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.

Title

The title clearly reflects the content of the article.

Abstract

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

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.

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**.

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.

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.

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 this change in 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.

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 trypanosomosis focusing on T. congolense.