COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by Rabindra Tirouvanziam (Emory University), January 14, 2021

Title: *Coronavirus infection of human lung epithelium and leukocytes: mechanisms and treatment*

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NIH Project #: 2032273

YouTube Recording with Slides

January 2021 CIC Webinar Information

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Transcript

Rabindra Tirouvanziam:

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Thank you for the opportunity and uh you know it's it's it's nice to be closing the session after such a good series of talks. I'm an immunologist and an engineer here at Emory University in Atlanta and the work that I'm going to be talking about was funded by an EAGER award by a CIBET, and it was done really by a grad student in my group, Brian Dobosh a lot of the bioinformatics done by a post document group, Diego Moncada and all the [inaudible] work really work with the virus itself was done in collaboration with Keivan Zandi, and in the laboratory of Raymond Schinazzi, who's a, you know a prominent virologist and pharmacologist here in our university. So, as you guys know-

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SARS-CoV-2 is infecting a number of cells throughout the body, it's causing that disease COVID-19 which is really a multi-organ disease. Even though, you know, I think we need to think about the different organs that are being affected, most of the morbidity mortality in patients is linked to the lung manifestation and it is really due to the infection of the cells lining the lung, the epithelial cells, and that leads to, in the complications of the disease, the influx of monocytes and neutrophils from blood and then these cells sort of compound on the the initial issue that was you know caused by the infection of the epithelium.

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So, our mandate really was to use a system that could develop for other diseases in which we grow human airway cells at air-liquid interface so that they mimic the conditions in which they grow in the lung, and we can infect them with the virus for different periods of time, and then we can let different sets of immune cells, primary immune cells from human blood, transmigrate and meet the virus on the other side, so we're really trying to mimic the sequence of events, so the viral infection and the monocytes coming in and the neutrophils. We can add drugs at any point in time to affect infections or immunal response, and the we can obviously analyze the different components in that model, and we use a lot of different omics methods - our goal really is the characterize the steps in pathogenesis and also to check for potential benefits of candidate drugs, and I'm gonna-

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show you a few data that basically reports on our progress on the epithelial side of things, obviously you want to make sure that in our system, the virus behaves similarly to what we've been seeing *in vivo*. This is really the case, I'm showing here a quick comparison of SARS COVID 2 with pr8 which is an H1N1 Influenza A virus, and OC43 that you can see here is one of the common cold coronal viruses. And right away, you can see by rna sequencing and heat maps that I'm showing here of a few families of genes, that, you know, with the with the influenza virus, antiviral genes are really hot so they're red, but the coronaviruses are really much colder, so this is one of the the areas of interest in pathology and also in therapeutics coronavirus seems, especially SARS-CoV2 seem to be very good at preventing the activation of antiviral pathways in epithelial cells. On the other hand if you look at the cytokine genes here there's really discrepancies between the three viruses and we can see right away that SARS-CoV2 is able to activate an il-10 response, but not so much an ilh response so it's really promoting more of a monocytic inflammation to begin with and neutrality inflammation comes after, so this is really what what we see *in vivo*.

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Now the model is really unique in its ability to combine epithelial cells and virus and immune cells so we can, for example, look at in the process of this of this infection of those two cell types we can look at the effect of drugs, so Baricitinib is an immunomodulator that was approved by FDA and designers and antiviral and they work in through different mechanisms of action. There's obviously interest in combining them so we can see that we can combine both drugs, can actually block the migration of monocytes secondary to the infection of the epithelium.

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So that might be responsible for some of the benefits that we see for those drugs when they are combined *in vivo*. We can also look at a viral burden in the different compartments of our model in the epithelial cells in the monocytes in the exercise fluid and we can combine all of those to look at the total viral burden and you can see again that the combination of Remdesivir and Baricitinib in you know six to ten different replicates here shows a decrease in the total viral burden.

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More importantly we can also look very much in depth at the molecular response in terms of transcription and all other functions that you're interested in the epithelial cells in the leukocytes. In this case I want to illustrate our ability to show for example in the context of no drug, that the monocytes that are infected by SARS COVID-2 show a huge decrease in the transcription on each of interferon and also the STING RNA sensor but by the same token the infection is increasing the transcription of IL-1 beta and also IL-8, which we know are going to lead to the recruitment of neutrophils. And again we can look at the effect of single drugs or drug combinations in that system at the transcriptional level.

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what's really interesting is that um you know there was a paper in *Nature* yesterday showing that alveolar macrophages show a huge burden of SARS-CoV2 at the time we were you know working on our study we actually didn't have a lot of data going in that in that direction so we realized by computational means this is work that we did in collaboration with Ghosn Lab at Emory, some single cell RNA-seq data from Bronchoalveolar lavage of mild and severe COVID patients were all hospitalized and we found a population of monocytes in the lung that show exactly the same type of transcriptional activation upon encounter with the virus where they are very high for IL-8 and I1 beta so we think our model mirrors in vivo data both on the epithelial side also on the leukocyte side

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So, in summary, we have the ability to recruit monocytes infect them by SARS-CoV2, they produce a preentrophilic response all of this is mirrored you know between our the in vitro model and in vivo situation there are a number of questions obviously that we're asking in this model both in terms of the virology and the immunology we have now this model under provisional patent for drug testing because we think this is sort of the most urgent effort that needs to be put together. And we're testing a number of immunomodulatory antiviral and prorepair drugs, you know, more in the next few months on this.

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I'm just going to finish here by acknowledging folks in my lab folks in the Schinazi Lab, Ghosn Lab, Gibson Lab at Georgia Tech who helped us with some of the transcriptional analysis and again the EAGER award that was instrumental in having us, you know, start this project and pivot from our working long immunology to COVID-19 research. And this is my contact, I'm going to stop there and now I'm happy to take questions in the chat thank you.