Peer Community In Infections

Whole genome transcriptome reveals metabolic and immune susceptibility factors for Trypanosoma congolense infection in West-African livestock

Concepción Marañón *based on peer reviews by 2 anonymous reviewers*

Moana Peylhard, David Berthier, Guiguigbaza-Kossigan Dayo, Isabelle Chantal, Souleymane Sylla, Sabine Nidelet, Emeric Dubois, Guillaume Martin, Guilhem Sempéré, Laurence Flori, Sophie Thévenon (2022) Whole blood transcriptome profiles of trypanotolerant and trypanosusceptible cattle highlight a differential modulation of metabolism and immune response during infection by Trypanosoma congolense. bioRxiv, ver. 2, peer-reviewed and recommended by Peer Community in Infections.
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African trypanosomiasis is caused by to the infection of a protozoan parasite of the Trypanosoma genus. It is transmitted by the tsetse fly, and is largely affecting cattle in the sub-humid areas of Africa, causing a high economic impact. However, not all the bovine strains are equally susceptible to the infection (1).

In order to dissect the mechanisms underlying susceptibility to African trypanosoma infection, Peylhard et al (2) performed blood transcriptional profiles of trypanotolerant, trypanosensitive and mixed cattle breeds, before and after experimental infection with *T. congolense*.

First of all, the authors have characterized the basal transcriptional profiles in the blood of the different breeds under study, which could be classified in a wide array of functional pathways. Of note, after infection some pathways were consistently enriched in all the group tested. Among them, the immune system-related ones were again on the top functions reported. The search for specific canonical pathways pointed to a prominent role of lipid and cholesterol-related pathways, as well as mitochondrial function and B and T lymphocyte activation.

However, the analysis of infected animals demonstrated that trypanosusceptible animals showed a stronger transcriptomic reprogramming, highly enriched in specific metabolic and immunological pathways. It is worthy to highlight striking differences in genes involved in immune signal transduction, cytokines and markers of different leukocyte subpopulations.

This work represents undoubtedly a significant momentum in the field, since the authors explore in deep a wide panel of cattle breeds representing the majority of West-African taurine and zebu in a systematic way. Since the animals were studied at different timepoints after infection, future longitudinal analyses of these datasets will be providing a precious insight on the kinetics of immune and metabolic reprogramming associated with susceptibility and tolerance to African trypanosoma infection, widening the application of this interesting study into new therapeutic interventions.

References:

1. Berthier D, Peylhard M, Dayo G-K, Flori L, Sylla S, Bolly S, Sakande H, Chantal I, Thevenon S (2015) A Comparison of Phenotypic Traits Related to Trypanotolerance in Five West African Cattle Breeds Highlights the Value of Shorthorn Taurine Breeds. PLOS ONE, 10, e0126498. https://doi.org/10.1371/journal.pone.0126498

2. Peylhard M, Berthier D, Dayo G-K, Chantal I, Sylla S, Nidelet S, Dubois E, Martin G, Sempéré G, Flori L, Thévenon S (2022) Whole blood transcriptome profiles of trypanotolerant and trypanosusceptible cattle highlight a differential modulation of metabolism and immune response during infection by Trypanosoma congolense. bioRxiv, 2022.06.10.495622, ver. 2 peer-reviewed and recommended by Peer Community Infections. https://doi.org/10.1101/2022.06.10.495622.

Reviews

Evaluation round #2

Reviewed by anonymous reviewer 1, 09 January 2023

Althought I still believe that the work would be benefited from more advanced analyses, I now understand the rationale of the authors for including only basic analyses. The rest of the commentaries have been adequately addressed. Overall, I congratulate the team for their good article.

Reviewed by anonymous reviewer 2, 31 December 2022

Dear Editor,
I am happy with the revised version of the manuscript and believe that it is now suitable for publication.
Kind regards,

Evaluation round #1

DOI or URL of the preprint: https://doi.org/10.1101/2022.06.10.495622
Version of the preprint: 1

Authors' reply, 06 December 2022

Dear Recommender

Please find enclosed a revised version of our manuscript entitled:

Whole blood transcriptome profiles of trypanotolerant and trypanosusceptible cattle highlight a differential modulation of metabolism and immune response during infection by Trypanosoma congolense

By M. Peylhard, D. Berthier, G-K. Dayo, I. Chantal, S. Sylla, S. Nidelet, E. Dubois, G. Martin, G. Sempéré, L. Flori and S. Thévenon

We thank you and the reviewers for considering our manuscript and making relevant comments.

Our reply to specific reviewer comments is in the uploaded file, in blue text. One of the reviewers makes interesting suggestions regarding data analyses. We agree that our dataset could be analysed using different statistical approaches (e.g. longitudinal methods or meta-analyses and even multivariate methods), in addition to the classical one, based on contrasts, that we selected. We nevertheless think that performing pairwise comparisons as we did remains a relevant way to explore the kinetics of host response to infection in each breed and the basal differences between breeds, and this allows to meet the main objectives of this study. Considering the significant amount of results already described in our article, we prefer to keep the structure as initially proposed, without including additional analyses that would make the article confusing. All data will be freely available as described below, and can be reanalyzed by ourselves and other teams using complementary approaches with a different perspective.

Raw sequence data (fastq files, gene count matrix, experimental design) have been deposited at GEO (https://www.ncbi.nlm.nih.gov/geo/) under accession number GSE197108 and they will be publicly available as soon as our manuscript is recommended or published. Scripts and intermediate tables (bioinformatics pipeline for raw sequence mapping, statistical analysis of differentially expressed genes, input tables for IPA® analyses, output tables from IPA® analyses) are publicly available in Cirad Dataverse under https://doi.org/10.18167/DVN1/L9SHAX. SNP genotypes of the experimental cattle are publicly available in Cirad Dataverse under https://doi.org/10.18167/DVN1/APTZOC and in WIDDE (http://widde.toulouse.inra.fr/widde/).

Hoping that you will find the revised manuscript suitable for recommendation in PCI Infections, sincerely yours,

Sophie Thévenon

CIRAD INTERTRYP

Download author's reply

Decision by Concepción Marañón, posted 07 October 2022

revision needed

Dear Dr Thévenon and collaborators,

I am glad to inform you that the review process for your manuscript "Whole blood transcriptome profiles of trypanotolerant and trypanosusceptible cattle highlight a differential modulation of metabolism and immune response during infection by Trypanosoma congolense", submitted to PCI Infections, has now been completed. First of all, I want to apologize for the time it has taken.

Two independent reviewers have evaluated your manuscript. Both agree that the work is interesting and sound. One reviewer raised a minor question about the extent of the interpretation of the data. The second reviewer raised a few comments regarding data analysis that should be addressed before a final decision can be made.

Please, respond to all the reviewers' comments through the PCI infections website and upload an accordingly edited version of the manuscript in the Preprint server.

Thank you very much for believing in Peer Community In.

Concepción Marañón
Recommender for PCI Infections

Reviewed by anonymous reviewer 1, 12 July 2022

In this preprint written by Peylhard et al., whole blood transcriptome profiles of five cattle breeds infected by Trypanosoma congolense were compared in order to find molecular differences between resistant and non-resistant breeds to trypanosomosis. Authors observed transcriptomic changes before and after infection in all breeds. Differentially expressed genes were also detected between tolerant and susceptible breeds and, based on these, the importance of different molecular functions for the trypanosomosis tolerance is discussed. The novelty of the work is, mainly, the studied breeds, since some of them had been overlooked until date. The introduction explains clearly the context of the study and it can be easily understanded by non-expert readers. Nevertheless, there are some aspects of the article that may be improved before submission:

1. I miss information about why was expected to find Trypanosoma congolense RNA in the bovine blood samples. Was this described previously? What mechanism introduces the RNA of the parasite into de host blood?
2. Some figures may be improved. For instance, some labels in Figure 2 are unreadable, so it would be desirable to replace them by different shapes. Furthermore, the colors of Figure 4 should be more friendly.
3. Differential expression analysis was performed through multiple pairwise comparisons. Given that this is a longitudinal experiment, I recommend exploring other methods designed for this kind of data that could return results overlooked by the pairwise comparisons approach.
4. Authors should clarify why an FDR threshold of 0.001 is adequate because 19 comparisons were performed. In addition, they should provide more details about the rationale of choosing different FDR thresholds for the functional analyses.
5. I recommend considering meta-analyses as the approach to compare the results between comparisons. Comparing the lists of genes that pass arbitrary thresholds may lead to miss relevant information.

Reviewed by anonymous reviewer 2, 22 September 2022

The manuscript entitled "Whole blood transcriptome profiles of trypanotolerant and trypanosusceptible cattle highlight a differential modulation of metabolism and immune response during infection by Trypanosoma congolense" is a very comprehensive study which aimed at improving the knowledge of the biological processes involved in trypanotolerance versus trypanosusceptibility using experimental Trypanosoma congolense infections in cattle. To this end, a whole blood genome-wide transcriptome of three trypanotolerant taurine breeds (N'Dama, Lagune and Baoulé), one susceptible zebu (Zebu Fulani) and one African taurine x zebu admixed breed (Borgou) were profiled by RNA sequencing at four time points, one before and three during infection. Moreover, most work performed by others in the past only consists of a comparison between one trypanotolerant and one trypanosusceptible cattle breed or only focusses at one particular time point. Hence, the manuscript presented now consists of a more thorough and kinetic study which strengthens the relevance of the observations (even be it at the gene-level). Moreover, this study revealed previously overlooked features that might contribute to susceptibility/tolerance towards T. congolense infections such as a strong disturbance in host metabolism and cellular energy production that differentiates trypanotolerant and trypanosusceptible breeds.

Therefore, I believe this research provides a unique opportunity as well as the basis for better understanding of the biological mechanisms at work during African trypanosome infections, especially concerning the interplay between immunity and metabolism that seems differentially regulated depending on the cattle breeds. Below I give a brief yet detailed overview of the strength/weaknesses of the manuscript.

1. Title

The title clearly reflects the content of the article.

2. Abstract

The abstract is concise and presents the main findings of the study.

3. Introduction

The introduction gives a very good overview of how trypanosusceptibility and trypanotolerance is defined as well as the current status regarding technologies used to understand trypanotolerance. To this end, relevant old/newer articles were sited. Moreover, the authors also provide a very good rational for using besides the well-characterized trypanotolerant N'Dama breed, also two overlooked trypanotolerant breeds, Baoulé and Lagune, the Borgou crossbred breed, and one trypanosusceptible breed, the Zebu Fulani. Hence, this would strengthening the relevance of the study! Furthermore, the authors clearly define what the study will focus on; i) breed-specific transcriptomic signatures in blood before infection, ii) main genes and biological functions that responded to infection, whatever the breed, iii) breed-specific transcriptomic profiles during infection, and iv) basal and dynamic transcriptomic profiles that could be associated with trypanotolerance.

4. Materials and methods

This section contains detailed information with respect to the technologies used and the strategies used to analyze the massive amount of data. Consequently, this should be sufficient to allow replication by other researchers. Regarding the statistical analysis, I am not an expert in this aspect but according to me (based on many articles using the same technology) it seems that the statistical analyses are appropriate.

5. Results

All results are presented in a concise manner and the message the authors want to transmit is clear. The fact that different breeds of trypanotolerant animals are used and a kinetic study was performed further strengthens the relevance of the results. I am not an expert in statistical analyse and therefore cannot comment on this aspect.

Given the fact that (i) several of the authors are experts in the field and have a very good reputation and (ii) I am familiar with some of the work of the authors, I do not suspect scientific misconduct.

6. Tables and figures

All the figures and tables (including the supplementary figures/tables) are understandable without reference to the main body of the article. In addition, figures and tables have a proper caption.

7. Discussion

Though the discussion section is very elaborate it is well structured in subsections and discussed accordingly. Also, the discussion allows concluding that a T. congolense trypanosome infection has a major impact on the cattle blood transcriptome, whatever the breed. As pointed our correctly by the authors, this research provides a global transcriptomic picture of infection as well as during infection. Interestingly, the results obtained by others are confirmed in this very elaborate study such as a strong regulation of the immune system functions with an early activation of innate immune response, followed by an activation of humoral response and an inhibition of T cell functions at the chronic stage of infection. The fact this change in the transcriptome (i.e. DEGs, functions and biological processes) is observed in all breeds, yet there are differences in gene expression dynamics in these three trypanotolerant breeds suggests that AFT breeds, although subjected to the same selective pressure caused by trypanosomes, may have developed different adaptation mechanisms. This is again a very important conclusion that has been suggested by many others and further strengthens the importance of the work of the authors!

I also appreciated that the authors mentioned that "It would be worth exploring other African zebu breeds to confirm if this observation is a global feature of indicine breeds", which according to me would be very important to investigate.

Finally, the fact that the authors also referred to work performed in murine models of African trypanosomes and discuss similarities/discrepancies is also appreciated.

The only minor point of criticism I might have is that it is important to mention that this research is focused on T. congolense infected cattle, which is the major cause of Nagana within the African continent.

The authors mention at the end of the discussion that “this could pave the way to further refine the interactions between immune response and metabolism in cattle which in turn could improve preventive and curative measures of AAT and also other infectious diseases”.

Yet, cattle can also become infected with T. brucei brucei or T. vivax which can also cause AAT and within these infections, the genes/pathways affected might be different and the underlying mechanism involved in pathology (anemia, liver injury,;..) could be different. Therefore it would be very important to perform a similar study on these trypanosome infections before drawing general conclusions about AAT.

8. References

The authors used appropriate references to confirm/justify/explain their results and also refer to other relevant research that confirms/contradicts their work.

Overall this is a very well-written and impressive research paper that provides new and valuable data to contribute to a better knowledge of African livestock genomics and to decipher the pathogenic process in bovine trypanosomos

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