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Study Advance of Mirna in Hirschsprung's Disease

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Abstract: MicroRNA (miRNA) is a small endogenous non-coding RNA and plays an important role in posttranscriptional gene regulation. Studies have shown that miRNA is closely related to various diseases including Hirschsprung 's disease(HSCR). MiRNAs are mainly involved in the proliferation and migration of neural crest cells through target genes for the pathogenesis of Hirschsprung 's disease. Some miRNAs are also significantly higher in plasma, which can serve as new noninvasive biomarkers for early screening and diagnosis of Hirschsprung 's disease.

1.Introduction

Hirschsprung’s disease (HSCR), as a congenital disease with genetic abnormalities, is one of the most common diseases in pediatric surgery. The pathogenesis of HSCR is abnormal proliferation, differentiation and migration of neural crest cells(NCC). Genetic factors and abnormal intestinal environment during development are the main reasons for HSCR. Many studies have shown a variety of mutations have involved in HSCR which can’t explain all cases. Current studies have confirmed that microRNAs (miRNAs) play an important role in posttranscriptional gene regulation, thus participating in the occurrence and development of various diseases. Moreover, mi RNAs have potential application prospects in the diagnosis or screening of diseases, which has become a research hotspot in recent years. This study will summarize the role of miRNAs in the pathogenesis and diagnosis of HSCR.

2.Hirschsprung's Disease

Hirschsprung 's disease, also called aganglionosis, is a common polygenic hereditary disease in pediatric surgery. Since the fourth week of embryonic development, neural crest cells proliferate, differentiate and migrate from the neural canal along gut tube , and finally establish the enteric nervous system composed of neurons and glial cells network[1]. The pathogenesis of HSCR is the ENS developmental anomalies imposed by abnormal gene regulation during this stage[2]. Some genes have been reported play important role in the dysplasia including RET,EDNRB,IHH,SOX10,ZEB2, PHOX2B,Hedgehog / Notch, PHACTR4,COL6A etc., especially RET / GFRα1 / GDNF and EDNRB / ECE1 / EDN3 pathways[3–8]. In addition, aberrant epigenetic regulation system also contributes to HSCR including DNA methylation, histone modification and

RNA modification[9]. HSCR is characterized by the absence of enteric neurons in the submucosal and myenteric plexuses of the distal colon and the common clinical manifestations are constipation, abdominal distension and vomiting[10].

3. Mirna

MicroRNAs are high conservative short non-coding RNA molecule with 19-25 nucleotides in length, which can bind to the 3′untranslated region of target mRNAs and regulate genes expression post-transcriptional [11]. MicroRNAs mediate translation inhibition or mRNA degradation which result in target gene silencing by incorporating into RNA Induced Silencing Complex(RISC)[12]. While the molecular mechanism was still unclear. Numerous studies have shown that miRNAs involve in many biology processes including cell development, differentiation, proliferation, apoptosis etc. While the disfunction may cause different diseases such as cancers, hepatitis, diabetes, cardiovascular diseases, Alzheimer ' s disease, Parkinson ' s disease, allergic diseases, HSCR etc.[13,14].

4.Key Micrornas Associated with Hirschsprung's Disease

Some studies have demonstrated that miRNAs are involved in the differentiation and proliferation of neural stem cells. Therefore, miRNAs are intimately correlated to the development and differentiation of never system. In recent years, some studies screened miRNAs related to HSCR, then plasma levels were further detected. The results show that miRNAs are not only involved in the pathogenesis of HSCR but also show promise as noninvasive diagnostic biomarkers for HSCR.

4.1. Role of Mirnas in the Pathogenesis of Hirschsprung's Disease

Li et al. identified 168 miRNAs (104 upregulated and 64 downregulated) differentially expression in colon tissue of HSCR using microarray technology. Then, pathway analysis indicated that target mRNAs regulate cell proliferation and migration by RET and related signaling pathways including MAPK(the mitogen-activated protein kinase) and PI3K/AKT(phosphoinositide 3-kinase). And 6 RET targeted miRNAs differentially express,5(including hsa-miR-142-3p, hsa-miR-142-5p, hsa-miR-146b-5p, hsa-miR-369-3p, and hsa-miR-429) upregulated, and 1 (hsa-miR-885-3p) downregulated in aganglionic segment of colon. Results revealed that these miRNAs are correlated to HSCR pathogenesis[15]. Then, some other miRNAs were also found involved in pathogenesis of HSCR by regulating target genes to affect NCCs migration, proliferation and apoptosis (see Table 1).

Table 1 Mirnas Involved In Hscr Pathogenesis

MiRNAs	Function	Expression in aganglionic segment colon of HSCR	References
MiR-195,MiR-218-1,Hsa-miR-192-5p,Hsa-miR-200a-3p,Hsa-miR-200b-3p	Suppress NCCs migration and proliferation	Upregulation	[16–18]
MiR-939	Suppress NCCs	Upregulation	[19]

	proliferation		
MiR-200a/141,MiR-206,MiR-192/215,miR-770-5p	Promote NCCs migration and proliferation	Downregulation	[20–23]
MiR-483-5p	Promote cell apoptosis	Upregulation	[24]

4.2. Role of Mirnas in the Diagnosis of Hirschsprung's Disease

The diagnosis of HSCR depends on histopathological examination after rectal biopsy. At present, acetylcholinesterase enzyme (AChE) and calretinin histochemistry are the most commonly applied methods[25]. However, in view of the large trauma of rectal mucosa biopsy and high qualification requirements for hospitals, noninvasive diagnostic methods are still widely concerned. Expression of miRNAs in plasma are stable and prodigality which serve as a reliable and easy biomarker for associated diseases diagnosis. Xia et al. indicated that five miRNAs level increase in plasma which have potential for early diagnosis. Tang et al. found another three miRNAs increase in plasma (see Table 2). As a diagnosis biomarker for HSCR, miRNAs haven't applied to clinical samples, which need further research.

Table 2 Diagnosis Mirnas For Hscr

Researcher	MiRNAs	Serum level	References
Tang et al.	Hsa-miR-192-5p,Hsa-miR-200a-3p,Hsa-miR-200b-3p	Upregulation	[18]
Xia et al.	miR-133a,miR-218-1,miR-92a,miR-25,miR-483-5p	Upregulation	[26]

5. Conclusion

In summary, miRNAs are involved in the pathogenesis of HSCR by affecting NCCs proliferation, migration and differentiation and are expected to become a new noninvasive screening and diagnostic biomarkers for HSCR. However, researches are still at a rudimentary stage and further studies are needed.

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