Clinical Chemistry

Circulating microRNAs: What is their relevance?

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Guest:
Dr. Catriona Hilton is a clinical research training fellow at the Oxford Centre for Diabetes, Endocrinology, and Metabolism in Oxford, England.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

A paper in the May 2013 issue of *Clinical Chemistry* found that circulating microRNAs were deregulated in severe obesity, and the lead author of that study Dr. Francisco José Ortega from Spain joined us earlier for a separate podcast. That paper was accompanied by an editorial addressing the relevance of circulating microRNAs in plasma. The lead author of that commentary, Dr. Catriona Hilton from the Oxford Centre for Diabetes, Endocrinology, and Metabolism in Oxford, England, joins us today in this podcast.

Doctor, we are hearing a lot about microRNAs now and we've already had a few podcasts discussing them, but could you briefly review for today's listeners, what exactly are microRNAs?

Dr. Catriona Hilton: Well, microRNAs are small non-coding RNA molecules and until quite recently they were thought to just be the junk in the genome and it was thought that perhaps they didn't do anything very important, but we now know that that's not the case. So they act post-transcriptionally regulating expression.

And the way they do this is they buy into complementary or partially complementary regions to sequence within messenger RNA, and they are able to act on lots of different targets simultaneously and so they can modulate protein levels in lots of different pathways at the same time. And you are quite right when you say this is an important area in the literature and we are hearing a lot about them at the moment.

So microRNA has been shown to play an important role in a number of different diseases and issues, and there is a lot of research now in all sorts of conditions, such as cancer, and heart disease, and obesity.

Bob Barrett: What do we know about the presence of microRNAs in plasma? Do we know how they get there, how they might be removed, and whether they serve any function in circulation?

Dr. Catriona Hilton: Sure. The discovery of stable microRNAs in the plasma is very interesting. We might expect that they might be degraded by ribonucleases but actually that doesn't happen, and now we know that there is a number of different ways that microRNAs can be bound and transported within the plasma.

So firstly it seemed that the majority of them bound to RNA binding proteins such as Argonaute 2 and actually in itself this is really interesting because Argonaute 2 is one of the main proteins involved in the action of microRNAs on their targets.

We really don't understand at the moment whether protein bound microRNAs are actively secreted themselves or whether they might be passively released from dead or dying cells. And we are not really sure whether they are targeted to recipient cells or whether they are taken up or they are functional in anyway.

We also know that microRNAs can be transported by HDL in the blood, and it's actually been shown the profiles of microRNA within HDL can differ in different disease states, and that they can be transferred from HDL into cells and that they can be functional there.

And then lastly, we know that microRNAs can be carried in the blood in exocomes and microvesicles, and we know that these are actually actively transported out of cells and it seems that there is a subpopulation of microRNA which is selective exportation.

Now we already know that exosomes are involved in cell-to-cell signaling and actually there has been some experiments in vitro and in vivo which is suggesting that exosomes and microvesicles are able to transport microRNA between distant cells and that they can be taken off, and they can be functional within the recipient cell.

So I suppose to answer your question, we know a little bit about microRNAs in the plasma. We know a bit about how they get there and we know a bit about how they might function and they might play a role in cell-to-cell signaling but there is an awful a lot still to discover about that.

Bob Barrett: How could the presence of microRNAs in the blood be of interest clinically?

Dr. Catriona Hilton: So firstly they could be of interest as biomarkers of disease, so the hope might be that you would be able to take a simple blood test, and then by examining microRNAs profiles in the blood, perhaps you could diagnose disease or risk-stratify people.

There is also a hope that by identifying microRNAs in the blood, in different conditions, perhaps we could learn a bit more about the molecular pathways underlying disease. And then there is very attractive but quite speculative idea, that if these microRNAs in the blood are playing a role in terms of signaling then perhaps we might be able to manipulate them or target them in some way which would be therapeutic. So that's an exciting idea, but as I say, still very, very much speculative.

Bob Barrett: In this issue of *Clinical Chemistry* Dr. Ortega and his colleagues published a study looking at circulating microRNA profiles in obesity. Could you summarize the main findings of that study?

Dr. Catriona Hilton: This study looked at genome Y profiles with microRNA relating to obesity and to weight loss, and the authors were able to identify signatures of microRNAs relating to morbid obesity. They also identified some microRNAs that were regulated with weight loss and some of these microRNAs were the same ones that were changing cross-sectionally with obesity. And so this is really interesting because as far as I am aware the first paper which is showing changes in circulating microRNAs with obesity or weight loss. And potentially by understanding a bit more about these and what they are doing, we might be able to understand a bit more about the molecular pathogenesis of this obesity and the pathways involved.

Bob Barrett: Well we know every study has its limitations. What were your concerns regarding this study?

Dr. Catriona Hilton: So the authors didn't identify how the microRNAs were transported, and I think this might be important in trying to understand what role they might be playing.

They also weren't able to identify where they are coming from, and it's tempting of course because they are related to obesity and weight loss to speculate that coming from fats. But this isn't necessarily the case, and the fact that some of the microRNAs changed with surgery but not diet induced weight loss implies that perhaps this isn't a simple relationship with fats and perhaps there is more complicated things going on here.

And also from this study we are not able to say if these microRNAs play any kind of a functional role. So the authors

identified some of the potential targets of these microRNAs and they examined the expression of these targets and were able to show a negative correlation with some of them, which is interesting, but we don't know whether or not this is causative.

Bob Barrett: Well finally, doctor, where do we go from here regarding the study of the significance of circulating microRNAs? What needs to be learned so that we can work out if and how we can apply the results of studies like this one in *Clinical Chemistry* to clinical settings?

Dr. Catriona Hilton: So I think that's a really important question. I am trying to understand what role, if any role, these circulating microRNAs are having on the whole body level, it's very, very complicated and difficult.

We need to learn more about where these microRNAs are coming from, which cells transport them and export them, and whether they are actively or passively exported, and we need to learn more about whether specific subpopulation microRNA are selected by specific cells for exportation, and if so how this occurs.

We also need to learn more about if and how microRNAs might be targeted to destination tissues or recipient cells, and how they might be taken up by these cells. And then if we think that they are involved in signaling in some way, we need to learn a bit more about what kind of levels of circulating RNA that might need to be, to have any kind of a functional effect on a whole body level.

And it might be that we do this work and we look back and decide they are not doing very much in the whole body level, but I think it's a really attractive idea that perhaps they are involved in some kind of paracrine signaling within the body.

I thing regardless of what microRNAs are doing with regards to signaling, I think they certainly have a lot of potential as biomarkers of disease and I think this is one area we are likely to see moving into the clinical setting in the next few years, the use of microRNAs in diagnosis.

Bob Barrett: Dr. Catriona Hilton is a clinical research training fellow at the Oxford Centre for Diabetes, Endocrinology, and Metabolism in Oxford, England. She has been our guest in this podcast from *Clinical Chemistry*.

I'm Bob Barrett, thanks for listening!