Microbial shifts during an acute exacerbation of chronic obstructive pulmonary disease

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Chronic obstructive respiratory disease (COPD) is the 3rd leading cause of death worldwide and is associated with high disease and economic burden. People with COPD harbor different microbiota profiles in comparison to healthy individuals, and their dynamics shift within different disease stages. Acute exacerbations of COPD (AECOPD) are highly heterogenous events of symptoms worsening that play a pivotal role in the disease trajectory. Viral and bacterial infections have been pointed as the main cause of AECOPD. Nevertheless, these pathobionts have also been identified in COPD stable state (stCOPD) making a simple causal relationship unlikely.

For that reason, we queried the role of airway microbiota in the onset of an AECOPD event. We hypothesized that shifts in the whole microbial community concomitant with intra-species diversification and strain-specific immune response could trigger an AECOPD.

To test our hypothesis, we followed the disease course of a patient with COPD (♂, 77y, GOLD III, FEV1pp: 43, GOLD B) for 7 months, comprising stCOPD and AECOPD states. Sociodemographic, anthropometric, clinical data and saliva samples were collected monthly during stCOPD, while in AECOPD the patient was clinically evaluated twice (onset and after 21 days) and saliva samples were collected every two days. 16S rRNA sequencing was performed to establish microbiota profiles of stable and AECOPD periods. This gave us insight about species of interest for bacterial isolation, to understand differences between stCOPD and AECOPD. Optimization of bacterial culture conditions and isolation of strains/clones of interest followed by whole genome sequencing are being performed to evaluate intra-species diversification. At the same time, a deeper access of whole microbiome shifts, including viral and fungal descriptions, is being obtained by shotgun metagenomics.

Till the moment we have observed a microbiota composition shift towards increased frequencies of Proteobacteria, particularly Haemophilus genus (potentially pathogenic facultative anaerobe), and decreased frequencies of Prevotella genus (mainly a commensal anaerobe of airways) within the beginning of AECOPD. No significant differences were observed in alpha diversity between periods of stability and exacerbation. Moreover, we have established the conditions for isolation of Haemophilus and have isolated Haemophilus parainfluenzae and Haemophilus influenzae from patient's saliva samples.

Exploration of data is still ongoing, but by providing a detailed description of microbial shifts during the onset of an exacerbation along with clinical assessment, we believe we can contribute to understand the role of airway microbiota in COPD exacerbations.

Biomedicine

Impact of tRNA modifications for pathogenicity and host responses upon influenza A virus infection

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The Influenza A virus (IAV) is responsible for the main seasonal respiratory epidemics in humans. Its ability for genetic reassortments and rapid antigenic evolution hinder vaccine development and leads to occasional lethal pandemic infections. Hence, IAV becomes quickly resistant to current therapies, stressing the importance of discovering new antiviral treatments. IAV is completely dependent on the host cell translation machinery to synthesize its own proteins. Transfer RNAs (tRNAs) are the effector molecules of translation that recognize mRNA codons through their anticodons to decode the 20 standard amino acids. Generally, host codon usage reflects cellular tRNA levels, however the IAV RNA genome is highly skewed towards A/U-ending codons, while the human genome is biased towards C/G- ending codons. Nevertheless, IAV is still able to efficiently hijack the human translation machinery and select specific host tRNAs to optimize viral translation. To ensure translation efficiency and fidelity tRNAs are extensively modified post-transcriptionally by numerous tRNA modifying enzymes (tRNAMES). tRNA modification levels can change quickly in response to an external stimulus and genome recoding by coordinated alterations of tRNA modifications induces optimal translation of transcripts in response to cellular stress. As viral infections are sources of host cellular stress, changes in the host tRNA epitranscriptome are expected to guarantee the effectiveness of the viral genome translation. We propose to elucidate how IAV exploits the host tRNA epitranscriptome to facilitate viral propagation and evade host antiviral responses. To that end, we profiled the gene expression of all human tRNAMES in UniProt and Modomics involved in tRNA modifications using the Arraystar NuRNATM Human tRNA Modification Enzymes PCR Array to identify which tRNAMES were deregulated upon IAV infection. We found that several tRNAMES were deregulated at two-, four- and eight-hours post-infection, most of which catalyzing modifications at the tRNA anticodon loop region. Since tRNA modifications occurring at the wobble position directly affect the decoding of viral A-ending skewed codons, we selected ELP3 for further studies. We confirmed that ELP3 expression is significantly downregulated during IAV infection at both mRNA and protein levels. Upon ELP3 silencing in A549 infected cells we observe a significant decrease in the production of new viruses by the cells. Collectively, these results show that ELP3 may play an important role in IAV replication. More experiments are currently being conducted to comprehend the relevance of ELP3 in this context.

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