Clinical Chemistry

MicroRNA Analysis: Is It Ready for Prime Time?

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Guest:
Dr. Gregory Tsongalis is a Professor of Pathology at the Geisel School of Medicine at Dartmouth and the Director of Molecular Pathology at the Dartmouth-Hitchcock Medical Center and Norris Cotton Cancer Center.

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

Since their discovery, microRNAs have shown great promise in a wide array of clinical applications. MicroRNAs may serve as new diagnostic markers or even as targets for novel therapies. Scientists agree that this field of biology is an exciting area.

In the February 2013 issue of *Clinical Chemistry,* five leaders in the field of microRNAs joined moderator Gregory Tsongalis in a Q&A feature looking at where this field is heading. Dr. Tsongalis is a Professor of Pathology at the Geisel School of Medicine at Dartmouth and the Director of Molecular Pathology at the Dartmouth-Hitchcock Medical Center and Norris Cotton Cancer Center. He is our guest in this podcast.

Dr. Tsongalis, what exactly are microRNAs and when did we first learn about their existence?

Dr. Tsongalis: So, microRNAs are small sequences of nucleotides, usually between 12 and 20 base pairs in length. And we first learned about these probably in the early 1990s, mid 1990s, when some researchers were working with different organisms and came across them and realized that these weren't junk DNA or junk nucleic acids that were just degraded material, but they really had some specific biological functions.

Bob Barrett: In print, these are usually noted as miRNA, now that's a bit confusing for people, how do they differ from mRNA?

Dr. Tsongalis: Yeah, it's a great question. So microRNAs are quite different than messenger RNA or the mRNA. Messenger RNAs are the RNAs that are actually code for the proteins that are going to translated and give us a protein amino acid sequence.

MicroRNAs are quite different than that, in that they don't code for protein, but these sequences themselves have regulatory capabilities by binding other sequences of different genes.

Bob Barrett: Are the technologies used to test for microRNAs suitable for routine clinical laboratory?

Dr. Tsongalis: I think they are now, I think when microRNAs were first discovered, people were using very robust microchip technologies to assess the expression of the many different microRNAs. There are several hundred of them now. And that microchip technology may not have been ready for the clinical lab, but since then people have converted those types of assays to real-time PCR assays, which are done routinely in clinical labs around the country.

And so these new assays are very, very robust, they're very quick; they are very easy for your typical clinical molecular lab to perform. I want to make one other point that the microRNAs that we're talking about are very, very significant in the fact that they're very small. And in this case smaller is better, because they're less susceptible to degradation, like other types of RNA and even some types of DNA.

Bob Barrett: What are some of the latest and near future clinical applications of microRNAs in the clinical lab?

Dr. Tsongalis: I think these small molecules have been really, really exciting for us, because of a number of their different characteristics. One I mentioned already, that they were small and less amenable to degradation like other nucleic acids. But the other thing is that they are very specific and when they were discovered, it became apparent that certain microRNAs were not only tissue specific, but they were cell type specific.

And then if you add to that, they can become specific to either normal tissues and cells or disease tissues and cells. We had for the first time markers that could differentiate specific disease types from normal or the benign types of diseases, without having to do a lot of fancy analyses. And so the applications for these are almost limitless. There are a lot of different applications in using them as diagnostic markers and in particular, a lot of this work has been done in different cancer types.

There are lot of different applications using these as prognostic markers, and again, a lot this relates to the cancer work. And now there are potential applications of these in the infectious disease arena using them for response, the therapy types of markers for prognostic

markers, and so on. And so I think there are a lot of different applications that can be addressed by these.

Bob Barrett: Could these eventually become the new tumor biomarker?

Dr. Tsongalis: I think this is an exciting area and my lab is been involved in a lot of this work. And I think the excitement is really around, or revolves around, the fact of the specificity of these markers, that you know, they're up or down regulated in specific tissue types and we know now that in the different stages of the development of cancer, that you have up and down regulation of different microRNAs.

So not only can we use them as a diagnostic marker to confirm a diagnosis, or to help a pathologist make a diagnosis that might be difficult, just by looking at the morphology of the tissues and the cells under the microscope; we can also use these to differentiate which stage of the disease the patient could potentially be at. And those could eventually end up helping to direct specific therapies for early versus later or for a more benign, versus more aggressive types of diseases.

Bob Barrett: How likely is it that they might be targets of novel therapies?

Dr. Tsongalis: I think it's very likely. You know, there has been a lot of work going on creating what's been termed these antagomirs, which are just sequences against the microRNA sequence to hybridize those, and not allow them to function in their regulatory roles as they normally would, or as they would in some disease process.

So I think this is that aspect of it, but then there is the downstream aspect of it as well. We know biologically that one microRNA can regulate up or down, regulate the expression of more than one gene. And we also know that multiple microRNAs can up or down regulate the same gene sequence. And so if you think about what's happening in the cancer field, where we need to have, or we need to target, multiple proteins or multiple genes to treat the tumor effectively, you could potentially affect the up or down regulation of one microRNA, which would then downstream affect the up or down regulation of multiple genes in a particular cancer type.

And so I think the opportunity to use these -- maybe not directly, but indirectly, as potential therapeutics is huge.

Bob Barrett: Doctor, in this *Clinical Chemistry* feature you were joined by five experts. How differently did they find the field, and were there any areas where you disagreed?

Dr. Tsongalis: So I think you know overall the experts that were part of the Q&A publication agreed to the fact that these are very, very exciting biomolecules and biomarkers; that they can be used clinically. The question was, I think the big area of disagreement, was the timing of when these would make it to the clinical laboratory for actual patient testing.

You know, but without a doubt I think everybody realizes that within the next 5 to 10 years these will be something we'll be looking at routinely. Some people like myself felt that that would be much sooner, while some people felt that that might be a little bit later. I think the other point of agreement was the therapeutic value to these, and again, there were some questions about the timing of all that, but everybody who was onboard said, there's a huge potential here for these.

Bob Barrett: Finally, doctor, you mentioned the future. Let's look ahead. Where do you see this field five, even ten years from now?

Dr. Tsongalis: So, I think you know one of the questions we tried to address in the Q&A was whether we could envision a time when we would have FDA approved kit-based assays for these. I think a lot of people felt that this was certainly possible. And so I think, five/ten years out we will have very specific assays designed around either two or three microRNAs or maybe more, or a more extensive panel for specific disease types and for specific clinical applications.

I don't know that we would use the same panel as a diagnostic panel versus a prognostic panel, and so on. But I think it's going to evolve to a point where these become kit-based assays that we can run in the laboratory.

Bob Barrett: Dr. Gregory Tsongalis is a Professor of Pathology at the Geisel School of Medicine at Dartmouth and the Director of Molecular Pathology at the Dartmouth-Hitchcock Medical Center and Norris Cotton Cancer Center. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!