Computational Inference of Chemokine-Mediated Roles for the Vagus Nerve in Modulating Intra- and Inter-Tissue Inflammation

Computational immunology offers a set of tools to facilitate the modeling of cross-tissue inflammation across time. Traditional statistics have been leveraged in algorithms such as dynamic Bayesian networks, dynamic network analysis, and dynamic hypergraphs. These models can provide unique insights when considering the human body as a 4-dimensional space, namely the three physical dimensions of the body as well as time. Advanced machine learning approaches utilizing so-called "artificial intelligence" (AI) have been used for systems immunology in the context of single-cell 'omics, but have not proven useful for more common, smaller datasets. We have drawn inspiration from AI models used to analyze 3D videos to structure our datasets composed of concentrations of inflammatory mediators in multiple organs across several time points. The application of traditional statistics to this unique data-setup, viewing the human body in 4D, has resulted in numerous novel insights regarding the spatiotemporal spread of inflammation in pathologies such as sepsis, trauma, as well as for assessing the role of the vagus nerve in regulating cross-tissue inflammation.

One study in specific sought to model the effects of vagotomy on cross tissue inflammation. The vagus nerve innervates multiple organs, but its role in regulating cross-tissue spread of inflammation is unclear. We hypothesized that the vagus nerve may regulate cross-tissue inflammation via modulation of the putatively neurally regulated chemokine IP-10/CXCL10. Rate-of-change analysis, dynamic network analysis, and dynamic hypergraphs were used to model intra- and inter-tissue trends, respectively, in inflammatory mediators from mice that underwent either vagotomy or sham surgery. This analysis suggested that vagotomy primarily disrupts the cross-tissue attenuation of inflammatory networks involving IP-10 as well as the chemokines MIG/CXCL9 and CCL2/MCP-1 along with the cytokines IFN-γ and IL-6. Computational analysis also suggested that the vagus-dependent rate of expression of IP-10 and MIG/CXCL9 in the spleen impacts the trajectory of chemokine expression in other tissues. Perturbation of this complex system with bacterial lipopolysaccharide (LPS) revealed a vagally regulated role for MIG in the heart. Further, LPS-stimulated expression of IP-10 was inferred to be vagus-independent across all tissues examined while reducing connectivity to IL-6 and MCP-1, a hypothesis supported by Boolean network modeling. Together, these studies define novel spatiotemporal dimensions of vagus-regulated acute inflammation.

Biography

Ashti Shah is a fourth-year medical student at the University of Pittsburgh School of Medicine. She is a scholar of the Physician Scientist Training Program where she completed a year of fully-funded research under the mentorship of Dr. Yoram Vodovotz. Prior to matriculating to medical school, Ashti completed her undergraduate degree at the Massachusetts Institute of Technology, where she first developed her love for computational biology. Ashti aspires to be an academic urologist who builds a practice centered on both urologic surgery and computational immunology research. Outside of work, Ashti is an avid reader and Pilates enthusiast.

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