doi: 10.3978/j.issn.2095-6959.2020.06.035
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2020.06.035

·综述·

MiR–17–92 簇的研究进展

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[摘　要]　MiR-17-92是一个高度保守的基因簇，该基因簇主要有6个成员，包括miR-17，miR-18a，miR-19a，miR-20a，miR-19b-1和miR-92a。这些基因通过调控靶基因参与肿瘤的发生、发展，参与一些细胞的免疫反应，并在内分泌系统中发挥一定的作用。

[关键词]　miR-17-92簇；肿瘤；免疫；内分泌系统

Research progress of miR-17-92 cluster

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Abstract　MiR-17-92 is a highly conserved gene cluster with six members, including miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a. These genes are involved in the development of tumors, which participate in some immune responses of cells, and also play a role in endocrine system.

Keywords　miR-17-92cluster; tumor; immunity; endocrine system

微RNA(miRNA)是高度保守的非编码小RNA，通过与3'-非编码区(3'-UTR)结合引起靶基因mRNA的降解或翻译的抑制，从而调节基因在转录后水平的表达[1]。MiRNA通常位于miRNA簇的多顺反子基因中，通过共表达不同的组织从而影响细胞生长、细胞周期和细胞分化[2-3]。目前在人类基因组中发现了300多个miRNA簇，包括miR-35-41簇和miR-17-92簇等[4-5]。MiR-17-92簇与哺乳动物多器官的发育、肿瘤的发生、发展密切相关[6]。MiR-17-92簇是研究最多的miRNA簇之一。MiR-17-92基因簇位于人类基因组染色体13q31.3上，编码6个成熟的miRNAs(miR-17，miR-18a，miR-19a，miR-20a，miR-19b-1和miR-92a-1)。MiR-17-92簇是一个高度保守的基因簇，其成员在各种环境中表现出至关重要的作用，包括正常发育、免疫疾病、心血管疾病、神经退行性疾病和衰老等[7]。据报道，miR-17-92簇的6个成熟miRNA具有会聚靶基因并协同调节细胞如神经元和内皮细胞的生长作用[8]。研究[9]显示：miR-17-92簇与肿瘤的发生密切相关，具有癌基因和抑癌基因双重功能。

1 MiR-17-92 簇与肿瘤

MiR-17-92簇作为高度保守的基因簇，是被发现的第1个miRNA致癌基因家族[7,10]。MiR-17-92簇的显著过表达可能在肺癌的发展中起作用，尤其

收稿日期 (Date of reception)：2019–12–01
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基金项目 (Foundation item)：国家科学自然基金 (81770810)。This work was supported by the National Natural Science Foundation of China (81770810).

是在最具侵袭性的小细胞肺癌中[4]。MiR-17-92还参与雌激素受体-α诱导的信号调节的转录反应。在乳腺癌患者中，miR-18a，miR-19b和miR-20b靶向并下调基因ERalpha，其机制为一部分pri-miRNA衍生的miRNA抑制ERalpha转录p160协同激活物AIB1的蛋白质翻译。通过miRNA转录调控的相互作用，能够协调雌激素的细胞反应[11]，为乳腺癌的分子机制以及可能的作用靶点提供了科学依据。在大肠癌研究[12]中，miR-17-92家族中的各个成员表达均显著上调，提示miR-17-92基因簇在某些功能上具有一致性。MiR-17-92簇可能作为胃癌早期检测的潜在血清生物标志物[13]。该研究通过测试胃癌患者、肠上皮化生患者和健康对照组的miR-17-92簇成员的水平，来评估家族在胃癌早期诊断中的临床价值。此外，miR-17-92可能成为骨肉瘤患者肿瘤复发和生存的标志物[14]。研究[15]将miR-17-92簇强制引入非雄激素依赖性DU145前列腺癌中破坏细胞增殖和凋亡间的平衡，明显促进了肿瘤细胞生长。MiR-17-92簇的过表达显著改善DU145细胞的迁移和侵袭，这归因于整联蛋白β-1的诱导。

MiR-17-92簇还参与肿瘤的新生血管的形成，并进一步调控肿瘤细胞的增殖、侵袭、转移等。以miR-17-92基因簇作为肿瘤治疗的靶点，可以通过阻断血管生成，进而抑制或阻断肿瘤复发转移等多个环节。因此将miR-17-92基因簇作为治疗肿瘤的新靶点具有很好的应用前景。

2 MiR-17-92 簇与免疫

MiR-17-92簇在免疫系统中参与先天和适应性免疫细胞反应，包括B细胞、T细胞亚群、调节性T细胞、单核细胞/巨噬细胞[16]。MiR-17-92簇广泛参与B细胞的发育，在鼠B细胞谱系中，miR-17-92在祖B细胞中水平最高，并且在从前B细胞过渡到成熟B细胞的过程中急剧下降[17]。MiR-17-92缺失导致B细胞发育受损，尤其是在后期的pro-B细胞成熟为大型pre-B的过程中[18]。MiR-17-92基因簇影响B细胞的发育。系统性红斑狼疮、多发性硬化或支气管哮喘患者外周血$CD4^+$T细胞中的miR-17-92显著上调[19-21]。此外，miR-17-92基因簇还影响调节性T细胞功能，从而增强或降低其免疫抑制作用。在小鼠受到抗原刺激后，$CD4^+$T细胞中miR-17-92的缺乏会增强Foxp3表达，且miR-17-92过表达能抑制Treg分化，其中miR-17和miR-19b发挥关键作用[22]。此外，敲低miR-17可以增强Treg的抑制功能，其过表达通过靶向Foxp3而降低Treg的功能[23]。在巨噬细胞分化过程中，转录因子PU.1诱导早期生长反应2(Egr2)，进而抑制miR-17的表达[24]。通过免疫方面的研究，miR-17-92基因簇的功能更加精细化。

3 MiR-17-92 簇与内分泌

近年来，miR-17-92基因簇与内分泌关系的研究也有了新进展。MiR-17-92簇不仅参与新生儿胰岛β细胞的分化和发育，而且参与β细胞的成熟，这对于获得葡萄糖刺激的胰岛素分泌(GSIS)功能至关重要[25]。动物实验[26]已证实：断奶后2~5 d内营养变化会导致miR-17-92表达发生变化，从而诱导β细胞增殖和GSIS功能获得。进一步的机制研究[26]表明：miR-17和miR-20a通过靶向PFKP(磷酸果糖激酶)、TGFBR2(转化生长因子β受体II)、PTEN(磷酸酶和张力蛋白同源物)、GPD2(甘油3磷酸脱氢酶2)、MDH1(苹果酸脱氢酶1)和c-Myc参与β细胞增殖和GSIS功能获得。MiR-17通过直接靶向Menin促进β细胞增殖，这与各种糖尿病小鼠模型和MIN-6细胞系中的基因转录，细胞周期和细胞凋亡调控有关[27]。

MiR-17-92簇也参与肝、骨骼肌和脂肪组织的胰岛素信号转导。在肥胖患者的脂肪组织中，miR-92a-1表达降低而趋化因子配体2(CCL2)的表达增加，后者可能引发炎症反应，进而导致全身性胰岛素抵抗[28]。研究[29-30]表明：miR-17在高血糖下调节丝裂原活化蛋白激酶(MAPK)蛋白表达，这在骨骼肌胰岛素抵抗的发展中起至关重要的作用。

糖尿病性心肌病(diabetic cardiomyopathy，DCM)是一种糖尿病性心脏病，miR-17-92簇参与DCM的许多重要的生理和病理过程，包括心肌细胞肥大、心肌纤维化、心肌细胞凋亡、线粒体功能障碍、心肌细胞电生理重构和表观遗传修饰[31-32]。因此，对相关miRNA的干预可以改善DCM，可能成为预防和治疗DCM的新方法。

笔者前期就糖尿病的并发症之一——糖尿病足溃疡(diabetic foot ulcer，DFU)与miR-17-92簇的关系进行了研究[33]，结果显示：在用蛆虫清创治疗DFU后，miR-17-92簇表达显著上调，这为miRNA对于糖尿病足的机制提供新思路。

4 结语

综上，miR-17-92簇在肿瘤、免疫、血管生成

和内分泌方面有重要作用，虽然miR-17-92基因簇的功能及作用机制尚未完全明确，但其在临床和科研的指导作用是毋庸置疑的，随着miR-17-92簇的各种分子生物学作用机制被逐步了解，其家族会有更加广阔的应用前景。

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本文引用：张洁, 陈金安, 孙新娟, 董磊磊, 王爱萍. MiR-17-92簇的研究进展[J]. 临床与病理杂志, 2020, 40(6): 1547-1550. doi: 10.3978/j.issn.2095-6959.2020.06.035

Cite this article as: ZHANG Jie, CHEN Jin'an, SUN Xinjuan, DONG Leilei, WANG Aiping. Research progress of miR-17-92 cluster[J]. Journal of Clinical and Pathological Research, 2020, 40(6): 1547-1550. doi: 10.3978/j.issn.2095-6959.2020.06.035