Metabolomic fingerprint biomarkers to guide antibiotic therapy and reduce resistance development

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1. Introduction

Patients with severe community-acquired pneumonia (CAP) receive empirical treatment with broad-spectrum antibiotics awaiting laboratory results. These results may confirm bacterial etiology and guide towards targeted narrow-spectrum antibiotic treatment. However, current laboratory tests such as culturing of sputum or blood are associated with turnaround times up to 48 hours. Other available tests only asses the presence of specific pathogens. Combined, these tests are still inconclusive in up to 50% of patients. This can lead to unnecessary treatment with antibiotics in patients that do not have a bacterial infection, and unnecessarily long use of (broad-spectrum) antibiotics, which may promote antimicrobial resistance (AMR). Hence, an unmet need exists for novel biomarkers that can rapidly i) discriminate between bacterial and viral infections and ii) guide optimal antibiotic treatment based on patient-specific host-response to the infection. Previous studies suggest that the host metabolome may be a relevant unexplored source of host-response biomarkers to infectious pathogens.[1,2]

2. Approach

This project aims to identify and validate novel metabolomics-based biomarkers to guide antibiotics treatment in patients hospitalized with CAP to reduce the risk of AMR, and which can be implemented as a rapid assay for diagnostic use. Specifically, we aim to i) identify metabolite biomarker profiles that can discriminate between bacterial and viral etiologies; ii) identify time course metabolite biomarker profiles that are associated with disease progression; and iii) to obtain a further mechanistic understanding of observed metabolite profiles in relation to bacterial infections.

To these aims, patient time course serum samples from a previously conducted randomized controlled trial in patients hospitalized with CAP (n=304)[3] are analyzed using multiple targeted and biologically-relevant metabolomics platforms. We will apply multivariate regression and classification approaches to identify metabolite signatures associated with causal pathogens and disease severity and treatment response. We will use pathway and metabolite interaction network databases to obtain insight into the mechanistic basis of the identified signatures[5]. The obtained metabolite biomarkers will be validated in separate cohorts of patients with CAP and suspected bacterial infections of different origins.[4]

3. Results & Discussion

Preliminary results for metabolites from the class of biogenic amines allowed separation of metabolite profiles from CAP patients with atypical bacterial infections, including *Mycoplasma pneumoniae* and *Legionella* species, from patients with a *Streptococcus pneumoniae* bacterial infection or a viral infection (Figure 1).

Future work will focus on expanding our dataset and analysis with additional classes of metabolites, and to explore their role in the immune response to pathogens involved in CAP.

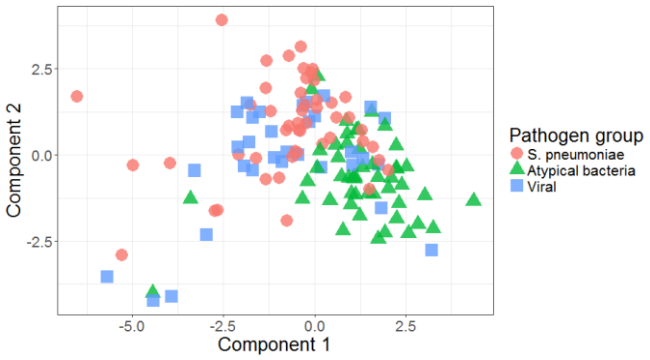

Figure 1. PLS-DA score plot of biogenic amines metabolomics data based on human serum from CAP patients infected with S. pneumonia (n=50), atypical bacteria (n=50) and viruses (n=34).

References

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