Karolinska Institutet

Department of Neuroscience

# Tissue responses and host transcriptomics in bacterial infections

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Samuelssonsalen, Scheeles väg 2

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# Abstract

Bacterial infections can damage host tissue and are as such a potential threat to their hosts. To protect themselves from pathogens, hosts therefore can employ diverse immune reactions. When bacteria are recognized by their hosts, complex signaling cascades are triggered that lead to an influx of specialized immune cells into the infected tissue and a change in tissue integrity. The inflammation that is mounted may eliminate the pathogens, but will also cause substantial tissue damage. The foundation for the inflammatory process is laid early, in the first 12 hours of infection. This thesis aims to reveal host responses within this early time frame.

While *in vitro* studies can yield highly detailed data on subjects as protein-protein and cell-bacterial interactions, they cannot reproduce all aspects that occur in a live animal, such as immune infiltration, nerve, and hormone effects. We have developed a kidney infection model of bacterial infection to study early whole-host responses to bacteria. Using micropuncture techniques, we delivered bacteria to a known nephron, from where the infection progressed. Within hours, we observed numerous physiological changes of the tissue volume bordering the infection. Infection kinetics could be visualized and showed markedly faster host responses to haemolysin (Hly)-carrying bacteria compared to Hly-knockouts. Tissue oxygen levels decreased in response to infection, possibly caused both by blood flow restriction combined with epithelial oxygen consumption. Blood flow shutdown at the infected nephron was due to activation of the coagulation cascade. Coagulation also protected against sepsis, as animals died due to bacteremia when this cascade was inhibited. Some of these phenomena could be found in the host transcriptome. We also found that a core of common gene expression exists in live host innate immune responses by applying bioinformatic methods on the gene expression measurements. This core had a strong IFN-$\gamma$ signature, a cytokine which we consequently found increased in the blood stream, and expressed by cells in the spleen. We go on to show that IFN-$\gamma$ downregulates transcription of several neutrophil-attracting chemokines, and that this does not occur through canonical effectors of either IFN-$\gamma$ or inflammatory signaling pathways.

The data I present here show that using a live host infection model can reveal host processes that cannot be found using *in vitro* models. By combining this model with analysis methods that yield detailed data, early responses could be studied. The data show the importance of live models for discovering unknown contributors and functions in inflammation, which may lead to possible future medicine development.


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