High-throughput transcriptomics in human metabolic disease research

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Dr. Iain Gallagher completed his PhD in immunology at the University of Edinburgh in 2006 before moving fields to work in transcriptomics and human physiology at Heriot-Watt University in 2007. From there, he moved to a postdoctoral position in the Medical School of the University of Edinburgh in 2009, where he continued to research human muscle pathology and developmental biology. He returned to immunology in a postdoctoral position at the Roslin Institute in 2011 before taking up his current role at the University of Stirling.

Thermo Fisher Scientific: Can you introduce yourself and your research?

Iain Gallagher: I'm a lecturer at University of Stirling, in the faculty of Health Sciences and Sport. My research interest really centers around the effects of disease in muscle functions, including metabolic disease and type 2 diabetes. I also have a particular interest in the effects of chronic diseases on muscle wasting—diseases like cancer cachexia, cardiac disease, and lung disease.

I do quite a lot of work with high-throughput transcriptomics, usually looking at the effects of disease on muscle functions. We use microarrays for that, although I have done some RNA-Seq analysis.

Thermo Fisher: What are your main research objectives?

Iain Gallagher: One of the research projects we were working on was defining the transcriptomic landscape in type 2 diabetes. Type 2 diabetes is one of the cornerstones of metabolic syndrome, which comprises a cluster of metabolic abnormalities [that includes] cancer and cardiovascular disease and has accompanied the secular rise in obesity we're seeing across the world. In type 2 diabetes, people get sensitive to the hormone insulin, and the skeleton, muscle, liver, and tissue are no longer able to respond to it. As a result, glucose builds up in the blood stream and that brings pathology of type 2 diabetes with it. So, in this project, we were aiming to define genes that changed in response to interventions that improved insulin sensitivity in people who were type 2 diabetic or on the way to becoming type 2 diabetic.

> "Type 2 diabetes is one of the cornerstones of the metabolic syndrome ..."

Thermo Fisher: What made microarray technology the ideal match for you?

Iain Gallagher: We had done some previous work on type 2 diabetes using the Applied Biosystems™ GeneChip™ Human Genome U133 Plus 2.0 Array, and we'd actually found that, in people who are type 2 diabetic, you can't actually see much difference versus normal people in gene expression in the muscle. Our tool of choice in this more recent study was the Applied Biosystems™ GeneChip™ Human Transcriptome Array (HTA) 2.0. We were concerned with increasing the signal-to-noise ratio on these microarrays, so we undertook an extensive remapping of the probes on the microarray. We took all 7 million probes on the microarray and used the same technology as RNA-Seq researchers to realign the current build of the human genome.

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So, one of the things that was useful for us in terms of the GeneChip HTA was that we had access to the metadata for the probes. This allowed us to get the probe sequences and the probe positions on the genomes, and enabled us to do the remapping exercise. And that was essentially our starting point in terms of defining probes that were giving us signal as opposed to probes that were giving us more noise.

For us, the depth of information you can get from the GeneChip HTA and now the Applied Biosystems™ Clariom™ D Assays is comparable to RNA-Seq. But, you'd have to spend a lot more money to get the same amount of information from RNA-Seq. Also, the bioinformatic infrastructure you need to analyze RNA-Seq data is much larger than what you need to analyze microarray data. So, from the bioinformatic point of view as well, it is much cheaper to use microarrays.

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Thermo Fisher: What value has using microarrays brought to your research?

Iain Gallagher: Certainly it's brought us benefits in terms of the depth of the result we've been able to get; improving the signal-to-noise ratio definitely helped to expand the depth of information we were able to pull from the microarray data set that we had.

In addition, we've been able to examine both protein coding and noncoding transcripts, and that's something I can see microarrays being used for more and more in the future. Our clinical collaborators keep an extensive biobank, and microarrays certainly present a cost-effective solution for a global transcriptomic look at the gene expression differences in that biobank across both normal and clinical populations.

Thermo Fisher: What were the key outcomes of the study?

Iain Gallagher: Using the filtering approach, we were able to robustly identify a set of genes, a set of transcripts, and a skeletal muscle that were altered by an exercise intervention that also improved insulin sensitivity. Additionally, using the rich data sets, we were able to cross-validate a number of these genes and the independent data sets. And that validation in independent data sets is the gold standard of reproducibility. These results were published last year [1], and we not only were able to identify coding genes and transcripts that changed with exercise intervention and mapped to or improved insulin sensitivity, but also identified a number of noncoding genes as well, which is important and becoming increasingly so in the study of many diseases.

The next steps here in terms of type 2 diabetes would be to take this core set of genes, and using some knockout/knock-in technology, examine the effects of knocking in or knocking out these genes on insulin sensitivity in cell culture or perhaps in animal models.

Thermo Fisher: How does Thermo Fisher fit into your workflow?

Iain Gallagher: One of the advantages of working with Thermo Fisher is the extensive portfolio of products that they offer; there's an ability to choose the technology that is best suited for the follow up study. We've always found them open to communication and we really like the choice that's available.

Reference

1. Timmons JA, Atherton PJ, Larsson O et al. (2018) A coding and non-coding transcriptomic perspective on the genomics of human metabolic disease. *Nucleic Acids Res* 46(15):7772-7792.

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