MicroRNAs as promising biomarkers and therapeutic tools in hereditary hemorrhagic telangiectasia

Heredity hemorrhagic telangiectasia (HHT) is a genetic disorder that results in potentially fatal blood vessel abnormalities. Currently, there is no cure or universally effective treatment for the condition, which remains underdiagnosed and underdiagnosed. MicroRNAs have emerged as new biomarkers for human diseases and hold great promise for the improved diagnosis and treatment of HHT. A recent review publication by Anthony Cannavuci, PhD candidate at the Institute of Medical Science, University of Toronto, discusses the utility of microRNAs as circulating biomarkers and potential therapeutic targets in HHT. His work underscores the importance of studying these non-coding RNAs to further understand disease pathogenesis.

HHT is inherited in an autosomal dominant fashion with varying penetrance and expressivity. There are at least three types of HHT differentiated primarily by the genetic cause, signs, and symptoms. Type 1 (HHT1) is caused by mutations in the ENG gene on chromosome 9, and type 2 (HHT2) is caused by mutations in the ACVRL1 gene located on chromosome 12. A smaller percentage of individuals have a mutation in the SMAD4 gene on chromosome 18, which causes a juvenile polyposis/HHT overlap syndrome.

Each of the three genes implicated in HHT encodes a protein involved in the transforming growth factor beta (TGF-β) / bone morphogenetic protein (BMP) signalling pathway. This signalling pathway is important in the regulation of many cellular processes, including growth, differentiation, apoptosis, and vascular remodelling and maintenance. In patients with HHT, mutations in either ENG, ACVRL1 or SMAD4 lead to a reduction of functional protein products, known as haplosufficiency. Abnormalities in their protein products cause the malfunction of TGF-β/BMP signalling in endothelial cells, resulting in the defective formation of blood vessels. Interestingly, disease severity and its clinical manifestations vary greatly between patients and even among members of the same family. This suggests that genetic mutations alone are not entirely responsible for disease dysregulation in HHT. This work has the potential to identify unique therapeutic targets and aid the development of novel diagnostic tools for HHT.

CHARACTERISTICS OF HHT

HHT is an extremely underdiagnosed condition, and without management, it can lead to serious morbidity and mortality. Currently, HHT is diagnosed in combination by a clinical criterion known as the Curacao criteria alongside genetic testing. However, many HHT patients do not present a clear diagnosis or do not show pathogenic mutations in known HHT genes. Furthermore, approximately 50% of patients have occult polycythemia. AVMs, 80% develop hepatic AVMs, 10% develop cerebral AVMs, and 1% develop spinal AVMs, all of which can lead to life-threatening bleeding and other complications. Screening patients with HHT is therefore crucial, but current diagnostic screens are costly, inaccessible, and expose patients to unhealthy doses of radiation. This has prompted the need to identify additional biomarkers of the disease.

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MiRs as Potential Biomarkers in HHT

MiRs represent a new class of small, non-coding RNAs that are transcribed from DNA and are translated into protein and include miRs, a class of short non-coding RNA (~21–25 nucleotides), and long non-coding RNAs (lncRNAs) consisting of more than 200 nucleotides. Acting to regulate gene expression at both the transcriptional (regulation of the conversion of DNA to RNA) and post-transcriptional level (regulation at the RNA level before translation into protein), miRNAs are known to play important roles in almost all cellular processes. MiRs are the best-studied group of non-coding RNAs. They were first discovered in 1993 by the Ambros and Ruvkun groups and have revolutionised the field of molecular biology. Over 2000 miRs have been identified, and it has been suggested that they regulate 30% of known genes. MiRs regulate gene expression by directing their target miRNAs for degradation or translational repression. Over the past decade, it has become clear that miR expression is dysregulated in a wide range of human diseases. MiRs have been extensively studied in oncology, where they have shown to have stable diagnostic and prognostic attributes and are being pursued as potential therapeutic targets. However, a growing class of miRs is being used in other fields, such as cardiovascular disease, and the potential of miRs as therapeutic targets in HHT is an exciting area of research.

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MiR-26, which is enriched in the endothelial lining of the blood vessel walls, has recently been shown to be involved in vascular stability by directly targeting SMAD1, a family of proteins that plays a role in the TGF-β signalling pathway. Loss of this miR in a zebrafish model led to an increase in SMAD1, resulting in vascular smooth muscle cell dysregulation and hemorrhage.

Another study demonstrated that overexpression of miR-148b increased endothelial cell migration, proliferation, and angiogenesis by targeting SMAD2.
In plant cells, the microRNA is usually perfectly complementary to its target mRNA. The microRNA will bond with it, repress, or otherwise modulate the function of the target mRNA. Given the high degree of complexity and specificity of microRNAs, they serve as alternative therapeutic targets and for identifying new biomarkers.

In HHT-related pathways, such as blood vessel formation and development, microRNAs have been found to be involved in the development of the disease. Indeed, evidence to support this came from the work of Torring et al. (2014), which demonstrated that 42 IncRNAs were significantly dysregulated in telangectasia nasal mucosa compared to non-telangectasia nasal mucosa from the same HHT patients. Interestingly, these IncRNAs were enriched in HHT-related pathways; such as blood vessel formation and development. Whole-genome sequencing led to a deeper understanding of the role of IncRNAs in HHT. It is an exciting area of study for discovering therapeutic targets and for identifying new biomarkers.

Within the exact role of any class of microRNA is yet to be fully characterized in HHT, it is a field of study that holds great promise. With further research, microRNAs may prove to have both diagnostic and therapeutic applications for those with HHT.

Dysregulation of IncRNAs in HHT

IncRNAs can be classified according to their genomic location—nuclear and cytoplasmic—and can activate, repress, or otherwise modulate the expression of target genes through various mechanisms. Although only a small number of IncRNAs have been characterized functionally, increasing evidence suggests that they are involved in a variety of cellular functions and could serve as alternative therapeutic targets.

MALAT1, which is among the most abundant and highly conserved IncRNA, is highly expressed in endothelial cells and is thought to be involved in the angiogenic response of these cells by promoting cell proliferation and migration under low oxygen conditions (hypoxia). Singh et al. (2016) were the first to show differential expression of IncRNAs, including MALAT1, in endothelial cells in response to TGF-β. Given that TGF-β signaling is linked to HHT, IncRNAs look likely to play a role in the development of the disease. Indeed, evidence to support this came from the work of Torring et al. (2014), which demonstrated that 42 IncRNAs were significantly dysregulated in telangectasia nasal mucosa compared to non-telangectasia nasal mucosa from the same HHT patients. Interestingly, these IncRNAs were enriched in HHT-related pathways, such as blood vessel formation and development. Whole-genome sequencing led to a deeper understanding of the role of IncRNAs in HHT. It is an exciting area of study for discovering therapeutic targets and for identifying new biomarkers.

References