A155 · Multimodal data-driven approaches for discovery and validation of pneumonia sub-phenotypes

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Rationale: Elucidating pneumonia sub-phenotypes can improve host-based therapeutics. Pneumonia involves heterogenous and dysregulated histopathology responses, but these histopathological changes within the lungs have not been explored for sub-phenotyping. Objective: To investigate whether pneumonic lungs can be clustered into sub-phenotypes based on histopathology and examine whether these sub-phenotypes re-emerge in a new cohort. Methods: H&E slides from subjects with pneumonia diagnosis (n=276) or with no known lung disease (n=16) at autopsy were scored across 18 histopathology features (Necrosis, Fibrosis, Edema etc.,) by two pathologists (discovery cohort). Consensus clustering was used to group samples into clusters, and distance and variation-based clustering metrics were used to select the optimum number of clusters. 5 different leukocytes were quantified in a subset of patients (n=159) using multispectral immunofluorescence assay. A new cohort of samples were scored (n=104) using the same framework (validation cohort). Both cohorts were co-clustered to validate sub-phenotypes in the second cohort. Results: Our approach showed pneumonia samples cluster into seven different sub-phenotypes with distinct histopathology patterns including necrosuppurative, suppurative & chronic interstitial pneumonias. These sub-phenotypes also vary in their composition of immune cell patterns. Validation using a different cohort showed that when co-clustered with the original cohort, all seven sub-phenotypes re-emerge, with consistent histopathology signatures. Conclusions: Human pneumonias segregate into sub-phenotypes based on host responses and sub-phenotype markers could be further explored for therapeutic purposes. By illuminating a spectrum of histopathologies and discriminating discrete sub-phenotypes of pneumonia, a foundational framework emerges for developing and testing host-directed therapies for subsets of pneumonia patients.

Multimodal data-driven approaches for discovery and validation of pneumonia sub-phenotypes

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Objective: To investigate whether pneumonic lungs can be clustered into sub-phenotypes based on histopathology and examine whether these sub-phenotypes re-emerge in a new cohort.
Methods: H&E slides from subjects with pneumonia diagnosis (n=276) or with no known lung disease (n=16) at autopsy were scored across 18 histopathology features (Necrosis, Fibrosis, Edema etc.,) by two pathologists (discovery cohort). Consensus clustering was used to group samples into clusters, and distance and variation-based clustering metrics were used to select the optimum number of clusters. 5 different leukocytes were quantified in a subset of patients (n=159) using multispectral immunofluorescence assay. A new cohort of samples were scored (n=104) using the same framework (validation cohort). Both cohorts were co-clustered to validate sub-phenotypes in the second cohort.
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Conclusions: Human pneumonias segregate into sub-phenotypes based on host responses and sub-phenotype markers could be further explored for therapeutic purposes. By illuminating a spectrum of histopathologies and discriminating discrete sub-phenotypes of pneumonia, a foundational framework emerges for developing and testing host-directed therapies for subsets of pneumonia patients.