

## Open peer review and authors' responses

### A BID-MTCH2 love story: Energizing mitochondria until apoptosis do them part?

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Reviewer 1: Nikolay Popgeorgiev

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Manuscript reviewed 2023-12-12: *Only major points included.*

#### Reviewer 1

In this manuscript Pr. Atan Gross is presenting seminal findings and recent results on the link between the pro-apoptotic BID protein and the Mitochondrial carrier homolog 2. The story behind these two proteins and the physiological consequences on the mitochondria dynamics, bioenergetics and apoptosis is written by a first-hand observer. It retraces in detail the intimate liaison between these mitochondrial proteins and draws an interesting hypothesis about some open questions in the field.

It would be interesting for the audience if the author incorporates the recent finding that tBID is acting not only as a BH3-only protein but also as BAX-like effector of apoptosis (Flores-Romero et al., 2022 EMBO J). This could be interesting as tBID is a cardiolipin binder and MTCH2 may have a potent scramblase activity.

#### Author

Many thanks for your excellent comments!

See lines 262-264 in revised MS:

*Interestingly, tBID was demonstrated to also act as a BAX-like effector of apoptosis (Flores-Romero et al 2022), suggesting that tBID and MTCH2 can execute their function independent of BAX and BAK.*

#### Reviewer 1

Caution should be used in the citation of Raemy et al 2016 article as in this paper authors showed that the sole inhibition of Cardiolipin synthesis does not abolish the tBID-induced BAX activation, or for apoptosis following TRAIL treatment. This is achieved by simultaneously downregulating MTCH2 and cardiolipin synthesis.

#### Author

See lines 103-105 in revised MS:

*However, it should be noted that the authors of this paper found that abolishment of tBID-induced apoptosis can be achieved only by simultaneously downregulating MTCH2 and cardiolipin synthesis.*