PhD defence Bart Cuypers

A systems biology approach for a comprehensive understanding of molecular adaptation in Leishmania donovani

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Summary:

Leishmania is the causative agent of leishmaniasis, a disease of major clinical importance with 350 million people at risk worldwide. Particularly concerning is the increasing threat of drug resistance, while little or no new drugs are in the development pipeline. Moreover, the parasite has shown remarkable adaption skills to drug pressure *in vivo* and *in vitro*. Untargeted 'omic approaches including genomics, transcriptomics, proteomics and metabolomics have opened a new avenue to identify the responsible molecules and pathways for molecular adaptation of these organisms. However, a systems view is currently lacking as these findings have been predominantly linked to only a single 'omic layer. An integrative study of different 'omic layers could shed light on how the parasite is able to adapt to new environments on the system level. Despite the high potential of these type of studies, there has been little integration so far in the *Leishmania* field.

The **goal** of this thesis was to study how genomic variation in *Leishmania* impacts the variation observed at downstream functional layers. To this end, a systems biology approach was undertaken, in which we aimed to integrate the molecular profiles obtained with genomics, transcriptomics, proteomics and metabolomics.

Our first hypothesis stated that both genomic sequence and structure variation ultimately drive the variation observed at the metabolome. Consequently, combining the profiles of genome and metabolome could lead to novel insights in molecular adaptation linking together drivers (genome) and effects (metabolome). To validate this hypothesis and as a proof-of-concept for this approach, we compared and integrated genomics and metabolomics data from two genomically distinct *L. Donovani* populations: ISC1 and the Core Group (CG). ISC1 is currently emerging genotype, predominantly found in the Nepalese highlands, while CG caused the last outbreak of VL in the Indian Subcontinent. The results obtained with genomics and metabolomics showed overall correspondence and pointed towards the same pathways and functions. Indeed, both approaches highlighted dissimilarities related to membrane lipids, the nucleotide salvage pathway and the urea cycle in ISC1 versus CG. Finally, a direct link was found between genome and metabolome in context of the argininosuccinate synthase gene (ASS, urea cycle), which is essential for the virulence of the parasite. ISC1 had a lower copy number of this gene, which was linked to reduction in ASS activity and highlights the importance of gene dosage in molecular adaptation. Altogether, our data predict major functional differences in between ISC1 and CG parasites, including virulence. Therefore, particular attention is required to monitor the fate of this emerging population in the ISC, especially in a post-VL elimination context.

Secondly, we hypothesized that gene dosage has a major adaptive and functional impact by directly affecting the final transcript and protein levels. To answer this question, we studied and integrated the genomes, transcriptomes and proteomes of three sets of strains with genomic structure variation ranging from a single local CNV to high degrees of aneuploidy. Remarkably, we found very strong correlations between gene dosage, transcript levels, and protein levels at chromosome level and within the same life stage. Interestingly, our findings also suggest that a large number of transcript and proteins

respond to gene dosage in a 'buffered' manner and change to a lesser extent than predicted by gene dosage. While this remains to be validated, it might be the first clue towards a global dosage compensation mechanism in *Leishmania*.

In summary, this integrative 'omics study is the first of its kind in the *Leishmania* field and could pave the way for future integration work by providing an essential and general understanding of how genomic variation drives downstream 'omic layers. Possibly, some of the results could also be relevant for Eukaryotes in general, as the absence of several regulation layers in *Leishmania* might offer a unique viewpoint on (the remaining) regulation mechanisms.