Host immune response and macrophage behaviour during Burkholderia cepacia complex infection in zebrafish embryos

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Résumé

Chronic respiratory infection in cystic fibrosis patients is characterized by a high level of pro-inflammatory cytokines, leukocyte infiltration, and inflammation in the lungs due to colonization by pathogenic bacteria. Chronic infections caused by bacteria belonging to the Burkholderia cepacia complex (Bcc) can be symptom free, but often cause pulmonary exacerbation with progressive worsening of lung function, sometimes resulting in acute fatal necrotizing pneumonia and sepsis. The reasons for these unpredictable, sudden transitions are not understood.
Using zebrafish embryos, which have an innate immune system very similar to that of humans, we previously found that B. cenocepacia K56-2, belonging to the epidemic ET12 lineage, is highly virulent for zebrafish embryos; it causes a rapidly fatal (2 days) systemic inflammatory infection. In contrast, embryos can control infection with strains such as B. stabilis LMG14294, which cause a persistent infection. Intravenously injected bacteria are rapidly phagocytosed by macrophages, and we found that an intracellular stage is important for fatal infection.

In an attempt to better understand the molecular basis for B. cenocepacia K56-2 or B. stabilis LMG14294 infection outcomes, we performed a global host transcriptome analysis during different stages of both infection types. RNA-seq analysis revealed interesting infection responsive host gene expression patterns. Whereas many host genes were differentially regulated during early (3 hours) as well as later (24 hours) stages of infection caused by B. cenocepacia K56-2, only few genes showed changes in expression level upon persistent infection with B. stabilis LMG14294. In particular, the innate immune response with Toll-like receptor (TLR), NOD-like receptor and apoptosis pathways were strongly activated during acute infection. The "silent" intracellular persistence of B. stabilis coincided with increased expression of genes encoding complement proteins. We will discuss how we are using the zebrafish model to further study the role of the TLR pathway, including the central adaptor protein MyD88 and intracellular stages in the induction of the highly excessive innate inflammatory response.

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Mots-Clés: Innate immune response, macrophage, Burkholderia cepacia complex, zebrafish embryos