The histone modifier KDM5 links cell cycle regulation with endocrine control of development in *Drosophila*

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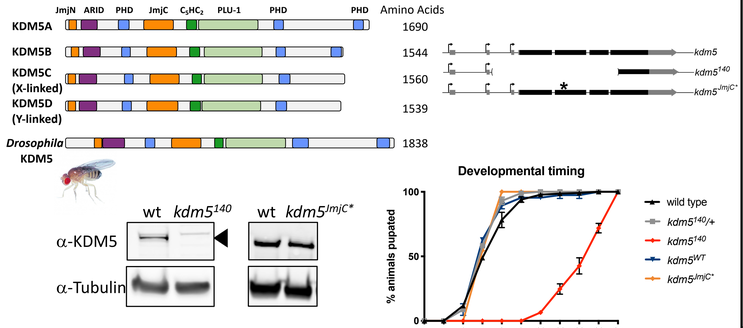
KDM5 null mutant model: *kdm5^{140}*

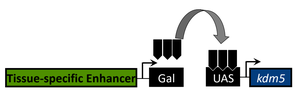
- In contrast to mammals, *Drosophila* have a single, highly-conserved ortholog of KDM5, an H3K4me3 histone demethylase.
- We have generated KDM5 null mutant (***kdm5^{140}***) and demethylase dead (*kdm5^{JmjC*}*) models.



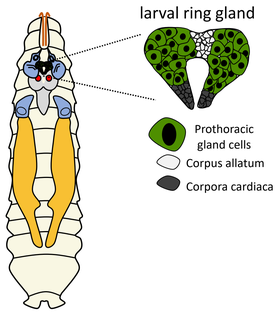
- Homozygous loss of KDM5 in *kdm5^{140}* animals results in a **developmental delay** and **lethality** in the pupal stage, but these phenotypes are independent of losing the demethylase activity.

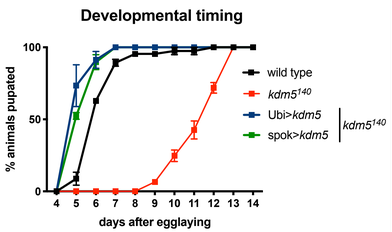
KDM5 reexpression in larval prothoracic gland rescues *kdm5^{140}* developmental delay and lethality

- Using the Gal4-UAS system, we screened for which tissues could rescue the phenotypes of *kdm5^{140}* animals through reexpression of KDM5.



Gal4 Driver	Expression pattern of driven KDM5	% of expected flies
None	-	0
Ubi-Gal4	Ubiquitous	83.5%
Mai60-Gal4	Prothoracic gland, Larval brain Imaginal discs	62%
Phm-Gal4	Prothoracic gland Leg and wing discs	44.5%
Spok-Gal4	Prothoracic gland	39%
CG-Gal4	Fat body, Hemocytes	0%
Dilp2-Gal4	Insulin-secreting cells of brain	1.5%
Akh-Gal4	Corpus cardiaca	0%
Aug21-Gal4	Corpus allatum, Salivary gland	2%

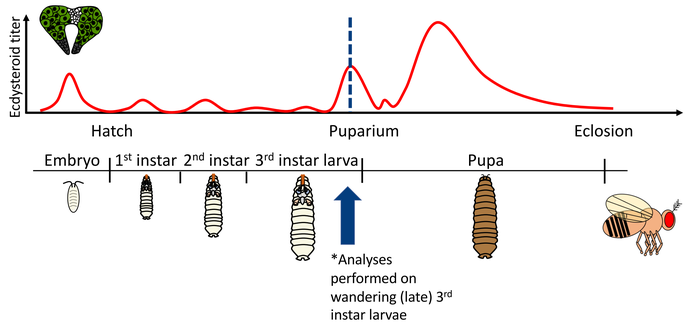




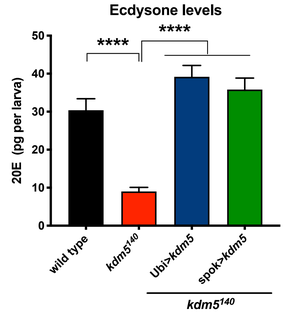
- Reexpression of KDM5 in the larval **prothoracic gland** alone via **spok-Gal4** is sufficient to rescue the defects in growth and adult viability due to loss of KDM5.

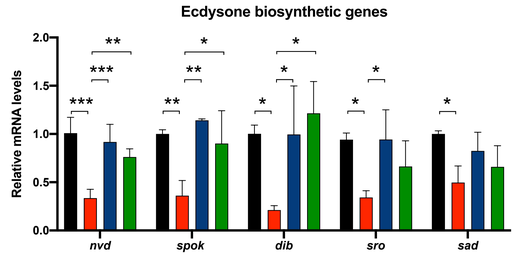
KDM5 plays a role in endocrine regulation through activating steroid hormone ecdysone biogenesis via Torso and the MAPK pathway

- The prothoracic gland is an endocrine tissue that produces the steroid hormone **ecdysone**, a master regulator of growth and developmental transitions throughout the life cycle.

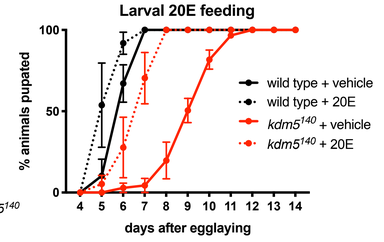


- **spok>*kdm5*** rescues the decreased circulating levels of the active form of ecdysone (20E) in *kdm5^{140}* animals.

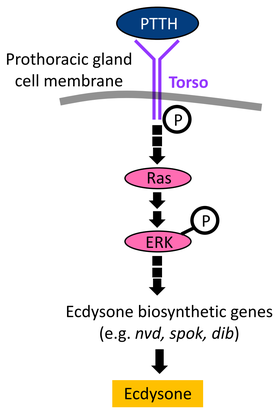




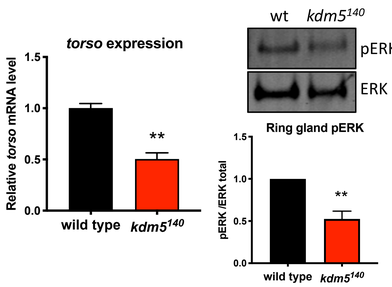
- **spok>*kdm5*** also rescues some of the *kdm5^{140}* defects in the expression of genes within the **ecdysone biosynthetic pathway**.



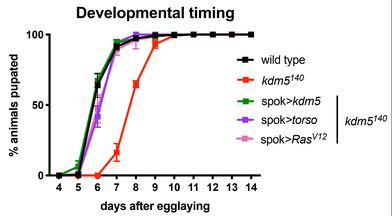
- Feeding *kdm5^{140}* larvae active ecdysone is sufficient to **rescue developmental timing, but not the lethality.**



- PTTH is a larval brain-derived neuropeptide that stimulates the prothoracic gland through the **Torso** receptor tyrosine kinase and downstream **MAPK pathway** to produce ecdysone.



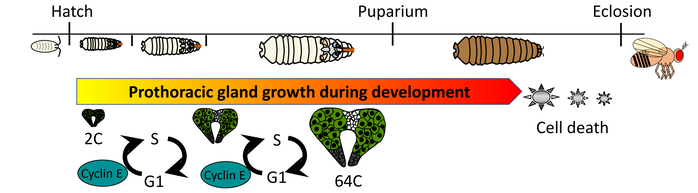
- *kdm5^{140}* larvae a show **reduced Torso** expression and **reduced MAPK signalin**g via phospho-ERK.



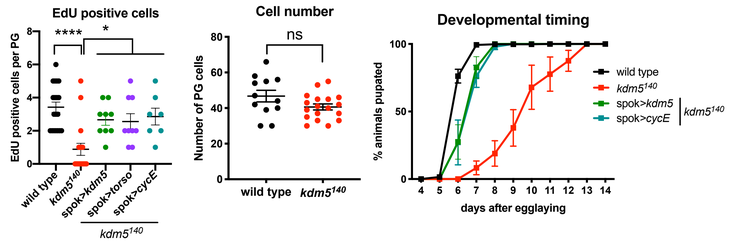
- Furthermore, ectopic activation of this **Torso/MAPK** pathway in the prothoracic gland using the via **spok>*torso*** or spok>*Ras^{V12}* **rescues both the developmental delay and lethality** of *kdm5^{140}* animals.

KDM5 promotes Cyclin E-mediated endoreplication in prothoracic gland cells

- Prothoracic gland cells undergo **multiple rounds of endocycles** that increase ploidy up to 64C and are thought to upregulate the ecdysone biosynthetic genes to produce the ecdysone pulses required for development.

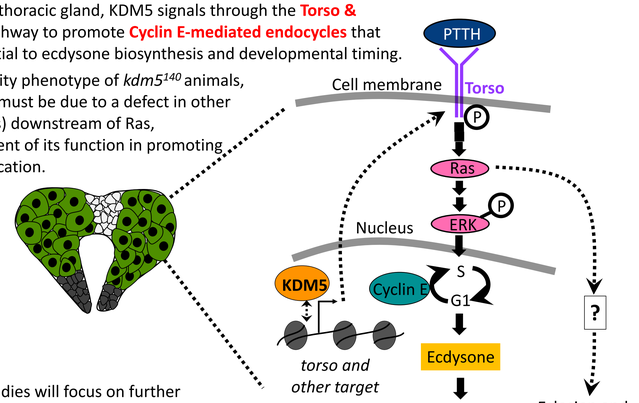


- *kdm5^{140}* mutants display defects in endocycling, and ectopically driving endocycles in the prothoracic gland via **spok>*cyclin E*** is able to **rescue developmental delay, but not lethality.**



Conclusions & Future Directions

- **KDM5** is an **essential gene** in *Drosophila* that plays several roles in coordinating proper developmental timing and adult viability.
- In the prothoracic gland, KDM5 signals through the **Torso & MAPK** pathway to promote **Cyclin E-mediated endocycles** that are essential to ecdysone biosynthesis and developmental timing.
- The lethality phenotype of *kdm5^{140}* animals, however, must be due to a defect in other pathway(s) downstream of Ras, independent of its function in promoting endoreplication.



- Future studies will focus on further characterizing the **KDM5-regulated cellular pathways** required for adult viability.
- We will also perform **transcriptomic and genomic analyses** to better understand the mechanisms and targets of KDM5 transcriptional regulation within prothoracic gland cells.

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