Universität Basel

Research Project

Elucidation of the interplay of cell autonomous and pathogen-derived factors on the susceptibility of individual host cells to infection by a protozoan pathogen

Third-party funded project

Project title Elucidation of the interplay of cell autonomous and pathogen-derived factors on the susceptibility of individual host cells to infection by a protozoan pathogen
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Several species of *Leishmania* protozoan parasites cause the disease leishmaniasis. In a study from a decade ago, it was estimated that almost 12 million people are infected with this parasite, over 350 million people are at risk, and approximately 7000 deaths are annually attributable to the *Leishmania* infection (Bern et al. 2008). In humans, the *Leishmania donovani* species causes the most severe, visceral form of leishmaniasis, in which the parasite reside within liver, spleen and bone marrow macrophages. Emaciation, anemia and increased susceptibility to a variety of infections can lead to very high mortality (Chatterjee 2009). Available treatments have high toxicity and have already elicited resistance in the parasites (Chappuis et al. 2007). Within human populations, clinical manifestations of the disease are highly heterogeneous, due to the parasite itself, as well as to the genetic background and environment of the individual (Saporito et al. 2013). The heterogeneous response of cells, organisms and individual immune systems to infectious agents is the basis for both the limited impact of epidemics as well as the limited efficacy of vaccines. For reasons that remain poorly understood, cells within an individual organism are not equally susceptible to infection.

In this study we will focus on a model system that is well established in the Bhattacharyya lab, namely the infection of mammalian macrophages with the protozoan parasite *Leishmania donovani* (Ld), aiming to uncover factors that contribute to the susceptibility of individual cells to infection. We will use macrophages from rodent species with distinct susceptibility to infection by this parasite and we will profile their gene expression both in the absence of any challenge as well as in time series after 'priming', through exposure to stimuli that are are known to affect the cytokine profile of macrophages (lipopolysaccharide (LPS), parasite-derived extracellular vesicles (EV) and supernatant from infected macrophages). By analyzing computationally the gene expression profiles, we will infer activities of regulatory factors - transcription factors and miRNAs - in macrophages from different genetic backgrounds, that were primed in various ways. In parallel, we will evaluate the susceptibility of these cell populations to infection by measuring the parasitic load after the exposure to the parasite. By relating the molecular profile prior to infection to the parasite load of the cells upon infection, we will uncover cell-autonomous factors that contribute to differential susceptibility and cellular pathways that are engaged by pathogen-derived components to modulate the susceptibility to infection. Furthermore, we will elucidate how the priming

of macrophages and their initial polarization affects their susceptibility to the infection with this protozoan parasite. We will then validate these findings by directly manipulating these pathways to reduce the susceptibility of host cells to infection. Finally, our data will provide a first glimpse into the single cell level heterogeneity of macrophages from various sites and genetic backgrounds, which is relevant for the immune response to a wide range of pathogens.

Keywords macrophage, single cell, Leishmania donovani, gene expression
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Add publication

Published results

4650312, Breda, Jeremie; Banerjee, Arka; Jayachandran, Rajesh; Pieters, Jean; Zavolan, Mihaela, A novel approach to single-cell analysis reveals intrinsic differences in immune marker expression in unstimulated BALB/c and C57BL/6 macrophages, 0014-5793 ; 1873-3468, FEBS Letters, JournalItem (Kommentare, Editorials, Rezensionen, Urteilsanmerk., etc. in einer wissensch. Zeitschr.

Add documents

Specify cooperation partners

ID	Kreditinhaber	Kooperationspartner	Institution	Laufzeit - von	Laufzeit - bis
4638948	Zavolan, Mihaela	Bhattacharyya, Suvendra Nath	Human Genetics Division CSIR-Indian Institute of Chemical Biology	01.03.2019	28.02.2023