核酸感受器与肿瘤的关系

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摘要 先天免疫系统提供了抵御病原体感染的第一道防线。它依赖于一种感受器——模式识别受体(pattern recognition receptors, PRRs), 可检测病原体相关分子模式和损伤相关分子模式信号。核酸感受器是PRRs主要亚型之一, 通过识别胞内或胞外的核酸导致多种促炎症细胞因子的产生, 从而诱导免疫反应以保护被病原体感染的寄主。研究表明, 这些核酸感受器也参与肿瘤的发展。该文就各种核酸感受器与肿瘤的关系进行了综述。

关键词 核酸感受器; 病原体相关分子模式; 免疫反应; 肿瘤

Relationship between Nucleic Acid Sensing Pattern Recognition Receptors and Tumor

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Abstract The innate immune system is one of the first and most important lines of defense against pathogen. It depends on a kind of receptors called PRRs (pattern recognition receptors), which recognizes pathogen-associated molecular patterns or damage-associated molecular patterns. Nucleic acid sensing pattern-recognition receptors are one of the major subsets of PRRs, which can induce the production of pro-inflammatory cytokine to trigger immunity activation by perceiving extracellular or intracellular nucleic acid, thereby protecting the host from being infected by the pathogen. Recent researches show that nucleic acid sensing pattern recognition receptors participate in progress and occurrence of tumor. This review focuses on the current knowledge about the relationship between nucleic acid sensing pattern recognition receptors and tumor.

Keywords nucleic acid receptors; pathogen-associated molecular patterns; immunity reaction; tumor

先天免疫系统提供了抵御病原体感染的第一道防线。它依赖于一种感受器, 称为模式识别受体(pattern recognition receptors, PRRs), 被用于检测病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)和损伤相关分子模式(damage-associated molecular patterns, DAMPs)信号[1]。先天免疫细胞的质膜、胞质和内体中存在多种PRRs[2]。PRRs通过识别PAMPs或DAMPs, 并经历一系列信号级联反应, 导致多种促炎细胞因子的产生, 从而激活免疫细胞以保护被病原体感染的寄主[3]。

PRRs主要亚型之一的核酸感受器是先天免疫的重要元件, 主要功能是检测胞内或胞外的DNA或RNA[4]。识别RNA的PRRs包括部分Toll样受体(Toll-like receptors, TLRs)、RIG-I样受体(RIG-I like recep-

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表1 几种重要的核酸感受器与肿瘤的关系

Table 1 Relationship between some important nucleic acid sensing pattern-recognition receptors and tumors

家族 Family	名称 Name	配体 Ligand	高表达的肿瘤组织 Tumor tissue with high expression
TLRs	TLR3	Virus dsRNA	Glioma, renal clear cell cancer, pancreatic cancer, gastric carcinoma, testis tumor, breast cancer, thymoma, non-small cell lung carcinoma
	TLR7/8	Virus ssRNA	
	TLR9	Unmethylated DNA from bacteria and viruses	
RLRs	RIG-I	Long dsRNA	Pancreatic cancer, prostate cancer, squamous cell carcinoma of the head and neck, gastric carcinoma, glioblastoma, breast cancer
	MDA5	Short dsRNA	
ALRs	AIM2	dsDNA	Cervical cancer, lung squamous cell carcinoma, non-small cell lung carcinoma, melanoma, liver cancer
	IFI16	dsDNA	
	cGAS	dsDNA	Colon cancer, gastric carcinoma, glioblastoma, breast cancer, lung cancer, endometrial carcinoma

tors, RLRs)[5]以及p62[6]。识别DNA的PRRs包括TLR9、cGAS-STING(cGAMP synthase-stimulator of interferon genes)、ALRs(AIM2-like receptors)、DDX(DExD/H-box)蛋白和Ku70[7]。以上受体中的大部分被激活后会产生I型干扰素、趋化因子或炎症细胞因子[5], 对宿主防御细胞内细菌和病毒至关重要[8-9]。多种证据表明, 这些核酸感受器也参与肿瘤的生长, 本文就各种核酸感受器与肿瘤的关系进行了综述(表1)。

1 Toll样受体

TLRs是一类在进化上保守的I型跨膜糖蛋白, 所有家族成员都具有介导识别PAMP的富含亮氨酸的胞外识别结构域、单次跨膜结构域和下游信号转导所需的胞内TIR(Toll/IL-1 receptor homology)信号结构域[10]。TLRs在人类中有10个成员(TLR1~TLR10), 小鼠中有12个(TLR1~TLR12)[10]。TLRs能够识别的PAMP包括脂类, 脂蛋白, 蛋白质以及细菌、真菌、病毒和寄生虫等多种微生物的核酸[11]。其中, TLR3能够识别双链RNA, TLR7和TLR8能够识别单链RNA, TLR13能够识别细菌核糖体RNA, TLR9能够识别单链DNA中未甲基化的CpG序列[12]。TLR3、TLR7和TLR9在静息状态下定位于内质网, 在溶酶体中与配体结合后, 发生同型二聚化或寡聚化从而被激活[13]。TLR7/8和TLR9被激活后, 募集MYD88(myeloid differentiation primary response protein 88)激活下游NF-κB(nuclear factor kappa-B)和IRF7(interferon regulatory factor 7)的表达, TLR3则通过TRIF(TIR-domain containing adaptor protein inducing IFN-β)依赖型途径激活NF-κB和IRF7, 从而释放I型干扰素以及其他炎症因子[14]。

TLRs广泛分布于免疫细胞和上皮细胞, 在多种肿瘤中也表达, 间接或直接调控着肿瘤的生长和功能。在早期非小细胞肺癌中, 肿瘤浸润基质中的免疫细胞的TLR3表达与PD-1(programmed cell death protein 1)具有相关性, TLR3在免疫细胞上的高表达和在肿瘤细胞上的低表达会形成一种免疫抑制环境, 使得患者预后不良[15]。因此, TLR3在肿瘤和免疫细胞上的表达差异, 可以作为评估早期非小细胞肺癌预后的指标。

部分肿瘤由于突变较少, 因而表面抗原较少, 缺乏免疫原性, 难以吸引足够的免疫细胞浸润, 免疫学上将这一类肿瘤定义为“冷肿瘤”[16]。由于缺乏免疫原性, 传统的免疫检查点抑制剂对此类肿瘤无效, 因此,“冷肿瘤”的治疗存在一定挑战。TLRs在将“冷肿瘤”转化为“热肿瘤”的过程中扮演着重要角色。TLR9通过识别肿瘤释放的DNA促进肿瘤中树突状细胞的积累、成熟和淋巴结迁移。之后在淋巴结内, 这些树突状细胞激活肿瘤特异性$CD8^+$ CTLs(cytotoxic T lymphocytes), CTLs扩散至肿瘤中并控制肿瘤生长, 从而将“冷肿瘤”转化成“热肿瘤”[17]。由于这种转化是基于TLRs的激活来实现的, 因此多种TLRs激动剂已被尝试用于肿瘤治疗, 但至今临床试验结果仍不理想[18], 这可能与TLRs在不同细胞中表达量存在差异有关。在胰腺癌中, TLR7/8在基质中普遍表达, 而在上皮中的表达相对罕见, 这使得TLR7/8免疫激动剂R848在体外和体内对胰腺癌细胞系KxPxCx、FC1242都有着很好的抑制作用, 而对FC1199没有明显作用[19]。

明确不同的TLRs在肿瘤中介导的独特信号传导途径, 对探索肿瘤发病机制以及开发基于TLRs的新型肿瘤治疗方法具有重要意义。

2 RIG-I样受体3

RLRs是一系列DExD/H-box RNA解旋酶, 通过识别致病性RNA, 来启动抗病毒免疫应答[20]。目前, RLRs家族已发现3位成员: RIG-I(retinoic acid inducible gene-1, 又称为DDX58)、MDA5(melanoma differentiation-associated gene 5, 又称为IFIH1)、LGP2(laboratory of genetics and physiology 2, 又称为DHX58)。这3种蛋白均定位在细胞质中[21], 且具有一定的同源性, 均具有1个DExD/H-box RNA解旋酶结构域(DExD/H-box RNA helicase domain)和1个C-端结构域(C-terminal domain, CTD)。其中, RIG-I和MAD5的N-端还有2个caspase活化和募集结构域(caspase activation and recruitment domain, CARD)负责与下游线粒体抗病毒信号蛋白(mitochondrial antiviral signaling protein, MAVS, 又称为IPS-1)相互作用[20]。RIG-I主要识别5′端具有三磷酸基团的RNA(5′-triphosphorylated RNA, 5′-pppRNA或3pRNA)和短的双链RNA(<300 bp), 而MAD5主要识别长的双链RNA(>1 000 bp)[21]。

RLRs不仅行使机体抵御病毒感染的功能, 还在肿瘤发生发展以及治疗中扮演着重要角色。RIG-I可以诱导胰腺癌、前列腺癌、头颈部鳞状细胞癌、胃腺癌、胶质母细胞瘤和乳腺癌等多种肿瘤细胞的死亡[22]。虽然RIG-I在多种肿瘤中表现为抑癌, 但在肿瘤中往往处于低表达状态。在胶质母瘤细胞中, E3泛素连接酶Mex3 A(muscle excess 3A)的高表达促进RIG-I通过泛素–蛋白酶体途径的降解, 促进肿瘤细胞的增殖[23]。免疫组化显示, 胃癌组织中RIG-I的表达量下降会促进胃癌细胞的侵袭与增殖, 与患者的预后密切相关[24]。此外, 抗CTLA-4(cytotoxic T-lymphocyte-associated protein-4)与抗PD-1免疫疗法联用的治疗效果也依赖于细胞质RIG-I的激活。在接受免疫检查点阻断治疗的黑色素瘤患者中, 较高的RIG-I转录活性预示着良好的临床反应[25]。虽然RIG-I对多种肿瘤具有抑癌活性, 但在卵巢癌中, RIG-I的过表达预示着更高的肿瘤等级和不良的预后, 因此, RIG-I可以作为评估卵巢癌进展与预后的生物标志[26]。

MDA5与RIG-I结构类似, 所以也具有诱导癌细胞生长停滞和凋亡的能力[27]。SETDB1(SET domain bifurcated 1)在许多癌症中都过表达, 该基因的缺失会触发急性髓性白血病细胞的可逆转座因子的沉默, 从而导致双链RNA的产生, MDA5会被这种内源性RNA激活, 从而诱导I型干扰素产生并促进癌细胞的凋亡[28]。RLRs还通过肠道菌群间接影响肿瘤的发展。缺乏RIG-I会导致肠道中免疫球蛋白A(immunoglobulins A, lgA)、Reg3γ(regenerating 3γ)的mRNA等肠道生物群的重要调节因子水平降低, 防御素(cryptdin, 肠道中的一种抗微生物肽, 对于维持肠道细菌的平衡至关重要)以及Il1b、Il6、Il11等炎症因子的水平增高, 调节因子水平异常会严重影响肠道菌群的活性, 从而增加结肠癌发生的风险[29]。综上, 提高RLRs的表达量或激活其表达是未来肿瘤治疗中的一个关键突破点。

3 AIM2样受体

ALRs家族在人类中有4个成员: AIM2(absent in melanoma 2)、IFI16(interferon-γ-inducible protein 16)、PYHIN1(pyrin and HIN domain family member 1)和MNDA(myeloid cell nuclear differentiation antigen)[30]。ALRs由N-端的PYD结构域和C-端的1~2个HIN结构域构成。PYD结构域由约90个氨基酸残基组成, 介导同类型蛋白相互作用。HIN结构域通过其寡核苷酸/寡糖结合折叠(oligonucleotide/oligosaccharide-binding folds, OB-folds)与DNA或其他蛋白相互作用[30]。AIM2定位在细胞质中, 能够识别来自细菌、病毒或其他宿主细胞的双链DNA[31], 在多种肿瘤中异常表达。AIM2在大多数结直肠癌细胞系中表达较低, 原发性结直肠癌组织中的AIM2表达明显低于癌旁和正常组织, 且AIM2的低水平与结直肠癌的侵袭深度、淋巴结转移等临床病理特征显著相关[32]。AIM2水平的恢复可阻止细胞周期从G_1期向S期转化, 同时抑制PI3K/PK3(phosphatidylinositol 3-kinase/protein kinase B)信号通路促进结肠癌细胞的凋亡[8]。在宫颈癌中, SIRT1(Sirtuin1)通过抑制AIM2炎性小体介导的免疫而使癌细胞生长。敲除*SIRT1*导致AIM2炎性小体上调, 促进宫颈癌细胞凋亡[33]。乙肝病毒X蛋白(hepatitis B virus X protein, HBx)会促进AIM2通过泛素蛋白酶体途径的降解, AIM2水平的降低会诱导肝癌细胞的上皮–间质转化, 促进肝癌细胞的转移[34]。除炎症反应外, AIM2还通过其他途径参与到肿瘤的调控中。

在非小细胞肺癌中, 高表达的AIM2能够抑制线粒体融合蛋白2的表达, 促进细胞活性氧ROS(reactive oxygen species)的产生, 从而激活MAPK/ERK(mitogen-activated protein kinases/extracellular regulated protein kinases)信号通路, 促进肿瘤的恶化[35]。

IFI16通过自身识别外源或内源的双链DNA被激活后, 除形成炎症小体外[36], 还会与cGAS一起刺激STING磷酸化和转位, 协同对STING的激活产生作用[37]。IFI16水平的升高可以激活p21、p53和pRb(retinoblastoma protein)介导的细胞周期阻滞, 引起细胞衰老, 但IFI16表达降低会促进细胞增殖, 是一种潜在的肿瘤的抑制因子[38-39]。

4 cGAS-STING途径

cGAS是一种细胞质DNA感受器, 含有1个核苷酸转移酶结构域和2个DNA结合结构域, 可激活先天免疫反应, 诱导干扰素的产生[40-41]。cGAS通过与DNA形成2:2的复合体, 催化ATP与GTP环化形成环GMP-AMP(cGAMP)[42]。cGAMP作为第二信使激活定位在内质网膜上的STING, STING通过募集并激活TBK1(TANK binding kinase-1)和IKK(inhibitory-κB kinase), 进而级联激活IRF3和NF-κB[43]。cGAS由双链DNA激活, 这种激活与DNA序列无关[41]。一些单链DNA自身的上下游互补形成的双链结构或含有1段鸟嘌呤残基突出端的单链DNA也可以有效激活cGAS, 但这种激活机制有待进一步研究[44]。

cGAS-STING途径是先天免疫系统识别肿瘤细胞的关键, 然而在多种肿瘤中该通路被抑制, 阻碍了细胞对DNA损伤的应答。STING缺陷型小鼠更容易被DNA损伤剂诱发结肠癌, 而且与正常小鼠相比, 携带肿瘤的STING缺陷型小鼠中抑制性白细胞介素-22结合蛋白(interleukin-22 binding protein, IL-22BP)表达较低, 研究表明, IL-22BP是一种预防结肠癌的关键细胞因子[45]。此外, 免疫组化显示, 与正常组织相比, 胃癌组织中STING蛋白表达显著下调, 低STING蛋白水平与肿瘤大小、浸润深度、患者存活率呈正相关。敲低胃癌细胞中的STING蛋白表达量还会增强癌细胞的增殖、迁移、侵袭能力[46]。cGAS-STING途径在肿瘤血管系统中也扮演着重要角色, 向肿瘤内注射外源性cGAMP可激活内皮细胞中的STING从而分泌IFN-β, 可增强$CD8^+$ T细胞的抗肿瘤活性, 从而有效控制肿瘤的生长[47]。在小鼠胰腺癌模型中, 放射治疗联合体外注射STING配体环二核苷酸, 能够很好地激活cGAS-STING通路, 促进T细胞依赖型肿瘤坏死[48]。

cGAS-STING途径与肿瘤外泌体也存在联系。外泌体是细胞脱落的囊泡(大小为30~150 nm), 存在于几乎所有体液中。外泌体携带着其起源细胞的多种分子, 包括跨膜/胞质蛋白、mRNA、microRNA和DNA, 在内环境中扮演着重要角色[49]。其中, 肿瘤外泌体由于含有肿瘤相关内含物, 被认为是一种潜在的肿瘤生物标志物。源自乳腺癌的外泌体会被树突状细胞摄取, 其中的DNA作为PAMP, 会被cGAS-STING通路识别, 从而启动抗肿瘤反应[50]。cGAS-STING通路在细胞信号转导中扮演着重要角色, 深入的探究可为癌症的治疗开发新的途径。

5 其他感受器

DDX蛋白家族广泛存在于从细菌到人类的生物体中, 包含8~9个保守的基序, 根据基序II中的氨基酸序列的差异, 除之前所介绍的RLRs外, 还有DEAD、DEAH、DExH、DExD等亚家族[51], 其家族成员既参与到转运、剪接、转录等多种RNA代谢中, 又与肿瘤的发生与发展密切相关。家族成员YTHDC2(YTH domain containing 2)通过展开mRNA的5′非翻译区促进翻译的起始, 诱导缺氧诱导因子(hypoxia-inducible factor-1alpha, HIF-1α)高表达, 从而促进结肠癌的转移[52]。DDX56在结直肠癌中表现为上调, 并且高表达的DDX56与肿瘤的淋巴浸润和远距离转移存在相关性, 表明*DDX56*是一种原癌基因, 具有成为结直肠癌预后生物标志物的潜力[53]。DEAD/H-box解旋酶基因*DDX41*突变会引起mRNA剪接和RNA加工的改变, 引起成人家族性急性髓性白血病综合征[54]。

非同源末端连接(non-homologous end-joining, NHEJ)在细胞周期中是必不可少的双链DNA断裂修复途径, Ku70/80异二聚体在其中扮演重要角色。DNA修复因子Ku70分子量约为70 kDa, 通过中心结构域与Ku80形成异二聚体, 以高亲和力与DNA末端结合, 可保护受损的DNA末端免于降解并招募修复所需的其他NHEJ因子[55]。抗癌因子RFC4(replication factor C4)通过与Ku70/Ku80相互作用促进NHEJ介导的DNA修复, 从而间接影响直肠癌的预后[56]。Ku70可与细胞溶质Bax(B-cell lymphoma

protein 2-associated x)[57]和c-FLIP(cellular FADD-like interleukin-1β converting enzyme inhibitory protein)[58]结合以增加其稳定性保护细胞免于凋亡, 目前, 已开发出组蛋白去乙酰化酶(histone deacetylases, HDACs)抑制剂, 可诱导Ku70乙酰化, 抑制其与Bax和c-FLIP的结合, 从而阻滞细胞周期的运行并诱导癌细胞的凋亡[59]。

LRPPRC(leucine-rich pentatricopeptide repeat-containing protein)属于PPR(pentatricopeptide repeat)蛋白家族, 通过C-端的多个PPR基序与RNA结合, 调节胞质和线粒体中的mRNA的稳定性和修饰[60]。LRPPRC在前列腺癌、胃癌、肺腺癌、食道鳞状细胞癌、乳腺癌、子宫内膜腺癌和结肠癌等多种癌症中高表达, 且与肿瘤的恶性程度、不良预后相关[61-62]。这种促癌功能可能通过调节表观遗传来实现。在膀胱癌中, 长链非编码RNA DANCR能够诱导LRPPRC稳定IL-11、PLAU(plasminogen activator urokinase)和Cyclin D1等蛋白的mRNA, 从而激活IL-11-STAT3信号通路, 促进膀胱癌的淋巴结转移和肿瘤细胞增殖[60]。

LRRFIP1/GCF2(leucine rich repeat of flightless-1 interacting protein 1/GC-binding factor 2)主要定位在胞质, 可直接与双链RNA或富含GC序列的双链DNA结合诱导IFN-β的产生[63]。LRRFIP1有3个结构域: N-端螺旋结构域、中心卷曲螺旋结构域和C-端核酸结合结构域[64]。LRRFIP1在肝癌中高表达, 高水平的LRPPRC会促进肝癌的上皮–间质转化。敲低LRRFIP1蛋白水平, 可提高E-catenin的磷酸化水平并降低其核定位, 同时下调β-catenin, 抑制肿瘤细胞的迁移与侵袭[65]。

p62是一种自噬受体蛋白, 包含多个结构域: C-端泛素相关结构域、LC3结合结构域、N-端PB1结构域。最近研究表明, p62具有识别vault RNA的功能。Vault RNA是一类由RNA聚合酶III转录的长度为88~100 nt的小非编码RNA, 能够与蛋白组成核糖蛋白颗粒vault。Vault RNA通过与p62的锌指结构域结合干扰p62的寡聚化, 从而抑制细胞自噬[6]。p62在肿瘤微环境中对细胞代谢的影响取决于细胞类型, 在肿瘤上皮细胞中具有促肿瘤作用, 但在成纤维细胞、肝星状细胞和巨噬细胞中起着抑瘤作用[66], 但其是否通过识别vault RNA介导肿瘤的发展过程仍有待研究。

6 展望

核酸感受器由于其重要的功能, 多种激动剂已经投入了研究, 但临床效果并不理想, 其中传统的poly(I:C)被广泛应用于核酸感受器的激活, 但其具有一定的毒性[67]。所以需要一种无毒、高特异性、高亲和力和低成本的新激动剂用于激活核酸感受器。核酸适体是短的单链DNA或RNA寡核苷酸链, 能够通过各种分子内相互作用折叠成三维结构, 与多种靶标形成形状互补且稳定的特异性复合物, 具有高特异性、低免疫原性、无细胞毒性、高特异性等优点[68]。DNA适体R14能够与LRPPRC特异性结合, 基于此设计的一种适体辅助的高通量系统, 筛选出一种LRPPRC的小分子抑制剂棉酚乙酸, 具有靶向治疗肺腺癌的潜力[69]。RNA适体CL9通过与RIG-I的DexD/H-box RNA解旋酶结构域以及C末端结构域结合, 进而激活RIG-I[70]。基于核酸感受器能够识别核酸并调控肿瘤的功能, 人工合成的核酸适体在核酸感受器的应用方面具有优良的潜力, 但针对核酸感受器的适体仍有待开发。

核酸感受器在先天免疫中发挥着重要作用, 与肿瘤的发生发展关系密切, 随着对各种核酸感受器的深入研究, 必将在对其抑制剂、激动剂、佐剂的开发方面取得新的突破, 为肿瘤的临床治疗提供新的途径。

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