Weill Cornell Medicine-Qatar

New hope in fight against cholesterol

Doha – November 2, 2015: A researcher at Weill Cornell Medicine-Qatar (WCM-Q) has discovered potential new therapeutic targets for the treatment of abnormal blood lipid/cholesterol levels.

Dr. Hani Najafi, assistant professor of cell & developmental biology at WCM-Q, has been studying micro-RNA (miRNA) in collaboration with other research centers including Massachusetts General Hospital, Harvard Medical School and Weill Cornell Medicine in New York. He has had previous success with the discovery that miRNA 33 plays a major role in homeostatic regulation of cholesterol levels in the human body. Since then he has continued to try to identify new miRNAs that could potentially be utilized as novel therapeutics for the treatment of cardiometabolic diseases.

Dr. Najafi decided to examine the enormous amount of data that has been generated from genomics studies, including the genome-wide association studies (GWAS) that seek to identify and link specific genes with certain diseases. These studies identify genes that potentially contribute to the phenotype (observable characteristics) of conditions like diabetes, high cholesterol levels, and other metabolic diseases, but also to cancer. The studies take the gene sequence and look for SNPs (single-nucleotide polymorphisms). These are variations that happen within the gene sequence and some of these variations can affect the function of the gene. If there is a strong association between an SNP and a particular characteristic (phenotype) or disease, that SNP will stand out as being significant. The researcher would then identify genes that include or are close to that SNP.

But Dr. Najafi saw that alongside the genes that were listed, there were also miRNAs embedded within the vicinity of the SNPs. Dr. Najafi and his colleagues asked if the miRNAs could be playing a role and contributing to the reported lipid abnormality, especially in cases where there was a lack of evidence for the function of the neighboring listed protein-coding gene in lipid metabolism.

Dr. Najafi said: “We found that overall 69 miRNAs were in close proximity to the signature SNPs associated with abnormal lipid levels. More surprisingly, we saw that more than 30 different genes that have a role in lipid metabolism are potential targets of the identified miRNAs.”

The research team selected four microRNA candidates and conducted a functional analysis and found that they all regulated two key players in lipid metabolism – LDLR (low-density lipoprotein receptor) and ABCA1. LDL receptors are known to be one of the most important transmembrane proteins required to clear excess LDL, which is more commonly known as bad cholesterol. Defects in the functioning of this gene are known to cause familial hyper-cholesterol, which can lead to death. Conversely, ABCA1 (also a transmembrane protein) increases the level of HDL (high-density lipids), otherwise known as ‘good’ cholesterol. MiRNAs that inhibits both of them will increase blood LDL and decrease blood HDL levels.

The SNPs cause abnormal lipid levels and increase the miRNA that negatively affects LDL and ABCA1. It turned out that those miRNAs could be used as therapeutic targets by using antisense oligonucleotide. This would then render the miRNAs useless, essentially correcting the level of miRNAs to what they should be.

Dr. Najafi said: “We tested this in vitro in mice and we saw an increase in HDL and a lowering of LDL. So this could potentially be used to alter the lipid levels in humans back into the normal range. We have also tested this on human liver cells and saw very similar effect as we observed in mice.”

He added: “To our knowledge, our studies represent the first systematic population-wide GWAS analysis focused on noncoding RNAs/miRNAs in any disease context. Moreover, we have taken several of the miRNAs uncovered

by these unbiased studies deep into functional validation in vitro and in vivo in relevant mouse models for cardiometabolic disease. We also provide the first data showing miRNA regulation of LDLR and LDL-C.

“A potential functional role of miRNAs (and other non-coding RNAs) in lipid abnormalities, or any other phenotype for that matter, has been overlooked in most GWAS to date. Indeed, while hundreds of genes have been noted as associated with SNPs, essentially no study has pointed out the fact that numerous miRNAs are also located in the vicinity of signature SNPs.

“The findings are extremely valuable. They could potentially lead to new therapies for high cholesterol, helping people to avoid cardiovascular disease.”

The work of Dr. Najafi and his colleagues is so significant that it has been published in the highly respected journal *Nature Medicine.*

Photo Caption: Dr. Hani Najafi

About Weill Cornell Medicine - Qatar

Weill Cornell Medicine - Qatar is a partnership between Cornell University and Qatar Foundation. It offers a comprehensive six-year medical program leading to the Cornell University M.D. degree with teaching by Cornell and Weill Cornell faculty and by physicians at Hamad Medical Corporation (HMC) and Aspetar Orthopedic and Sports Medicine Hospital who hold Weill Cornell appointments. Through its biomedical research program, WCM-Q is building a sustainable research community in Qatar while advancing basic science and clinical research. Through its medical college, WCM-Q seeks to provide the finest education possible for medical students, to improve health care both now and for future generations, and to provide high quality health care to the Qatari population.

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