Invadolysin, a conserved lipid droplet-associated protease interacts with mitochondrial ATP synthase and regulates mitochondrial metabolism in *Drosophila*

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ATP is the energy currency of the cell, essential for proper biological functioning. It is used for numerous processes including cell division, cellular migration, organelle transport and development. Oxidative phosphorylation within mitochondria generates most of the ATP. We investigated Invadolysin (inv), a conserved metalloprotease that is essential for fly development, showing that it binds to ATP synthase and might play a role in regulating mitochondrial function.

Invadolysin homozygous *Drosophila* mutants are third instar larval lethal and exhibit pleiotropic phenotypes. These include defects in cell cycle progression, nuclear envelope dynamics and germ cell migration, indicating that Invadolysin must have a critical role in *Drosophila*.

In order to better understand these roles, we identified genetic interactors of invadolysin by performing an enhancer/supressor misexpression screen. Screening against the Drosdel ‘deficiency kit’ identified numerous genetic interactors including genes linked to energy regulation, glucose and fatty acid pathways.

Human cell culture experiments showed the *H. sapiens* Invadolysin localises to the surface of lipid droplets (LD). Lipid droplets are highly dynamic organelles that are vital energy stores, but also important in protein sequestration, protein and membrane trafficking, and cell signaling. We investigated the *Drosophila* fat body, the ortholog of vertebrate liver and adipose tissue, linking the loss of invadolysin with lipid metabolism and storage, confirming the genetic data.

Then we generated transgenic fly lines to identify physical interactors of Invadolysin. Subsequent mass spectrometry analysis identified ATP synthase-α, -β and -δ as interactors. This result linked Invadolysin to mitochondrial regulation. Further *in vivo* and *in vitro* experiments confirmed this hypothesis. Taken together this data lead us to propose a model for the interaction between ATP synthase and Invadolysin, showing it to be essential for proper mitochondrial function in *Drosophila*. 