COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Airway Microbiome Manipulation To Counter Respiratory Infection

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New approaches for preventing and treating infectious diseases, particularly those originating in the respiratory tract, are needed. A promising solution is to reconfigure microbial communities (microbiomes) within the host in order to improve their ability to competitively exclude, directly attack, and/or enlist host defenses against the infectious agent. This approach should avoid two major problems with antibiotics: 1) Development of resistance; and 2) Destruction of resident microbiomes, which renders the host vulnerable to secondary infections. Probiotics and prebiotics for gastrointestinal infections offer a template for success. We seek to develop comparable countermeasures for respiratory infections. To this end, mouse airway microbiome constituents were recovered into culture, and then assessed for ability to re-colonize the mouse airway and confer protection against Burkholderia thailandensis (Bt), a bacterial respiratory pathogen related to Select Agents B. pseudomallei and B. mallei. Several airway isolates belonging to Bacillus and related genuses were found to display re-colonization activity (persistence in the airway for ≥7 days), and several others (a partially overlapping set) display anti-Bt activity (significant reduction in mortality when administered 3-7 days preceding pathogen challenge). Mechanism of action studies revealed niche exclusion effects as well as production of secondary metabolites (by airway isolates as well as host cells) that may mediate anti-Bt activities. Comparative nutrient requirement profiling of the airway isolates vs Bt enabled identification of candidate prebiotics. Current studies focus on determining whether the airway isolates provide protection against other respiratory pathogens; testing pairs of airway isolates, as well as pairings of airway isolates and candidate prebiotics (i.e., candidate synbiotics) for enhanced anti-Bt activity; and genetic engineering of re-colonizing airway isolates for in situ synthesis and secretion of peptides/nanobodies that neutralize respiratory pathogens or elicit productive immune responses. Our work demonstrates that reconfiguration of the airway microbiome is a viable and potentially powerful new approach to countering respiratory pathogens; and serves as a foundation for development of airway-embedded microbial factories for in situ production of medical countermeasures (e.g., sensors, therapeutics, vaccine antigens/adjuvants).