Review of: "Non-canonical Function of a Hif-1α Splice Variant Contributes to the Sustained Flight of Locusts"

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In this manuscript authors identified two HIF-1α splicing variants in Locustus, that both display transcriptional activity, and one (HIF-1α-1) is involved in canonical adaptive response to hypoxia, whereas the other (HIF-1α-2) is predominant in muscle and involved in adaptation to prolonged flight. The manuscript, besides providing important novel insight into HIFs function, is very solid, well designed experimentally and well written. The transcriptomic role of both HIF-1 isoforms was carefully considered and well supported by the data.

However, authors identified that the HIF-1α-2 isoform lacks one TAD domain (remaining transcriptionally active) **ad its resistant to oxygen depended degradation.**

This phenomenon requires deeper insight and discussion, since the Pro hydroxylation in ODD by PHDs is responsible for HIF-α oxygen-related destabilization. Its also hard to understand why PHDs knockdown results in this HIF-1α-2 rescue, if it was shown to be stable in normoxia.

This data are contradictory, and require revising – it may be helpful here to use PHDs inhibitors like DMOG. Furthermore, considering that the are different PHDs, with different oxygen requirements and HIF-α preference, it needs to be clear which of them were silenced.

The nuclear location signal NLS is at both C and N terminus of HIF-1α, so it should go to nucleus, however it would be also nice to know how these isoforms are interacting with β subunits, are they competing for them? This could provide better insight into transcriptional mechanisms.

Last -many of the conclusions is based on overexpression of these proteins from pcDNA vector, since previous studies on HIF1/2/3 shown that when overexpressed these α isoforms can either compete with each other or regulate the very same targets, *in vivo* the situation is not so clear. Hence, it would be beneficial for the readers to know how does overexpression model compares to these α physiological levels, and what is their relative ration in hypoxic conditions.

Finally, it has been shown for HIF-1α and HIF-2α as well HIF-3α that their levels are changing dynamically during hypoxia time course, it would be beneficial to test in the further studies the hypoxia related dynamics of these two HIF-1α isoforms.