Mythbusters: Single Cell Profiling of IPF

One of the main key findings in IPF Cell Atlas, this big effort at single cell profiling of IPF lungs, is the discovery that epithelial cells in the lungs changed dramatically. There is a dramatic decline in alveola epithelial cells and their replacement by cells in the airways, which obviously cannot do the work of breathing.

And one of the most amazing findings, and this was really impressive to us because you really don't need to play with the data for these cells to show up, is the presence of cells that we have never seen before. And we call them aberrant basaloid cells.

So, these are cells that have both progenitor cell features, basal cell features, but not complete pro-fibrotic features. They can activate fibrosis and a little bit of senescence. And these cells sit at a very unique area, sort of the edge of the myofibroblast focus, this lesion of pulmonary fibrosis.

And what is also interesting when you do a genomic study, usually are worried about replication. But we could find these cells, not only in our dataset, but actually in the data set of the group from Vanderbilt and also from groups from Pittsburgh and Northwestern. So again, previously published, these cells were there.

Of course, we will need to do cell culture. We will need to develop this. But the finding of a cell type that unique to pulmonary fibrosis is dramatically important.

We also found that other cells are really normal. Endothelial cells usually have a very characteristic, the cells of the lining of the blood vessels, people have not studied them as much in detail in fibrosis. And we found that basically, there was a shift in which endothelial cells that are usually at the lining of the airways go into the alveoli.

So, cells have a unique set of markers. And it's almost like you would say that the lung is being proximilized.

Now this is important because the lung, in a very general way, you could say has the tubes that basically bring in the air. And then it has these [vacuoles 00:02:39], the alveoli, in which gas exchange happens.

So, you would think that if cells that come from the airways start filling the alveoli, of course, gas exchange is impaired. And this goes to explain the shortness of breath, the deterioration of patients with IPF.

We found also multiple other abnormalities in different cell types. There has been a lot of talk, and actually, is it macrophages, the large immune cells that are considered? What is microphage? Basically, big eater. They have a lot of big, important roles in pulmonary fibrosis. And this data actually conferred, there is an abnormal population of pro-fibrotic microphages in the human fibrotic lung.

There's also a change in fibroblast populations. We did find the sort of the ominous myofibroblast, but we also found invasive fibroblast. And there's also a lot of other changes that we didn't even go in in this paper.

So, to summarize what we've learned all from this Hubble telescope of cells is the wealth of abnormalities in the IPF lung.

But the other thing that we've learned, that's really important, people think about fibrosis is a non-dynamic process, and is something that is stable, like a scar.

But actually what we found is that the fibrotic lung is actually extremely active, viable, and dynamic. And this is an important message because that would mean that potentially, with the right drugs, we could reverse this process.

Of course, when we do research, the most important thing for us is actually to impact the life of our patients, improve diagnosis, and improve management.

One of the things that we've been limited over the years is many things we knew about pulmonary fibrosis came from animal models of disease or from low resolution models. We have now two drugs that actually slow down the diseases, but what do they actually do? On what cell type?

By creating this IPF Cell Atlas, this tool, which actually describes every single anomaly that is in every single cell type in the lung, we could start designing treatment that actually will reverse fibrosis, because we could now look at the drug and say, is that inducing the changes that we want in the cell types that we want?

The other thing that we could do is, me and others in the field have over the years discovered biomarkers for the disease. There's been a problem with these biomarkers. Although they have been replicated, they've not been implemented widely. And part of the reason is because we never knew what these biomarkers actually tell us.

But now, for instance, one of these biomarkers that I discovered many years ago and has been replicated many times, every piece of it materializing, we actually know its cellular source. And it's actually not the cells we thought before. It comes from these aberrant basaloid cells.

This is just an example, of course. There's many other examples. But, by understanding the lung and what happens in the human lung, we can actually start having this plan to reverse fibrosis, to cure IPF.

The MythBusters session is ended with a discussion by the experts, Dr. Zea Borok, Joyce Lee, and Martin Kolbe. And basically, they were really impressed and expressed their enthusiasm about the whole increase in our understanding of pulmonary fibrosis.

They did not necessarily uphold the myth that single cells technologies will revolutionize the diagnosis and management of pulmonary fibrosis. But most of it was because there was a need for more time and more direct relationship between the finding and potential therapies.