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DGCR8结构及其生物学功能

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摘要　DGCR8(DiGeorge syndrome critical region 8)是一种非编码RNA结合蛋白, 主要由RNA结合血红素结构域(Rhed)、两个双链RNA结合结构域(dsRBD)和C-端尾部(CTT)组成。DGCR8通过与DROSHA组成微处理器(microprocessor), 指导DROSHA在pri-miRNA的正确位置剪切, 参与miRNA的合成。随着研究的深入, DGCR8的许多非经典功能也被发现。由于DGCR8广泛参与非编码RNA合成、mRNA可变剪切和转录后调控等重要进程, 因此DGCR8缺失可导致多种发育缺陷。而且, 除与DiGeorge综合征密切相关外, DGCR8在多种癌症和疾病中表达失调, 参与相关癌细胞的迁移、侵袭、转移以及多种疾病的发病过程。该文对DGCR8的结构及其发挥的生物学功能进行综述, 重点阐述其在细胞增殖、分化、凋亡、衰老, 机体的生长发育, 以及包括癌症在内的多种疾病中的作用。这些生物学功能的发现揭示DGCR8可能成为先天性发育缺陷疾病和相关肿瘤以及其他疾病的潜在治疗靶点, 为相关疾病的治疗提供新的思路。

关键词　DGCR8; 细胞; 发育; 癌症; 疾病

DGCR8 Structure and Biological Function

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Abstract　DGCR8 (DiGeorge syndrome critical region 8), a non-coding RNA-binding protein, comprises the Rhed (RNA-binding heme domain), along with two dsRBD (double-stranded RNA binding domains) and the CTT (C-terminal tail). DGCR8 participates in miRNA synthesis by forming a microprocessor with DROSHA and directing DROSHA to cleave at the correct position of pri-miRNA. The advancement of research has unveiled numerous non-canonical functions of DGCR8. Due to its extensive involvement in crucial processes such as non-coding RNA synthesis, alternative splicing of mRNA, and post-transcriptional regulation, deficiency of DGCR8 leads to a diverse array of developmental abnormalities. Additionally, apart from its close association with DiGeorge syndrome, DGCR8 exhibits dysregulation in various malignancies and disorders, playing a crucial role in the migration, invasion, metastasis of cancer cells and the pathogenesis of diverse diseases. This review provides a comprehensive overview of the structural characteristics and diverse biological functions of DGCR8, with particular emphasis on its pivotal roles in regulating cell proliferation, differentiation, apoptosis, senescence, body growth and development, as well as a variety of diseases including cancer. These findings unveil the potential of DGCR8 may be as a therapeutic target for congenital developmental defects and associated tumors and other diseases, offering novel insights for the treatment of related disorders.

Keywords　DGCR8; cell; development; cancer; disease

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迪乔治综合征关键区域基因8(DiGeorge syndrome critical region 8, *DGCR8*, 果蝇、线虫同源基因为*Pasha*[1-2])是非编码RNA结合蛋白, 因其与迪乔治综合征有关, 因此被命名为DGCR8。DGCR8的经典功能是参与miRNAs(microRNAs)合成, 基于此, 通过构建DGCR8敲除模型, 大量miRNA的功能被进行了广泛研究[3-5]。但是, 随着对DGCR8研究的不断深入, DGCR8的非经典功能被发现, *DGCR8*敲除或耗竭策略揭示该蛋白具有控制snoRNA(small nucleolar RNA)的稳定性[6-7]、维持异染色质稳定[8]和参与DNA修复[9-10]等功能。由于DGCR8广泛参与非编码RNA合成、mRNA可变剪切和转录后调控等重要进程, 还可以与lincRNA(long intergenic noncoding RNA)和snoRNA结合发挥功能, 因此, DGCR8参与了许多生物学过程, 例如细胞的增殖、分化, 生物体的生长发育, 肿瘤和其他疾病的发展等。

1 DGCR8的结构

DGCR8的经典功能是参与miRNAs合成。miRNAs是由21~22个核苷酸组成的单链小分子RNA, 转录后水平通过对基因的调控作用参与生物体生长发育的诸多过程, 包括基因组重排、细胞增殖、细胞凋亡、器官发生、发育时长、肿瘤发生和病毒防御等[11-16]。经典miRNA的生物合成涉及5个阶段: 基因转录、初级miRNA(primary miRNA, pri-miRNA)加工、前体miRNA(precursor miRNA, pre-miRNA)分子转运、pre-miRNA切割和miRNA链选择[17](图1A), 其中DGCR8和RNase III DROSHA组成微处理器, 实现对pri-miRNA的剪切[17-21]。如图1B所示, 微处理器(microprocessor)是由一个DROSHA和两个DGCR8分子组成的异源三聚体复合物[2,22]。人DGCR8蛋白由位于迪乔治综合征染色体区域(DGCR, 染色体22q11.2)的基因编码[23-24], 基因全长大于35 Kb, 具有14个外显子, 编码一个含有773个氨基酸的蛋白质。DGCR8包含一个核定位所需的N-端区域, 一个内含WW基序(WW domain)的RNA结合血红素结构域(RNA-binding heme domain, Rhed), 两个双链RNA结合结构域(double-stranded RNA binding domains, dsRBD)和一个C-端尾部(C-terminal tail, CTT)[25-29](图1C)。在微处理器(图1B)中, DGCR8是二聚化存在的, DGCR8的二聚化结构域嵌入在Rhed中, 并在与血红素的结合中发挥作用, 而Rhed中的WW基序在二聚化中也发挥重要作用[26]。同时, 研究发现DGCR8二聚体与pri-miRNA结合后可以三聚化形成六聚体。其中, DGCR8蛋白C末端两亲性α螺旋中的一个疏水性区域(729–750)对于结合pri-miRNA后DGCR8的三聚化是必需的[30]。而pri-miRNA上组装更高阶的DGCR8结构与后续DROSHA切割pri-miRNA存在直接联系。在此, DGCR8和DROSHA分子需要先进行结合和加工, 形成DGCR8-DROSHA异二聚体并鉴别需切割的特异性底物, 随后DROSHA在pri-miRNA的正确位置剪切。DGCR8和DROSHA之间存在一定的相互关系, 它们之间的作用不是截然没有联系的两个过程: DGCR8介导了pri-miRNA的识别以及DROSHA的募集与切割[31]。在pri-miRNA的结合和识别过程中, DGCR8分别通过Rhed和dsRBDs与pri-miRNA的顶端和茎相互作用[32]。DGCR8二聚体的两个Rhed结合位点位于pri-miRNA发夹的两端, 识别pri-miRNA末端环的UGU基序[25,33-34], 4个dsRBD识别结合pri-miRNA茎的上端部分。此外, 结合于Rhed的血红素辅因子是形成具备加工活性的DGCR8-pri-miRNA复合物所必需的[35], 因此在pri-miRNA的结合和识别过程中, DGCR8分别通过Rhed和dsRBDs与pri-miRNA的顶端和茎相互作用[36]。

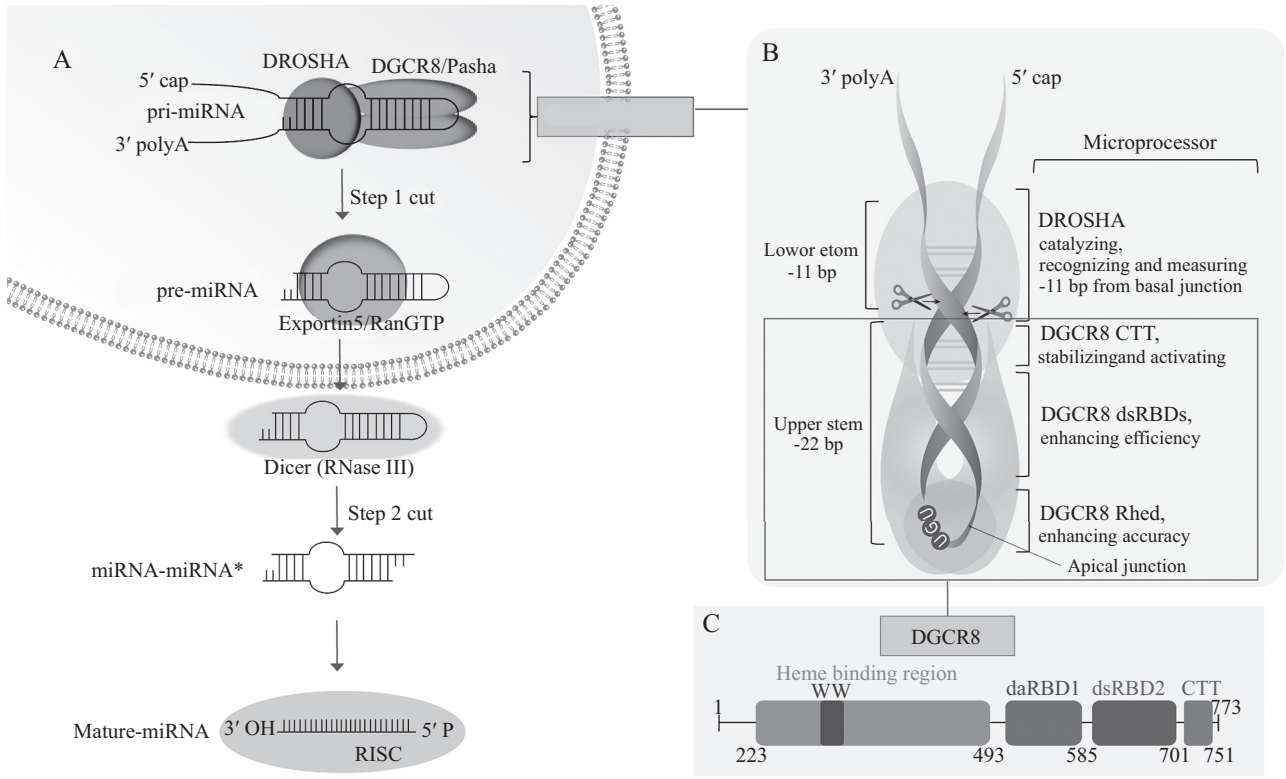
DGCR8的HITS-CLIP实验显示, 除了pri-miRNA之外, 微处理器还可以与大量结构类似于pri-miRNA二级结构的RNA结合, 包括数百个mRNA、lincRNA、snoRNA和转座元件等[7,37](图2)。研究表明*DGCR8* mRNA的5′UTR中发卡结构被微处理器结合和切割[38-40], 且研究发现*DGCR8*具有控制着人类端粒酶RNA组分(human telomerase RNA component, hTR/TERC)的稳定性[6]、维持异染色质稳定[8]和参与DNA修复[9-10]等功能。

2 DGCR8的生物学功能

由于*DGCR8*广泛参与非编码RNA合成、mRNA可变剪切和转录后调控等重要进程, 还可以与lincRNA和snoRNA结合发挥功能, 因此, *DGCR8*参与了许多生物学过程。本文分别从细胞的增殖、分化、凋亡、衰老, 组织器官的生长发育, 肿瘤和其他疾病的发生发展等方面综述*DGCR8*广泛的生物学功能(图3)。

2.1 *DGCR8*与细胞的增殖、分化、凋亡和衰老

2.1.1 细胞增殖和分化 *DGCR8*异常表达会影响



A: miRNA的经典生物合成过程; B: 人pri-miRNA微处理器模型(根据参考文献[22]修改); C: DGCR8(人)结构域示意图(根据参考文献[25]修改)。miRNA*表示的是miRNA的互补链。

A: the classical biosynthetic process of miRNA; B: microprocessor model on pri-miRNA molecules (human) (modified from the reference [22]); C: schematic representation of the DGCR8 (human) domain (modified from the reference [25]). miRNA* represents the complementary strand of miRNA.

图1 DGCR8及其结构域功能示意图

Fig.1 Schematic representation of the function of DGCR8 and its domains

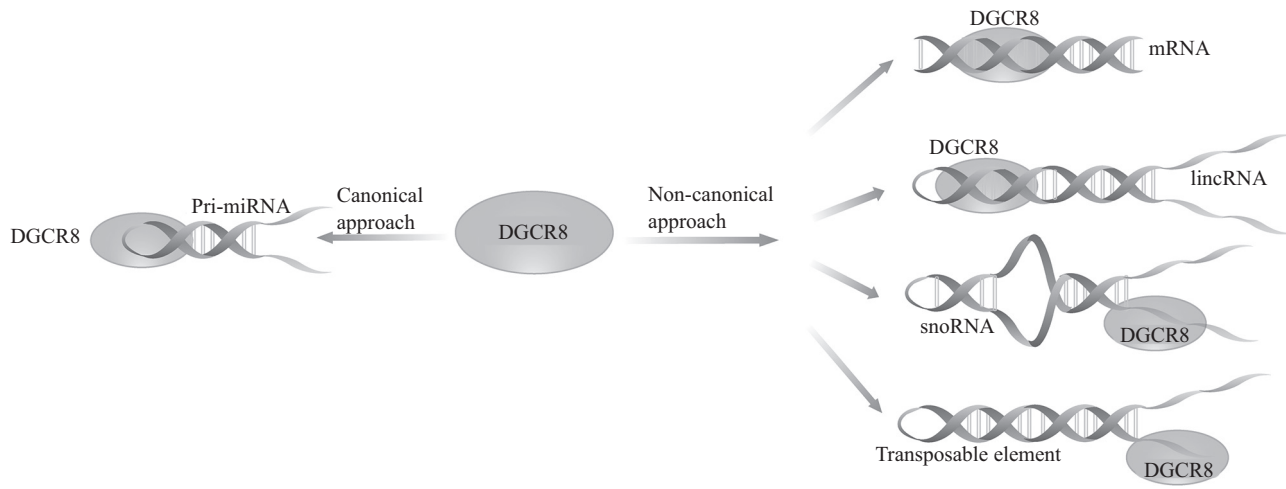


图2 DGCR8的经典和非经典途径示意图

Fig.2 Schematic diagram of canonical and non-canonical approaches for DGCR8

细胞周期进程、增殖和分化。人类或小鼠原代成纤维细胞中的*DGCR8*缺失可使细胞周期抑制基因*p21CIP1*高表达, 导致细胞出现显著的细胞周期阻滞、衰老和抗增殖反应[41], 在小鼠肝细胞中, *Dgcr8*失活延迟了G_1期到S期转变的时间, 进而影响了增殖[42]。近期研究发现, 敲除小鼠胚胎干细胞(mouse embryonic stem cells, mESCs) *Dgcr8*会导致G_1期细胞积累、增殖速度延缓, 且伴随上皮–间充质转化

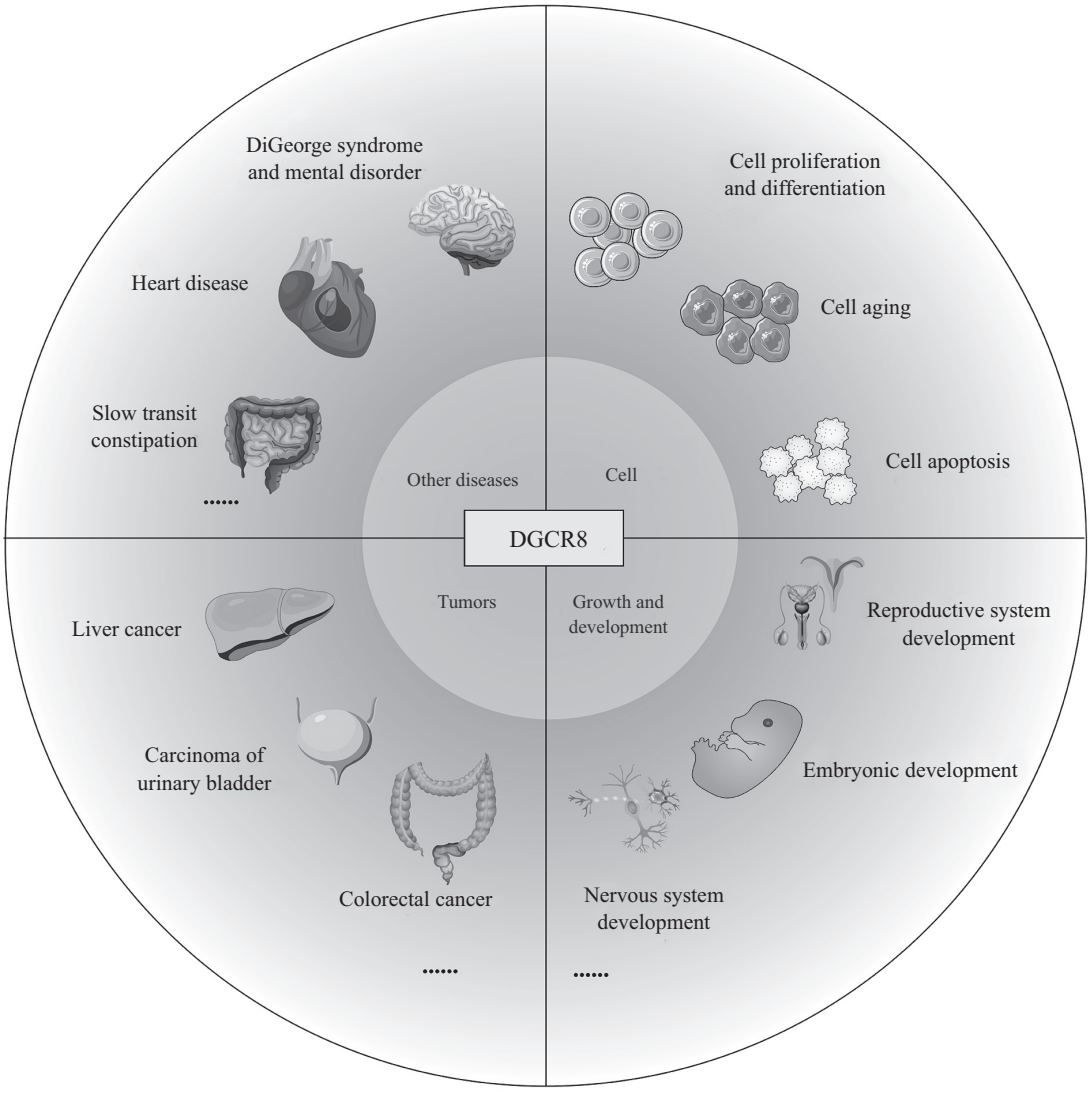


图3 *DGCR8*的生物学功能(在增殖、分化、凋亡、衰老, 动物的生长发育, 肿瘤以及其他疾病的发生发展等)

Fig.3 Biological functions of *DGCR8* (cell proliferation, differentiation, apoptosis, senescence, the growth and development of animals, and development of tumors and other diseases)

(pithelial-mesenchymal transition, EMT)标志物浓度升高等[43]。此外, 另一项在mESC中的研究发现, *Dgcr8*可通过与Tcf7l1直接作用, 促进其选择性剪接来调控细胞分化, *DGCR8*敲除会阻断多能性退出[44]。此外, 最新的研究发现, 骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMMSCs) DGCR8可与肾母细胞瘤1相关蛋白(Wilms' tumor 1-associating protein, WTAP)相互作用, 并以m6A依赖性方式加速pri-miR-29b-3p的成熟, 进而调节细胞分化[45]。

2.1.2 细胞衰老 *DGCR8*可以稳定异染色质从而缓解衰老。在使用Cas9和sgRNA靶向人间充质干细胞(human mesenchymal stem cells, hMSCs) *DGCR8*外显子3构建的*DGCR8*缺陷模型DR8^{ex3}中发现, DGCR8可通过与核膜蛋白Lamin B1、异染色质相关蛋白1(KRAB-associated protein 1, KAPI)和异染色质蛋白1γ(heterochromatin protein 1 γ, HP1γ)相互作用来维持异染色质稳定以及延缓衰老[8]。此外, *DGCR8*敲低的hMSCs也表现出严重的增殖缺陷和衰老相关表征, 包括活性氧(reactive oxygen species, ROS)的增加和超氧化物歧化酶2的表达显著下调。当在此模型中过表达miR-29a-3p和/或miR-30c-5p时, 表观遗传调节因子DNA甲基转移酶3A受影响, 同时ROS水平降低, 增殖缺陷、线粒体功能障碍和早衰等表型被挽救[46]。

2.1.3 细胞凋亡 *DGCR8*还参与细胞凋亡过程。在*Dgcr8*缺乏的小鼠B细胞祖细胞中,

μHC(immunoglobulin μ heavy chains)表达量降低并伴随祖B细胞发生凋亡, 阻止B细胞从pro-B期过渡至pre-B期[47]。*DGCR8*失活的心脏神经嵴细胞可以正常增殖和分化, 但是细胞凋亡程度增加[48]。

2.2 DGCR8与生长发育

作为miRNA合成过程中的关键酶之一, 研究发现*DGCR8*参与生物体生殖系统、胚胎和神经系统等的发育过程。

2.2.1 生殖系统发育 *DGCR8*缺失会导致严重的生殖发育缺陷。秀丽隐杆线虫*Pasha*(*DGCR8*同源基因)是卵母细胞成熟和排卵过程所必需的, *Pasha*基因突变或使其无法排卵导致不育, 或导致100%的胚胎致死率[49-51]。而*Dgcr8*缺陷的小鼠则会发生子宫发育不全, 出现子宫萎缩、子宫肌层缺陷、输卵管平滑肌畸形、生殖道无法排卵和急性炎症等表型, 即使胚胎植入也不能存活[52-54]。在脊椎动物中的研究发现, 在*Dgcr8*敲除的小鼠精母细胞中, 性染色体会在减数分裂前期发生融合[55]。在*Dgcr8*表达缺陷的人睾丸中, 精子发生受阻[55]。以上研究表明*DGCR8*对动物生殖系统的发育至关重要。

2.2.2 胚胎发育 在斑马鱼中, DGCR8在母体和受精卵早期胚胎发育过程中分别发挥不同作用。母体*DGCR8*缺失使miR-430表达量下调, 导致原肠胚形成异常、脑畸形、造血缺陷、心脏缺陷及身体曲率改变。而受精卵*DGCR8*缺陷虽然也同样导致早期胚胎的造血和心脏发育有缺陷, 但上调miR-430只能挽救部分发育缺陷[56] 。在牛*DGCR8*敲低模型中, 由于胚胎中miRNA的表达受影响, 桑葚胚向囊胚的转变被抑制[57]。因此, *DGCR8*是胚胎发育所必需的。

2.2.3 神经系统发育 *DGCR8*缺失会影响神经组织的发育。在无脊椎动物中, 果蝇*DGCR8*调节神经元形态发生[58]。在脊椎动物中, 小鼠*Dgcr8*影响新皮质发育[59], 且*Dgcr8*缺失会导致海马体发育缺陷和前额叶皮层兴奋性突触传递受阻[60-62], 而小鼠*Dgcr8*过表达则会促进胚胎新皮层的神经祖细胞扩张和抑制神经发生[63]。当特异性敲除小鼠中间神经元祖细胞的*Dgcr8*后, *Cxcr4*/*Cxcl12*依赖性海马齿状回的发育受到影响[64]。由此可见, DGCR8与神经系统的发育密切相关。

2.2.4 其他器官发育 *DGCR8*缺失除造成生殖和神经系统发育缺陷之外, 还影响其他组织或器官发育, 例如皮肤毛发再生、肾脏、骨骼等发育。在毛发再生过程中, *DGCR8*敲除的小鼠出现毛囊向下生长的缺陷, 毛发胚芽和更成熟的鳞茎都表现出普遍的细胞凋亡迹象[65-67]。小鼠*Dgcr8*缺失还会使肾小管系统出现严重的发育缺陷和肾功能衰竭, 导致肾积水和肾畸形[68]。非洲爪蟾的*DGCR8*缺失会导致其胚胎前肾发育缺陷, 包括水肿形成、肾上皮分化延迟等表型[69]。在骨骼发育方面, *Dgcr8*缺失导致小鼠股骨骨体积、骨小梁数量、骨小梁厚度增加, 以及破骨细胞吸收活性降低[70-71]。

2.3 DGCR8与肿瘤

现今, 研究者们已通过组学聚类分析、qRT-PCR等方法检测了*DGCR8*在不同癌症中的表达水平, 结果显示*DGCR8*在许多肿瘤中表达异常。*DGCR8*在甲状腺癌、家族性多结节性甲状腺肿伴神经鞘瘤病、松果体母细胞瘤、原发性肝细胞癌和肾透明细胞癌等肿瘤中表达下调; 在胶质瘤、唾液腺多形性腺瘤、原癌基因突变甲状腺髓样癌、扁桃体鳞状细胞癌、上皮性皮肤癌、胃肠道癌、结直肠癌、三阴性乳腺癌、卵巢癌、前列腺癌和浸润性导管癌等癌症中表达上调(表1)。进一步的结果证实, 敲低*DGCR8*可抑制胶质瘤、三阴性乳腺癌和卵巢癌癌细胞的增殖、迁移和侵袭[72-74]。

在肿瘤中发现了许多与*DGCR8*相关的mRNA, 以及miRNA、lincRNA等非编码RNA, 由此可见, *DGCR8*通过经典和非经典功能参与肿瘤的发生、发展过程。其中*DGCR8*通过与*CDX2*[74]、*YY1*[75]、METTL3[76-78]、METTL14[79]、*ING1*[80]、*LINC01198*[81]、$CCDC_{137}$[82]等基因/蛋白结合或相互作用参与相关癌症的发展。例如, DGCR8通过与METTL3相互作用以m6A依赖性方式正向调节pri-miR-221/222和pri-miR-34a的成熟, 随后分别促进膀胱癌和腹主动脉瘤的发展[76-77]。同样以m6A依赖性方式, DGCR8与METTL14相互作用正向调节pri-miR-126的成熟[79]。最近的研究发现DGCR8可与RNA结合蛋白$CCDC_{137}$相互作用, 通过DGCR8在mRNA定位中的新型非经典作用促进肝细胞癌发生[82]。与*DGCR8*相关的lincRNA有TUG1[83-84]、SNHG14[85]、TTN-AS1[86]等, 它们通过上调*DGCR8*分别促进前列腺癌、卵巢癌的迁移和侵袭以及乳腺癌的转移。此外, 在头颈部鳞状细胞癌中发现辐射可激活DGCR8/miR-27a-3p/SMG1轴, 进而增强放射敏感性[87], 而DGCR8/miR-106轴同样可以通过下调

*RUNX3*增强头颈部鳞状细胞癌的放射敏感性[88]。

*DGCR8*在不同肿瘤中表达水平的异常及其机制的深入研究表明, *DGCR8*在各类肿瘤的发生、发展过程中发挥重要作用。这些实验数据将为相应肿瘤潜在治疗靶点的研究提供一定的理论依据。

2.4 DGCR8与其他疾病

除了在肿瘤中发挥作用之外, *DGCR8*还在许多其他疾病中表达异常。研究发现*DGCR8*在染色体22q11.2缺失综合征(22q11DS, 又称腭心面综合征或迪乔治综合征)、原发免疫性血小板减少症、强直性脊柱炎和先天性心脏病等疾病中表达下调; 在亨廷顿舞蹈症、精神分裂症、非酒精性脂肪性肝病、多发性硬化、银屑病和慢传输型便秘等疾病中表达上调(表2)。

*DGCR8*与染色体22q11.2缺失综合征密切相关。基于22q11DS小鼠模型的研究发现, *DGCR8*的单倍不足引起了杏仁核外侧的丘脑输入处的突触形成缺陷, 导致了丘脑中多巴胺受体Drd2水平升高和丘脑输入的谷氨酸释放概率降低[108]。同时*DGCR8*的单倍不足还会导致miR-382-3p和miR-674-3p表达量降

表1 *DGCR8*在不同癌症中表达异常

Table 1 *DGCR8* expression is abnormal in different cancers

肿瘤类型 Types of tumour	*DGCR8*的表达水平 The expression level of *DGCR8*	参考文献 References
Thyroid cancer	Down	[89-93]
Primary hepatocellular carcinoma	Down	[94]
Clear cell carcinoma of kidney	Down	[95]
Pineoblastoma	Down	[96-98]
Familial multinodular goiter with schwannomatosis	Down	[98]
Hepatitis B virus causes various liver diseases (including chronic hepatitis, cirrhosis, and hepatocellular carcinoma)	Down	[75]
Pleomorphic adenoma of salivary gland	Up	[99]
Epithelial skin cancer	Up	[100]
Prostatic cancer	Up	[101]
Gastrointestinal cancer	Up	[102]
Medullary thyroid carcinoma with proto-oncogene mutation	Up	[102]
Colorectal cancer	Up	[103]
Squamous cell carcinoma of the tonsil	Up	[104]
Ovarian cancer	Up	[72]
Invasive ductal carcinoma	Up	[105]
Glioma	Up	[74]
Triple-negative breast cancer	Up	[73]

表2 与*DGCR8*相关的疾病

Table 2 Diseases associated with *DGCR8*

疾病名称 Name of disease	*DGCR8*的表达水平 The expression level of *DGCR8*	参考文献 References
Chromosome 22q11.2 deletion syndrome	Down	[106-110]
Primary immune thrombocytopenia	Down	[111]
Ankylosing spondylitis	Down	[112]
Congenital heart disease	Down	[113-114]
Huntington disease	Up	[115]
Schizophrenia	Up	[116-117]
Non-alcoholic fatty liver disease	Up	[118]
Multiple sclerosis	Up	[119]
Psoriasis	Up	[120]
Slow transit constipation	Up	[121]

低, 进而使靶基因*Drd1*的表达量升高, 从而导致侧脑室和第三脑室进行性扩大, 心室壁内层室管膜细胞的纤毛搏动减慢[110]。研究还发现, 22q11DS患者常伴有精神疾病, 例如, 个体存在精神分裂症, 主要表现为情绪记忆、预测、回忆和情绪的正确分配方面受损[108]。

*DGCR8*介导的经典miRNA的产生对调节性T细胞的稳定性和功能发挥至关重要。研究发现调节性T细胞*Dgcr8*缺陷会使*FoxP3*表达下调, 小鼠会自发地发展形成皮屑样疾病[122]。在条件敲除*Dgcr8*的小鼠中, 患有扩张型心肌病的概率也大大提高[123], 进一步的体外培养研究发现, miR-1和miR-541可挽救*DGCR8*条件敲除导致的心肌细胞缺陷[124]。此外, 在心肌梗死模型中, DGCR8通过与METTL3作用可以使增殖相关的miR-17-3p高表达, 进而促进大鼠心肌细胞增殖[125]。在慢传输型便秘中, DGCR8通过与METTL3相互作用, 以m6A依赖性方式调控miR-30b-5p/PIK3R2/Akt/mTOR轴, 促进谷氨酸诱导的Cajal间质细胞的凋亡、自噬和焦亡[121]。DGCR8在这些疾病中的分子机制研究将为更多其他疾病的研究提供研究思路和理论支撑。

3 问题与展望

DGCR8的重要性是毋庸置疑的, 它不仅参与miRNA合成、mRNA可变剪切和转录后调控等重要进程, 还可以与lincRNA和snoRNA结合发挥功能, 广泛参与生物的许多生物学过程。但是, DGCR8功能的多样性导致其相关作用机制尚未被完全阐明。近年来, 许多研究发现, DGCR8与METTL3等相互作用并以m6A修饰依赖的方式调节相应miRNA的合成。这一机制与许多癌症和疾病, 例如膀胱癌[77]、胃癌[126]、鼻咽癌[127]、多发性骨髓瘤[128]、骨折愈合[129]、子宫内膜异位症[130]、动脉粥样硬化[131]等相关。RNA修饰在近些年受到高度关注, 例如m6A、m1A、m5C、假尿苷、2'-O-Me等, 这些RNA修饰也与癌症等疾病密切相关[132-133]。DGCR8的相关研究只涉及到了m6A, 其功能的发挥是否也依赖于其他RNA修饰还需要更多的研究来验证。此外, *DGCR8*在影响神经发育且在神经类疾病中表达异常, 但目前相关分子机制并未被深入探究。更多的研究发现*DGCR8*参与干细胞或癌细胞增殖或分化, 但更多的研究集中于小鼠等脊椎动物的体外细胞系研究。利用具有丰富干细胞和特异性去分化细胞的高再生能力动物模型, 从体内追踪*DGCR8*调控细胞增殖或分化的新机制很有必要。我们将聚焦于具有丰富干细胞和高再生能力的扁形动物涡虫, 旨在探究体内环境下, *DGCR8*在干细胞的增殖或分化中扮演什么样的角色, 机制如何。这些机制的报道将为相关疾病的治疗提供新思路和新靶点。总之, 对DGCR8经典和非经典功能的探究仍需继续。

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