分诱导NLRC4炎性



CARD: CASP募集结构域; AD: 酸性反式激活结构域; NACHT: NAIP、CIITA、HET-E和TP1包含结构域; BIR: 杆状病毒抑制重复样域; X: 未知结构域; PYD: 热蛋白结构域; FIIND: 已发现结构域; 绿色椭圆代表富含亮氨酸的重复结构域。

CARD: caspase recruitment domain; AD: acidic transactivation domain; NACHT: NAIP, CIITA, HET-E and TP1 containing domain; BIR: baculoviral inhibitory repeat-like domain; X: unknown; PYD: pyrin domain; FIIND: find domain; the green ellipse represents the leucine-rich repeat domain.

图1 NLRs的结构组成(根据参考文献[4]修改)

Fig.1 Structure of NLRs (modified from the reference [4])

小体的活化[14]。NOD1和NOD2的CARD结构域可分别与iE-DAP(γ-D-glu-meso-diaminopimelic acid)及MDP(muramyl dipeptide)相互识别诱导NBD结构域发生寡聚化[2,9], 随后与丝氨酸苏氨酸受体互作蛋白2(receptor-interacting serine-threonine protein 2, RIP2)结合, 募集细胞凋亡抑制因子(cellular inhibitor of apoptosis protein, cIAP)、人杆状病毒IAP重复包含蛋白2/3(human baculoviral IAP repeat-containing protein 2/3)和X连锁凋亡抑制蛋白(X-linked inhibitor of apoptosis protein, XIAP)等泛素连接酶诱导RIP2的泛素化[6], 多聚泛素化的RIP2可以募集转化生长因子β激酶1(transforming growth factor-β-activated kinase 1, TAK1)、TAK1结合蛋白1(TAK1 binding protein 1, TAB1)、TAB2/3复合体, 而上述因子一方面能促进JNK、p38及MAPK对活化蛋白-1(activator protein-1, AP-1)的转录活性, 另一方面又能活化IKKα[inhibitor of NF-κB (IκB) kinase α]/IKKβ使其与NF-κB必要调节蛋白(NF-κB essential modulator, NEMO)形成复合物激活NF-κB的亚基入核, 进而诱导促炎性细胞因子的产生[6,10]。NOD1和NOD2识别细菌的iE-DAP和MDP后, 也可通过募集CARD9激活p38、JNK, 进而激活MAPK通路[40]。在志贺氏菌感染时, NLRP10通过促进NOD1与NOD1信号通路关键蛋白NEMO、RIP2和TAK1之间的相互作用, 诱导p38和NF-κB信号通路进一步激活, 从而促进促炎性细胞因子的释放[33]。此外, 细菌分泌蛋白VceC(bacterial secreted protein VceC)可与宿主细胞内质网上的分子伴侣结合免疫球蛋白(binding immunoglobulin protein, Bip)结合, 诱导肌醇需求因子1α(inositol-requiring enzyme 1α, IRE1α)将肿瘤坏死因子受体相关因子2(tumor necrosis factor receptorassociated factor 2, TRAF2)募集至内质网膜上, 通过激活内质网应激反应调节NOD1、NOD2及NLRP3介导的信号通路, 促进IL-6等炎症因子的释放[41]。有研究显示, NLRC4在鼠伤寒沙门菌、肺炎军团菌等感染时可激活CAPS1介导IL-1β的生成, 从而控制胞内菌的复制[14,20]。

最新研究发现, NLRs家族成员也可通过与细胞自噬相关蛋白相互作用影响细菌的感染过程[16]。据报道, NOD2识别配体后, 将自噬因子自噬相关16样蛋白1(autophagy related protein 16 like protein 1, ATG16L1)募集到质膜, 导致弗氏志贺氏菌和鼠伤寒沙门氏菌诱导自噬的能力增强[20,42]。NLRX1可通过与Beclin 1-UVRAG复合物之间的相互作用, 抑制内吞介导的A族乙型溶血性链球菌(group A Streptococcus, GAS)侵入宿主细胞[43]。NLRX1也可与线粒体蛋白质翻译延伸因子Tu(mitochondrial protein translation elongation factor Tu, TUFM)协同调节自噬复合物ATG12-ATG5-ATG16L1促进细胞自噬[38]。NLRP3炎性小体在诱导凋亡相关斑点样蛋白ASC(apoptosis related speck-like protein containing a C-terminal caspase recruitment domain)泛素化时, 也可

表1 NLRs家族成员的结构与功能

Table 1 Structure and function of NLRs family members

蛋白名称 Protein name	别称 Alternative name	基因ID Gene ID	分子量/kDa Molecular weight /kDa	分布 Distribution	靶蛋白 Target protein	功能 Functions
CIITA	MHC2TA	4261	130	B cell Macrophages Dendritic Cells	MHC class II molecules	Control the expression of MHC class II molecules[4]; enhance the transcriptional activity of MHC class I molecules; inhibit the activation of the classic NF-κB pathway[11]
NAIP	BIRC1	4671	155	Monocyte Macrophages	CASP3 CASP7 CASP9	Under pathological conditions, it acts as a mediator of neuron survival and inhibits motor neuron apoptosis; interfere cell apoptosis by inhibiting the activity of CASP3/7/9[12]; participate in the formation of NLRC4 inflammasome; involved in the recognition of flagellin and type 3 secretion system proteins[14]
NOD1	NLRC1 CLR7.1 CARD4	10392	108	All cells	iE-DAP RIP2 NLRP10	In bacterial infection, RIPK2 and IKKγ induce the activation of NF-κB signaling pathway; promote CASP9-mediated apoptosis[17]; participate in endoplasmic reticulum stress[18]; NOD1 can interact with MDA5 and TRAF3 to positively regulate antiviral response[19]
NOD2	NLRC2 CARD15	64127	115	Myeloid and Lymphoid cells	MDP ssRNA MAVS RIP2	After bacterial infection, it combines with RIPK2 to recruit ubiquitin ligase to activate MAPK and NF-κB signaling pathways or interact with ATG16L1 to participate in the formation of autophagosomes[20]; participate in endoplasmic reticulum stress[18]; identify viral ssRNA and interact with MAVS
NLRC3	CLR16.2 NOD3	197358	115	Dendritic Cells	STING NAIP	Interaction with STING (stimulator of interferon gene) prevents its downstream signal transmission[22]; inhibit the growth of colorectal cancer through the NLRC3/PI3K pathway[23]; down-regulate the antigen presentation function of dendritic cells and the ability of CD^{4+} T cells to enter Th1 and Th17 cells, and negatively regulate the antigen presentation function of dendritic cells through the p38 signaling pathway[3]
NLRC4	CARD12 CLAN CLAN1 IPAF	58484	116	Monocyte Lymphocytes	NAIP ASC NOD2 BCL10	Involved in the formation of inflammasome; regulating the response of influenza A virus-specific CD^{4+} T cells by FasL expression[24]; interacts with NOD2 to regulate signal pathway mediated by it[25]
NLRC5	CLR16 NOD27 NOD4	84166	205	Myeloid and Lymphoid cells	RIG-I	NLRC5 is involved in MHC class I-mediated CD^{8+} T cell activation[4]; negative regulation of NF-κB and type I IFN signaling pathway[26]
NLRP1	CARD7 NAC NALP1	22861	170	Macrophages Dendritic Cells	MDP NOD2 MEFV	Involved in the formation of inflammasome[27]; activated by MDP in a NOD2 dependent manner; interacts with MEFV to promote autophagy and prevent excessive inflammation mediated by IL-1β and IL-18[3]; promote the growth of metastatic melanoma by enhancing inflammasome activation and inhibiting apoptosis[28]
NLRP2	NALP2 NBS1 PAN1	55655	120	Lymphoid cells Thymocytes	IKK CARD8 TBK1	Formation of inflammasome; interacts with IKK complex to regulate NF-κB activation[4]; interacts with TBK1 to negatively regulate antiviral response[29]

续表1

蛋白名称 Protein name	别称 Alternative name	基因ID Gene ID	分子量/kDa Molecular weight /kDa	分布 Distribution	靶蛋白 Target protein	功能 Functions
NLRP3	NALP3 PYPAF1	114548	118	Macrophages Dendritic cells Lymphoid cells	dsRNA IRF4 DHX33 MEFV	Formation of inflammasome participate in the immune regulation process of a variety of pathogenic microorganisms[3]; interacts with MEFV to initiate autophagy and prevent excessive inflammation[7]
NLRP4	PAN2 PYPAF4	147945	114	Lymphocytes Testicular cells Oocyte	DTX4	Negatively regulate type I IFN signaling pathway[30]; inhibit the activation of NF-κB induced by TNFα and IL-1β[4]
NLRP5	NALP5	126206	135	Oocyte	ND[a]	Participate in the division of embryonic cells[4]
NLRP6	NALP6 PYPAF5	171389	99	Neutrophils Eosinophils	ND	Involved in the formation of inflammasome; helps self-renewal and proliferation of intestinal mucosa; during bacterial infection, it can negatively regulate inflammation signals[31]
NLRP7	NALP7 NOD12	199713	115	Monocyte	CASP1 IL-1β	Inhibit the secretion of inflammatory factors by interacting with CASP1 and IL-1β; participate in the differentiation of trophoblast cells[32]
NLRP8	NALP8 NOD16 PAN4	126205	120	Cardiomyocytes Lymphoid cells	ND	Participate in inflammation
NLRP9	NOD6 PAN12 NALP9	338321	113	Intestinal epithelial cells	DHX9 dsRNA	Participate in the formation of inflammasome
NLRP10	NOD8 NALP10 PYNOD	338322	75	Epidermal cell	NOD1 RIP2 TAK1	Inhibit CASP1 dependent IL-1β secretion[6]; negative regulation of NOD1 related signaling pathways[33]; prevent periodontitis[34]
NLRP11	NALP11 NOD17 PAN10	204801	118	Lymphoid cells Testicular cells	ND	Participate in inflammation
NLRP13	NALP13 NOD14	126204	119	Thymocytes	ND	Participate in inflammation
NLRP14	NALP14 NOD5	338323	125	Spermatogonia Spermatocyte	ND	Related to inflammation and spermatogenesis[37]
NLRX1	NOD26 NOD9	79671	108	All cells	MAVS TUFM	By inhibiting the interaction between RIG-I and MAVS, negatively regulate the antiviral response[4]; recruiting autophagy-related proteins ATG5 and ATG12 through interaction with TUFM to promote autophagy and type I IFN signaling pathway[38]; regulate MAVS dependent NLRP3 inflammasome activation to attenuate cell apoptosis[8]

ND: 未确定。

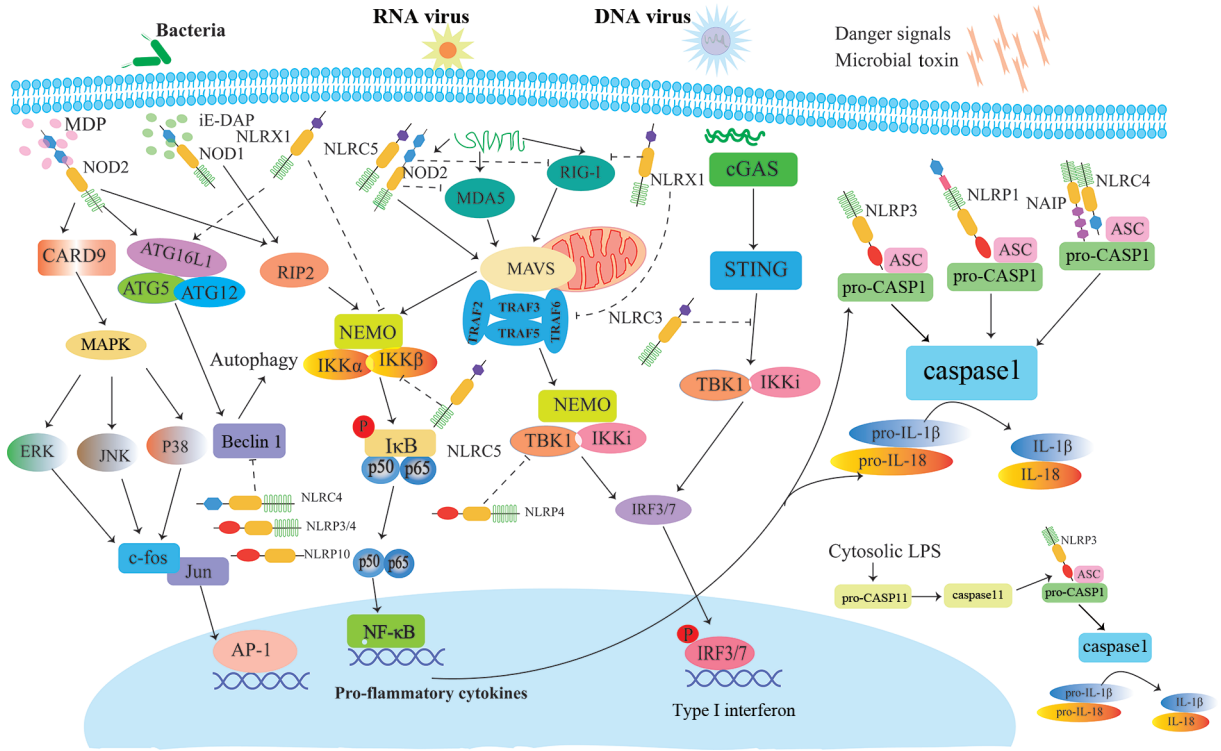
ND: not determined.

募集自噬相关蛋白SQSTM1(sequestosome 1)促进细胞自噬[44]。研究发现, 细胞自噬可抑制铜绿假单胞菌的3型分泌系统诱导线粒体的损伤及线粒体DNA的释放过程中NLRC4的激活[25,44]。当链球菌感染时, NLRC4、NLRP3、NLRP4和NLRP10均能使Beclin 1发生短暂解离, 在不同程度上调控自噬的发生[44]。此外, 在细胞自噬过程中活性氧(reactive oxygen species, ROS)的改变可激活炎性小体, 而炎症小体在某些病理条件下也可被细胞自噬直接降解。综上所述, NLRs家族成员不仅可以直接与细菌菌体蛋白相互作用, 而且还可通过细胞自噬和内质网应激等反应控制胞内菌的复制。

2.2 NLRs在病毒感染过程中的免疫调控作用

在病毒感染过程中, NLRs家族成员可通过形成炎性小体、识别病毒核酸或感应细胞内环境改变

来调节病毒的复制。在口蹄疫病毒、人巨细胞病毒、诺如病毒等感染时，NOD2可通过与病毒RNA结合激活线粒体抗病毒信号蛋白(mitochondrial antiviral signaling protein, MAVS)，一方面诱导泛素链的合成、IKKα/β的活化，而活化的IKKα/β与磷酸化的TBK1/IKKε形成复合物激活NF-κB的转录，另一方面活化干扰素调节因子3/7(interferon regulatory factor 3/7, IRF3/7)激活I型IFN信号通路相关因子的转录，最终促进IFN-α、IFN-β和炎性因子的分泌[21]。研究发现，NOD1可通过与黑色素瘤分化相关蛋白5(melanoma differentiation associated protein 5, MDA5)竞争结合MAVS参与抗病毒信号传导[19]。NOD2-RIPK2复合物可以通过磷酸化线粒体诱导物自噬样激酶1(autophagy-like kinase 1, ULK1)负调节禽流感病毒(avian influenza virus, IAV)感染过程中NLRP3炎性小体的激活，最终减少IL-18产生[42]。NLRC3通过阻止STING-TBK1(TANK-binding kinase 1, TBK1)相互作用，进而抑制DNA病毒介导的I型IFN信号的传导[22](图2)。在病毒感染过程中，NLRP1、NLRP3、NLRP10和NLRP12等可通过PYD结构域招募含有PYD和CARD



MDP: 胞壁酰二肽; NOD1/2: 核苷酸结合寡聚化结构域1/2; iE-DAP: 二氨基庚二酸; CARD9: 半胱天冬蛋白酶募集域蛋白9; ATG16L1: 自噬相关蛋白16样蛋白1; ATG5/12: 自噬相关基因5/12; MAPK: 丝裂原活化蛋白激酶; ERK: 细胞外信号调控的蛋白激酶; JNK: c-Jun N末端激酶; AP-1: 激活蛋白1; NLRX1: NLR家族成员X1; NLRC3/4/5: NLR家族CARD包含结构域蛋白3/4/5; RIP2: 受体相互作用蛋白2; NEMO: NF-κB必需调节蛋白; IκB: 核因子κB的抑制蛋白; NLRP1/3/4/10: 含热蛋白结构域的nod样受体蛋白1/3/4/10; MDA5: 黑色素瘤分化相关蛋白5; RIG-I: 视黄酸诱导基因蛋白1; MAVS: 线粒体抗病毒信号蛋; TBK1: Tank结合激酶1; IRF3/7: 干扰素调节因子3/7; cGAS: 环化GMP-AMP合成酶; STING: 干扰素刺激基因; NAIP: 神经元凋亡抑制剂蛋白; ASC: 凋亡相关斑点样蛋白; “实线箭头”代表一种蛋白可直接促进另一种蛋白的表达; “虚线箭头”代表一种蛋白可间接影响另一种蛋白的表达; “平箭头”代表发挥抑制作用。

MDP: muramyl dipeptide; NOD1/2: nucleotide-binding oligomerization domain-containing 1/2; iE-DAP: γ-D-glu-meso-diaminopimelic acid; CARD9: caspase recruitment domain-containing protein 9; ATG16L1: autophagy related protein 16 like protein 1; ATG5/12: autophagy related gene 5/12; MAPK: mitogen-activated protein kinase; ERK: extracellular signal regulated protein kinase; JNK: c- Jun N-terminal kinase; AP-1: activator protein 1; NLRX1: NLR family member X1; NLRC3/4/5: NLR family CARD domain containing protein 3/4/5; RIP2: receptor-interacting protein 2; NEMO: NF-κB essential modulator; IκB: inhibitor of nuclear factor kappa B; NLRP1/3/4/10: nod-like receptor pyrin domain-containing protein 1/3/4/10; MDA5: melanoma differentiation associated protein 5; RIG-I: retinoic acid inducible gene protein 1; MAVS: mitochondrial antiviral signaling protein; TBK1: Tank-binding kinase1; IRF3/7: interferon regulatory factor 3/7; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon gene; NAIP: neuronal apoptosis inhibitor protein; ASC: apoptosis-associated speck-like protein containing a CARD; “solid arrow” means that one protein can directly promote the expression of another protein; “dashed arrow” means that one protein can indirectly affect the expression of another protein; “flat arrow” means that it exerts an inhibitory effect.

图2　NLRs对微生物感染的调控作用

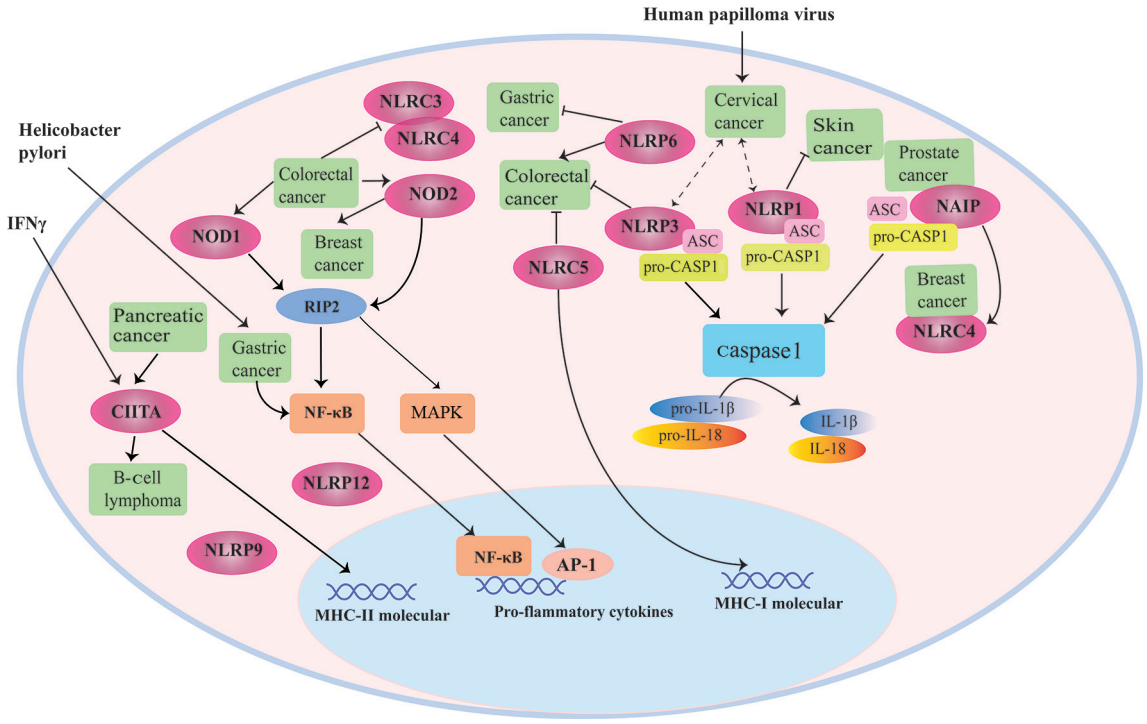
Fig.2　Regulation effect of NLRs on microbial infection

结构域的ASC, 而ASC通过与其CARD结构域相互结合招募pro-CASP1形成炎症小体, 并且pro-CASP1的聚集可激活其自我剪切活性, 形成成熟的CASP1并进一步介导pro-IL-1β和pro-IL-18裂解为成熟的IL-1β和IL-18, 引起“pyroptosis”性细胞死亡、内质网应激、细胞自噬等生理调节反应[42]。在病毒感染时, NLRX1可通过与视黄酸诱导基因蛋白-I(retinoic acid inducible gene protein-I, RIG-I)竞争性结合MAVS, 负调节RIG-I介导的抗感染免疫反应; 也可通过靶向TNF受体相关因子6(TNF receptor related factor 6, TRAF6)和IKKα/β-NEMO的复合物, 负调控TLRs诱导的NF-κB信号通路; 亦可通过增强ROS的产生促进NF-κB和JNK信号传导[4]。与NLRX1不同, NLRC5可与IKKα/β复合物相互作用抑制NF-κB信号的传导, 也可通过靶向RIG-I/MDA5阻断其与MAVS的相互作用从而抑制IFN-α、IFN-β分泌[26]。NLRC3和NLRP6是TLRs诱导的NF-κB和MAPK信号通路的负调节因子[5,45], 其具体作用位点仍需探索。在病毒感染或TLRs刺激后, NLRP4通过与TBK1结合募集E3泛素连接酶DTX4促进K48的多聚泛素化和TBK1的降解[30]。CIITA作为适应性免疫的调节剂, 可下调MHC II类分子的表达从而抑制人免疫缺陷型病毒(human immunodeficiency virus, HIV)和丙型肝炎病毒(hepatitis C virus, HCV)的复制, 并且CIITA的遗传变异与慢性乙型肝炎病毒(hepatitis B virus, HBV)感染相关[46-47]。CIITA通过与HTLV-1型病毒的转录因子Tax-1的相互作用, 抑制人T细胞淋巴病毒1型(human T-lymphotropic virus-1, HTLV-1)的复制[48-49]。

3 NOD样受体在肿瘤免疫中的作用

NLRs作为参与炎症反应的主要蛋白家族, 可通过与细胞凋亡及自噬相关蛋白相互作用, 调节癌症发生、发展过程中多种转录因子的活性从而参与肿瘤免疫过程。NLRA亚家族成员CIITA作为MHC II类分子激动剂, 可通过基因重排, 错义、无义和移码突变引发原发性纵隔大B细胞淋巴瘤[50]。在胰腺癌模型中, CIITA诱导的MHC II类分子的表达与肿瘤排斥和特定的抗肿瘤记忆反应有关。NLRB亚家族成员NAIP在乳腺癌组织中的表达量与肿瘤大小呈正相关关系[51], 并且乳腺癌以NLRC4依赖的方式促进血管内皮生长因子A介导的血管生成。NOD1和NOD2的单核苷酸多态性(single nucleotide polymorphism, SNP)与乳腺癌的发病率有关[4], NOD2介导信号通路的激活与乳腺癌的侵袭能力密切相关[4,52]。NAIP在前列腺癌组织中的表达与前列腺癌治疗药物的耐药性相关[3,14](图3)。在结肠癌组织中, NOD1和NOD2表达量上调, NLRC3和NLRC4表达量下调[7], 并且敲除*NAIP*可促进信号传导和转录激活因子3(signal transducer and activator of transcription 3, STAT3)的表达, 抑制抑癌基因*p53*的表达, 最终促进癌症的发生。有报道称NLRC3可通过抑制PI3K-mTOR信号通路减缓细胞增殖、诱导细胞死亡, 从而抑制结肠癌的发展[53], NLCR5作为MHC I类分子激活因子可参与结肠癌的发病并影响其预后[4]。在结肠癌浸润的巨噬细胞中, NLRP3抑制了肿瘤细胞的转移能力, NOD1和NOD2以干扰素调节因子4(interferon regulatory factor 4, IRF4)依赖性方式抑制TLRs介导的NF-κB和MAPK通路的激活, 进而参与结肠炎诱导的肿瘤发生[4,10]。据报道, NLRP6可通过下调白细胞介素-22结合蛋白(interleukin-22 binding protein, IL-22BP)促进CXC趋化因子5(chemokine C-X-C motif ligand 5, CXCL5)、IL-18和IL-6的产生进而参与结肠癌的侵袭过程[54], 也可通过诱导由p21和细胞周期蛋白D1介导的衰老来抑制胃癌细胞增殖[4]。在皮肤癌细胞中, NLRP1的下调降低CASP1的活性, 增加CASP2/3/7/9的活性, 进而以促进细胞凋亡的方式抑制癌细胞的扩散[4,28]。

最新研究发现, NLRs在微生物感染和细胞自噬异常引起的癌症中也发挥着重要作用[4,16]。在由人乳头瘤病毒(human papilloma virus, HPV)感染引起的宫颈癌中, NLRP1、NLRP3和IL-18的SNPs与HPV的感染周期和宫颈癌的发病率有关[55]。在幽门螺杆菌感染时, 下调NLRP9和NLRP12可导致NF-κB信号通路持续被活化, 最终诱导胃癌的发生[56]。幽门螺杆菌也可通过抑制miR-22增加NLRP3的表达, 进而促进上皮细胞增殖和胃癌的发生[57]。NLRP1、NLRP2、NLRP3、NLRP6、NLRP7、NLRP12及NLRC4等作为炎症小体受体, 可通过与ASC和pro-CASP1形成炎症小体激活CASP1, 使其与Beclin 1相互作用来诱导自噬和减少ROS的产生, 进而抑制肿瘤细胞的扩散[6]。据报道, CASP2和CASP8可以与自噬相关蛋白相互作用并将自噬转移至凋亡途径, 发挥抑制肿瘤的作用[42]。总之, NLRs与癌症的发生息息相关, 对NLRs家族成员功能的探索将为癌症的



NOD1/2: 核苷酸结合寡聚化结构域1/2; MAPK: 丝裂原活化蛋白激酶; AP-1: 激活蛋白1; CIITA: MHCII类分子激动剂; NLRX1: NLR 家族成员X1; NLRC3/4/5: NLR家族CARD包含结构域蛋白3/4/5; RIP2: 受体相互作用蛋白2; NLRP1/3/4/10: 含热蛋白结构域的nod样受体蛋白1/3/4/10; NAIP: 神经元凋亡抑制剂蛋白; ASC: 凋亡相关斑点样蛋白; “实线箭头”代表一种蛋白可直接促进另一种蛋白的表达; “虚线箭头”代表一种蛋白可间接影响另一种蛋白的表达; “平箭头”代表发挥抑制作用。

NOD1/2: nucleotide-binding oligomerization domain-containing 1/2; MAPK: mitogen-activated protein kinase; AP-1: activator protein 1; CIITA: class II major histocompatibility complex transactivator; NLRX1: NLR family member X1; NLRC3/4/5: NLR family CARD domain containing protein 3/4/5; RIP2: receptor-interacting protein 2; NLRP1/3/4/10: nod-like receptor pyrin domain-containing protein 1/3/4/10; NAIP: neuronal apoptosis inhibitor protein; ASC: apoptosis-associated speck-like protein containing a CARD; “solid arrow” means that one protein can directly promote the expression of another protein; “dashed arrow” means that one protein can indirectly affect the expression of another protein; “flat arrow” means that it exerts an inhibitory effect.

图3 NLRs对肿瘤发生的调控作用

Fig.3 Regulation role of NLRs in tumorigenesis

治疗提供新的理论支持。

4 展望

NLRs作为一类既参与天然免疫过程又参与获得性免疫过程的PRRs, 其家族成员不仅可作为接收器与病毒核酸及细菌细胞壁成分直接相互识别, 启动天然免疫反应; 又能作为适配器参与炎症小体的形成, 并在特定细胞系中与自噬相关蛋白及凋亡调控蛋白相互作用调控肿瘤的发生、发展及炎性因子的分泌; 还可作为调节器影响Toll样受体介导的信号通路、cGAS-STING信号通路、I型IFN信号通路、NF-κB信号通路、MAPK信号通路及自噬等通路的信号传导。该家族成员作为炎症反应的主要蛋白, 在短期刺激下可诱发急性炎症反应或抗炎反应, 长期作用时可与应激反应下的细胞自噬和细胞凋亡共同引发机体的免疫调控功能失衡, 最终导致免疫系统失调或癌症的发生。近年来, 关于NLRs在微生物感染及机体免疫功能紊乱相关疾病中的作用的研究越来越多。许多研究显示, NLRs家族成员的异常表达与II型糖尿病、克罗恩、多发性硬化症、痛风、系统性红斑狼疮、炎症性肠病、溃疡性结肠炎、肝炎、肾炎、关节炎、动脉粥样硬化、肿瘤及阿尔茨海默病等疾病的发生密切相关[6,33]。而上述疾病的发生与炎症反应有关, 适度的炎症有助于机体的恢复, 而过度的炎症反应又可导致疾病的恶化, 进而加速机体的衰竭甚至死亡, 故而有针对性地增强或减弱炎症反应可以微调宿主免疫应答反应控制疾病进展。因此, 深入探究NLRs的活化及调控机制可为相关疾病设计靶向干预策略提供更好的思路, 为复杂疾病提供新的治疗手段。

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