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Notch pathway inhibition with DAPT diminishes tumor growth and hormone secretion in GH3 xenografted NUDE/NUDE mice.

Zubeldia Brenner L, Carolina Cristina y Damasia Becú-Villalobos.

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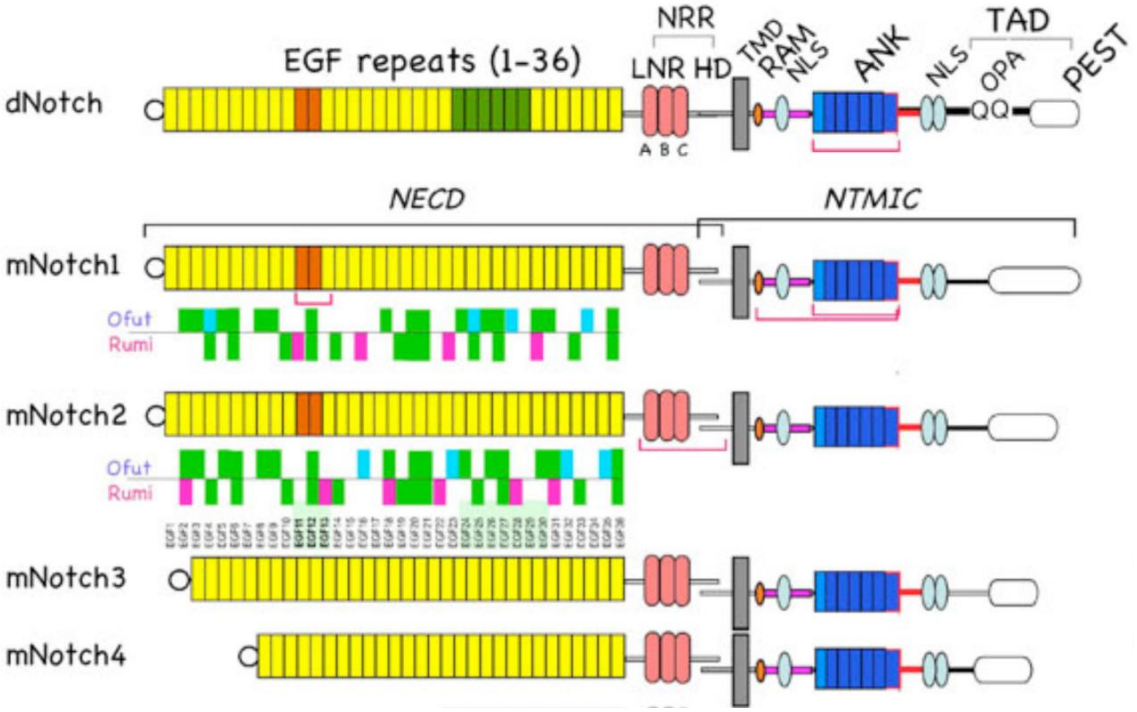
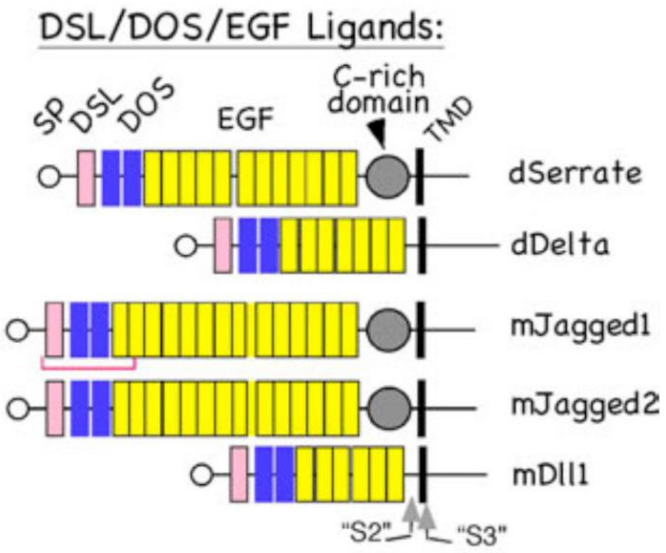
Notch System

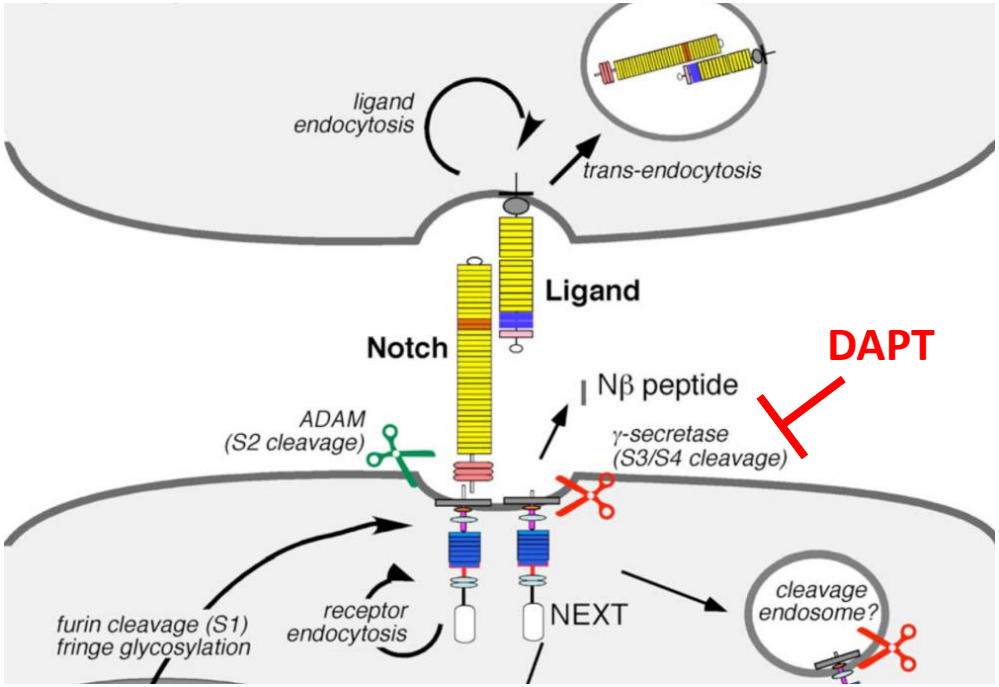
Receptors



Ligands



Notch pathway and tumor development.



- Cell-cell signaling system that primarily **governs cell-fate choices**.

- In a context dependent manner: **promotes or suppresses proliferation**.

- Controls the balance between commitment to differentiated state and repression of differentiation, **promoting proliferation of the undifferentiated cells. Also, has a critical role in angiogenesis.**

- **Misregulated Notch signaling has been demonstrated in various human cancers.**

Notch aberrant signaling has been described with critical roles in:

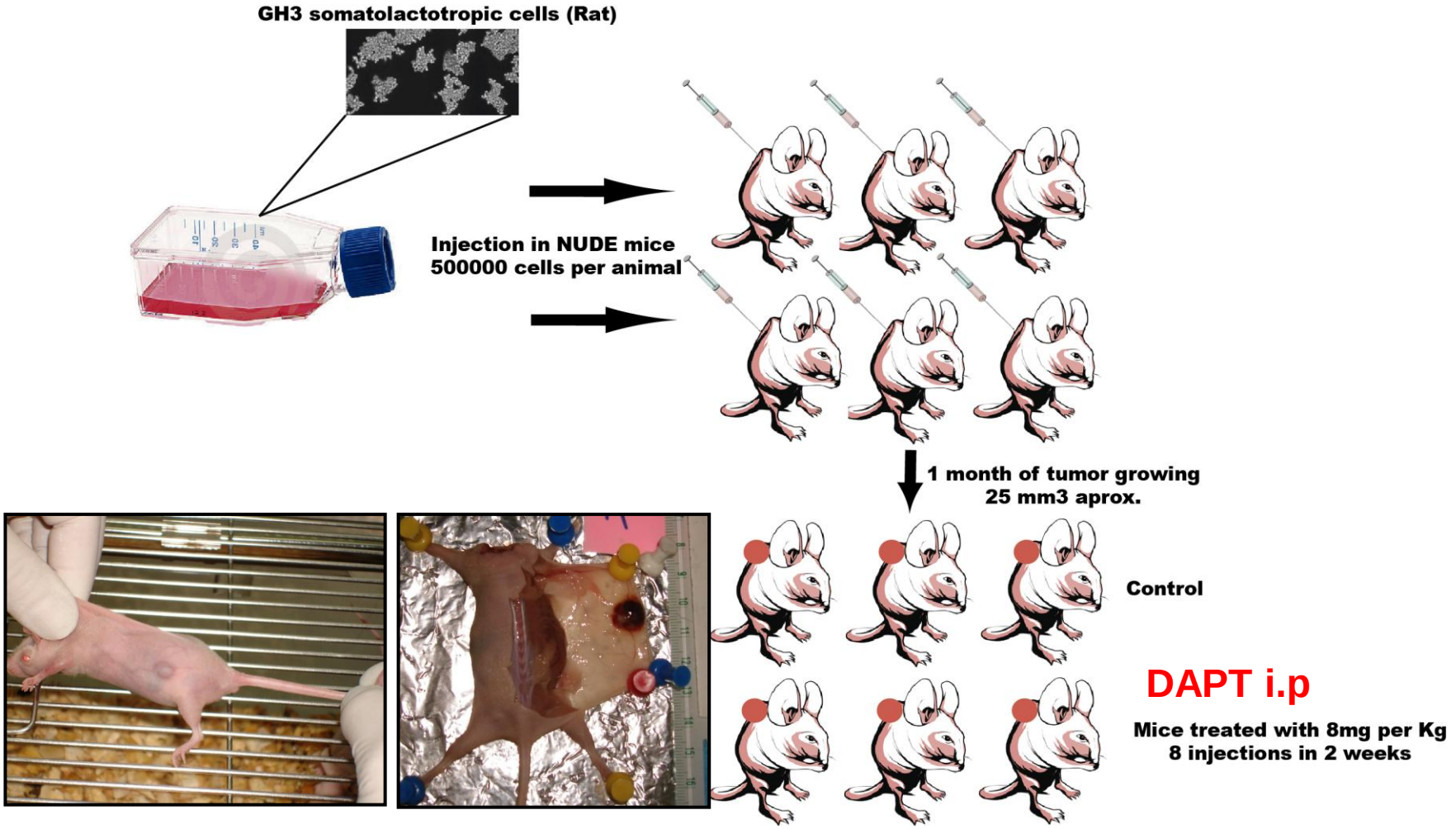
1. Breast cancer.
2. Colon cancer.
3. Pancreas cancer.
4. Lung adenocarcinoma.
5. T-cell acute lymphoblastic leukemia (T-ALL).
6. Others.

In some cases stimulating and in others inhibiting proliferation.

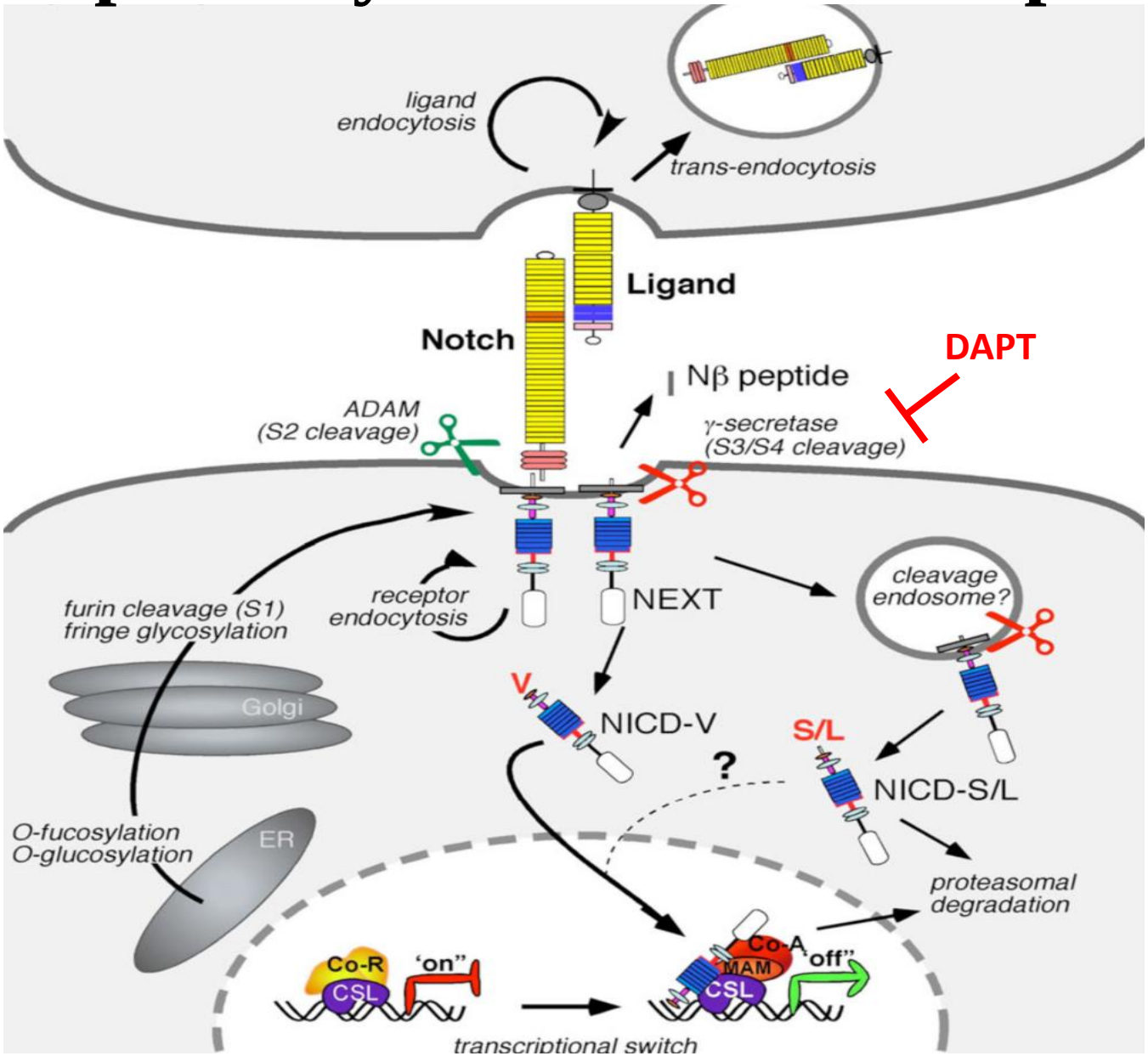
Main goal of the work

- **Determine the role of Notch signaling in pituitary tumor generation.**

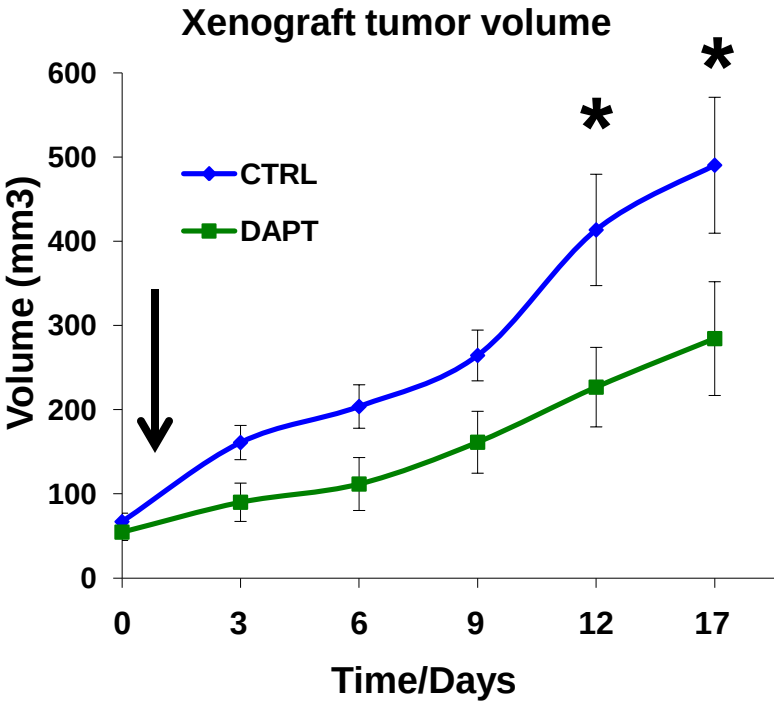
Experimental procedures: GH3 Xenografted tumors.

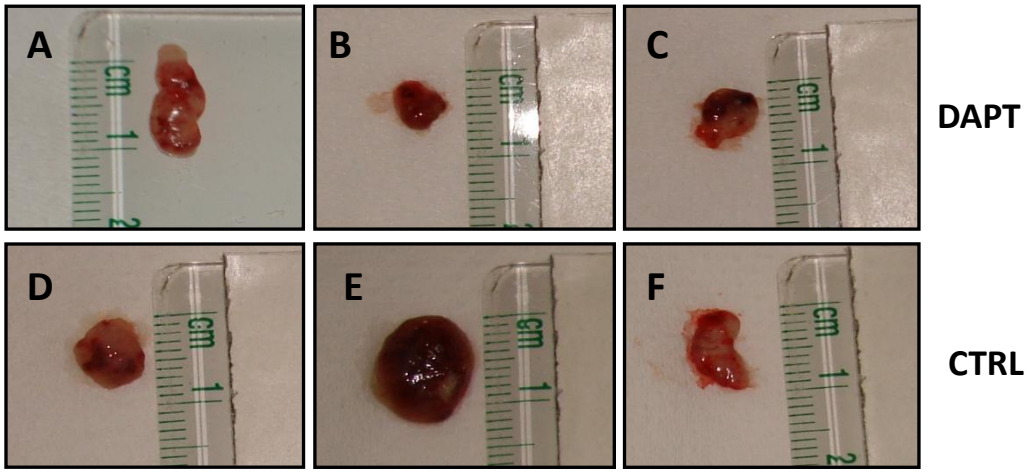


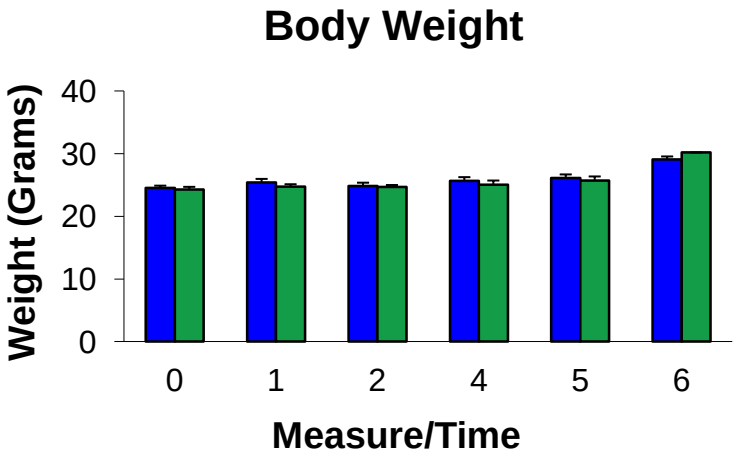
Notch pathway and tumor development.



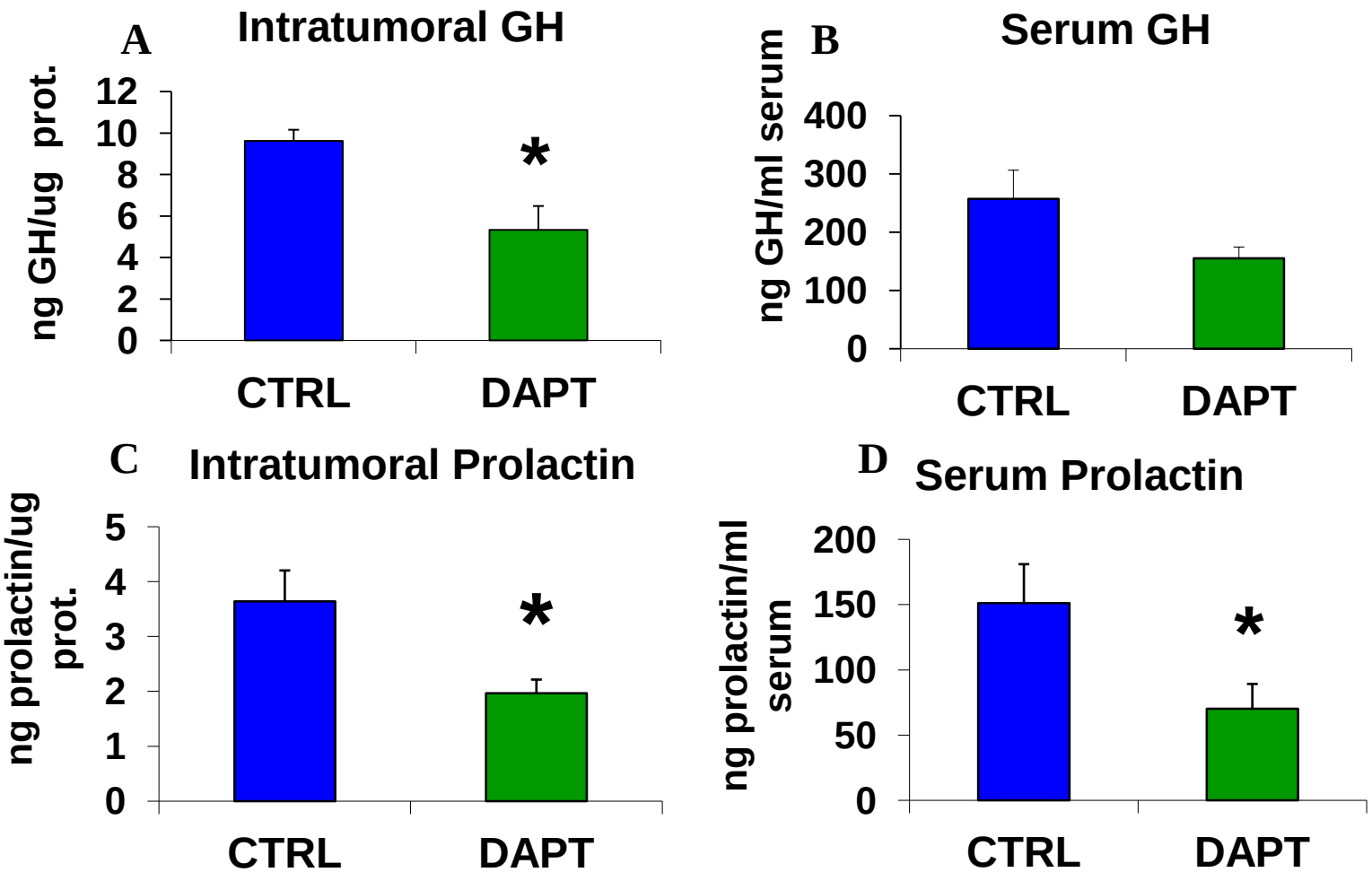
Notch pathway inhibition with DAPT blocks tumor growth.



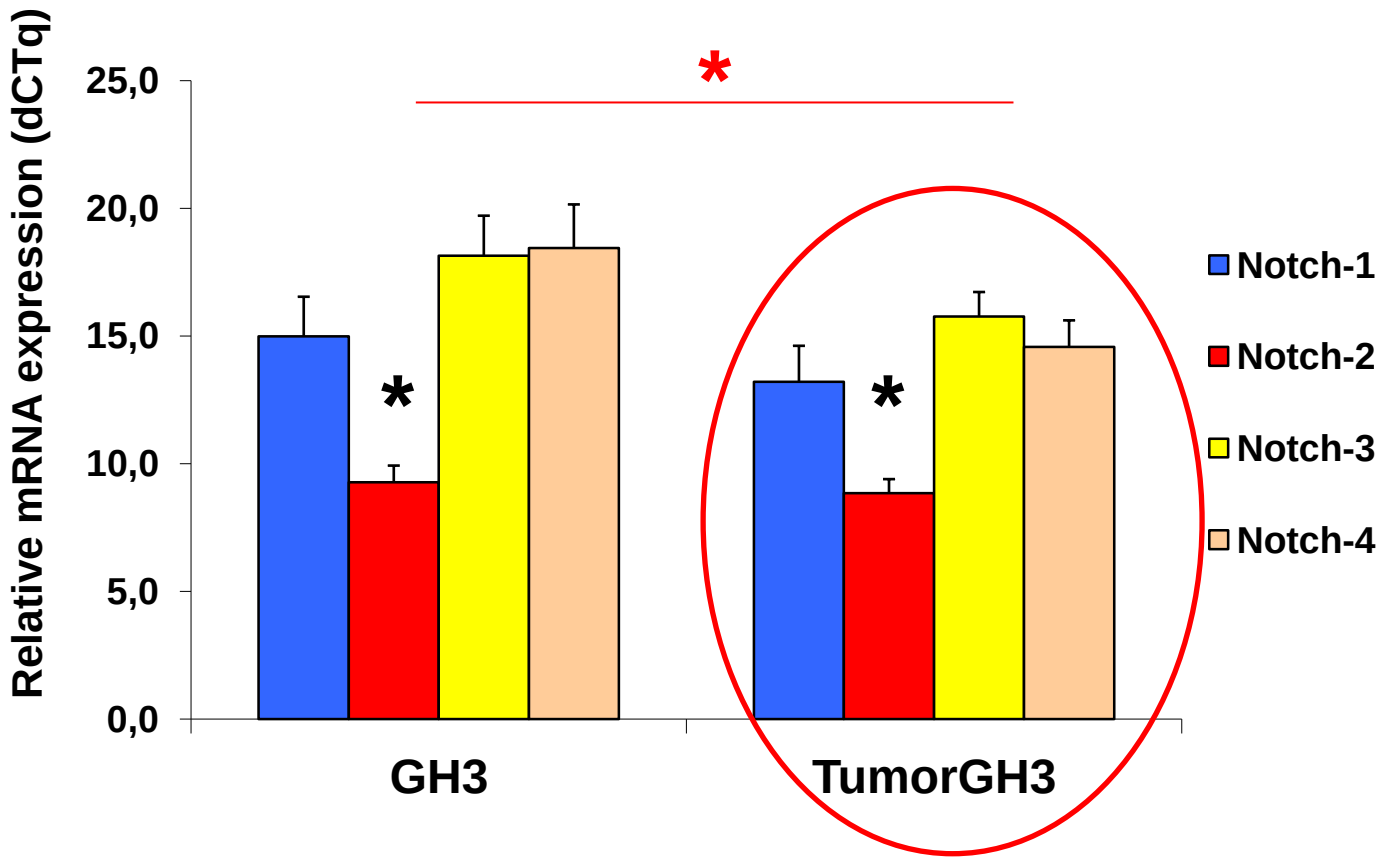




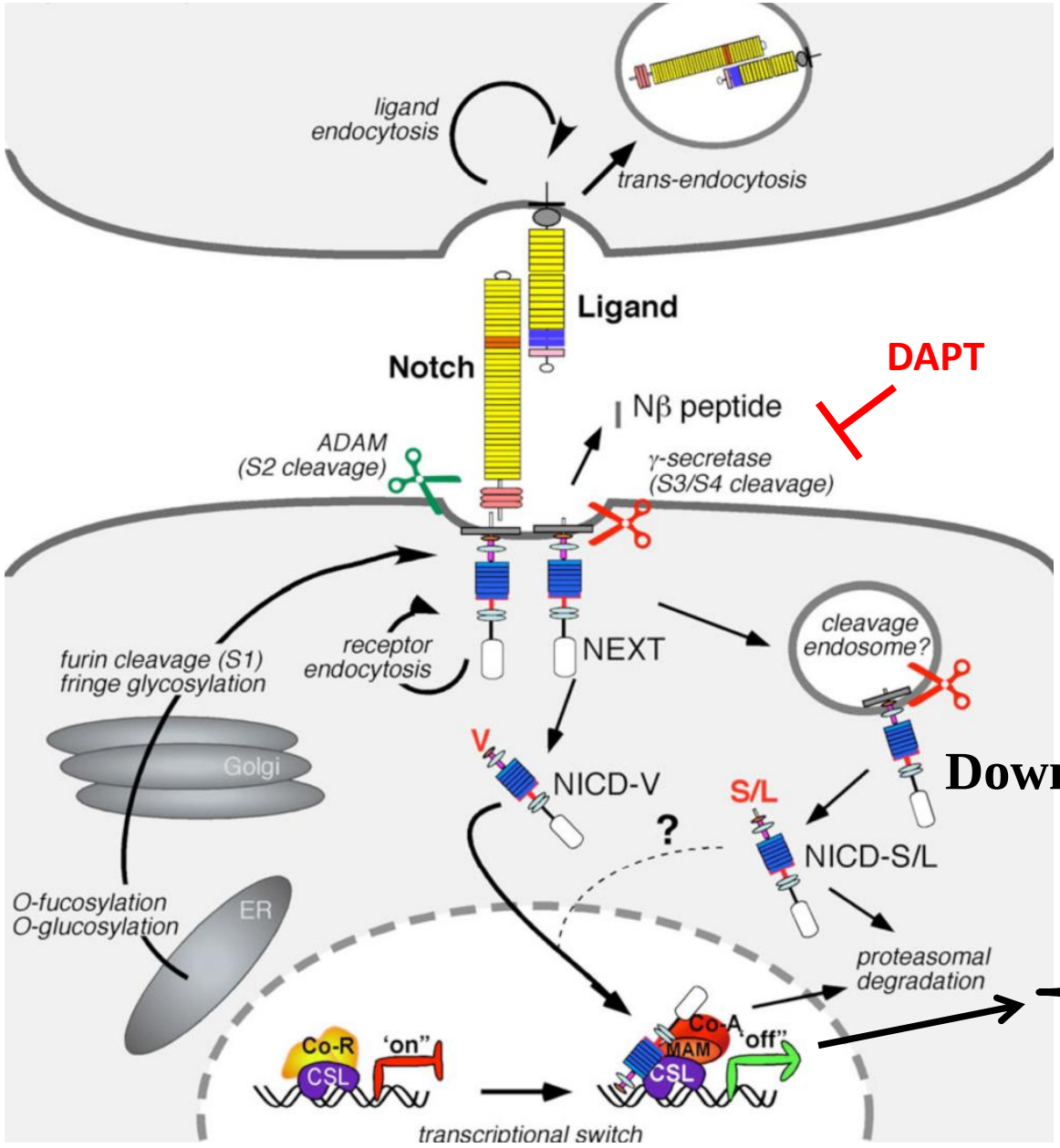
DAPT treatment modifies the tumor secretory activity.



Notch mRNA expression in the parental line and xenografted tumor.



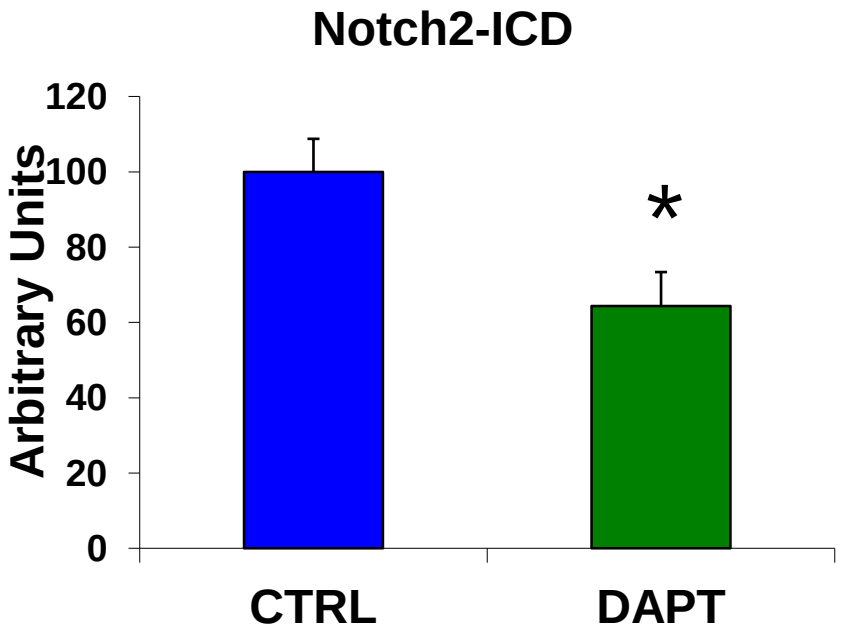
Notch pathway and its targets.

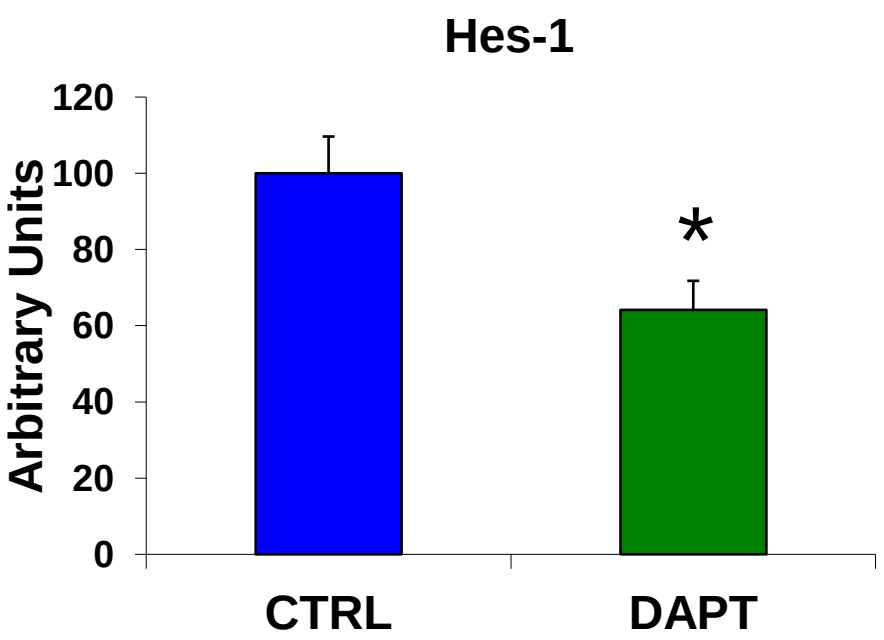


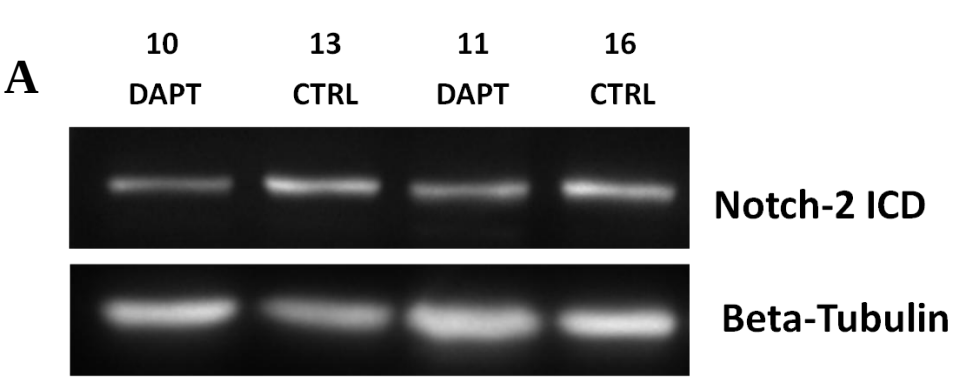
Downstream Effectors of Notch

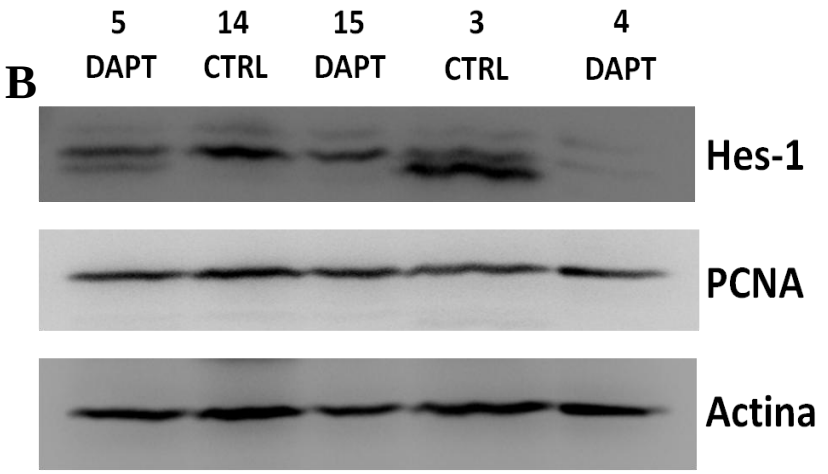
- Hes-1
- Hey-1
- Hey-2
- Cyclin D1
- Cyclin D3
- TGF beta

DAPT treatment decreases cleaved Notch-2, and Hes-1.

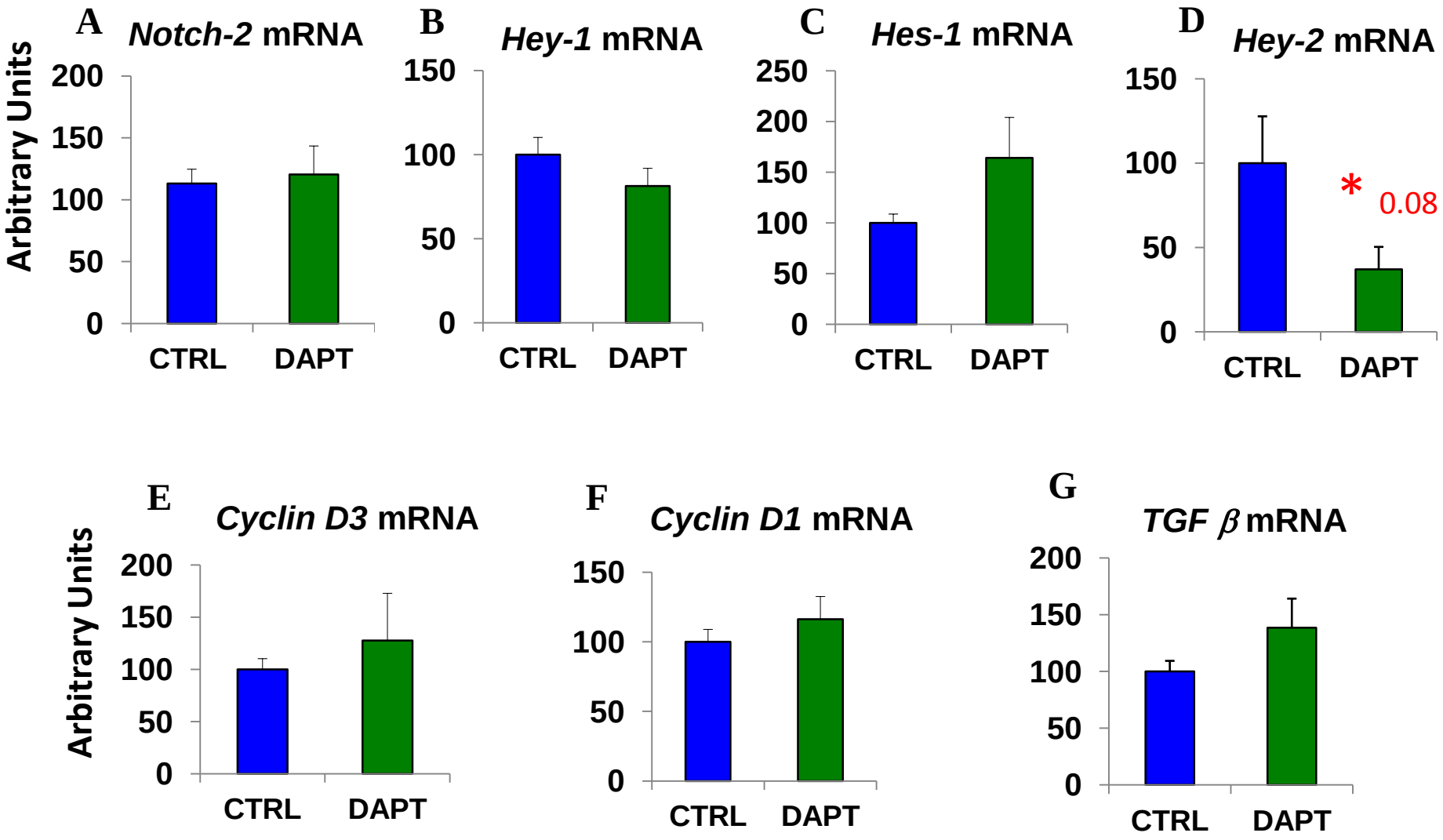






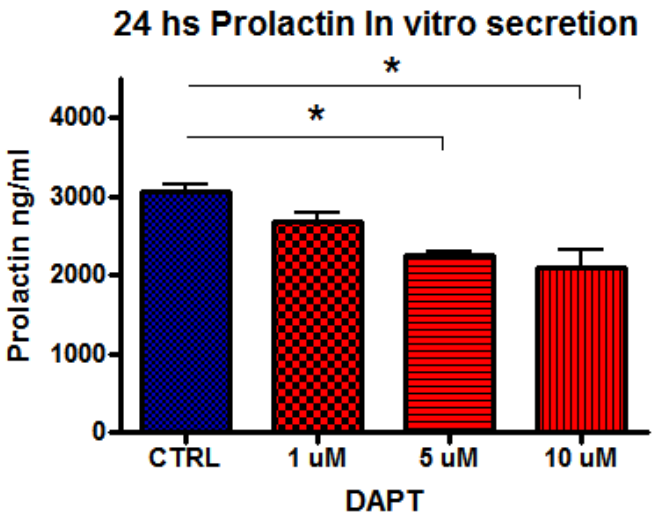


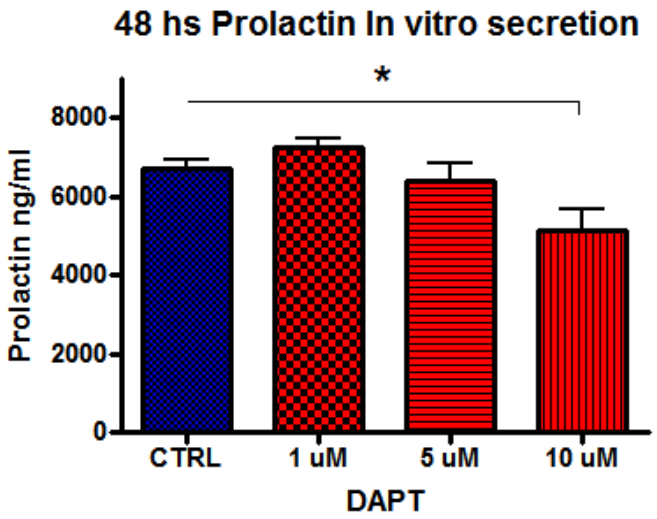
DAPT treatment modifies Notch pathway mRNA levels.

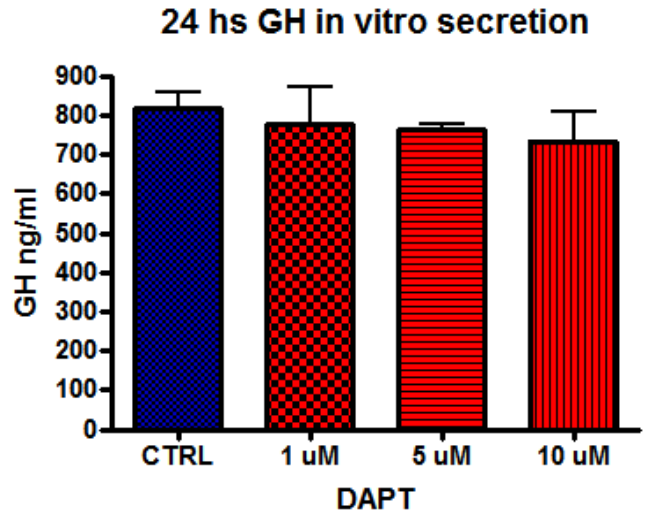


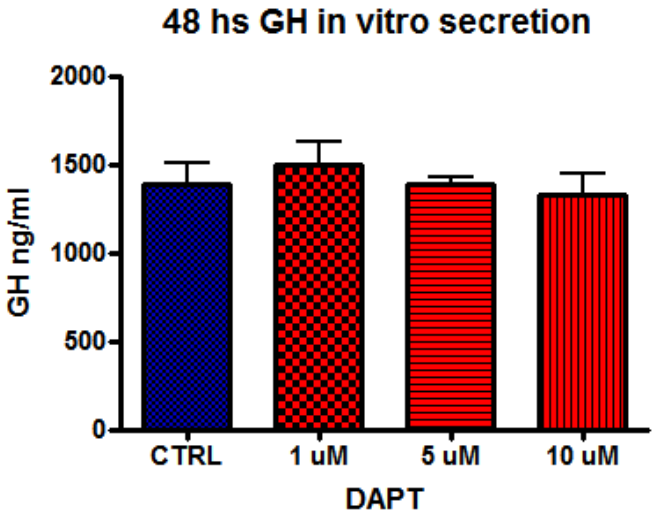
Effect of DAPT in Notch pathway in GH3 cells in vitro.

DAPT treatment modifies the secretory activity of GH3 cells *in vitro*.

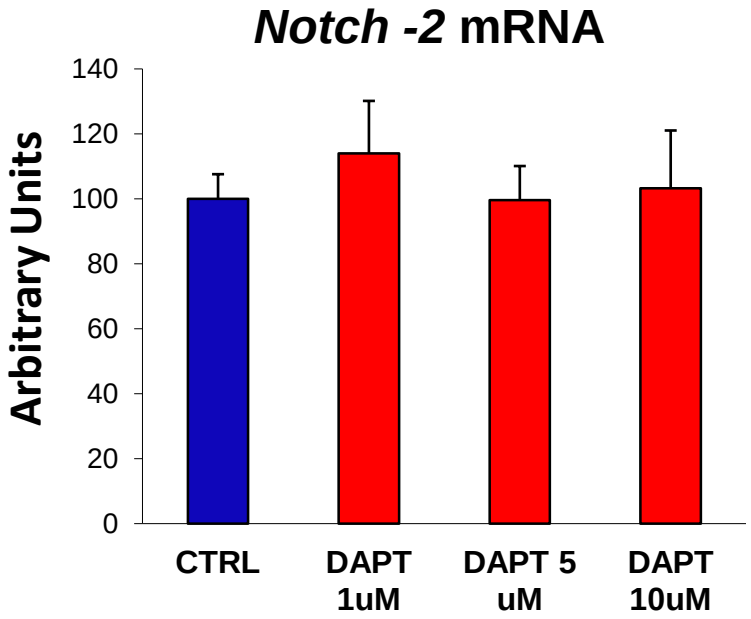


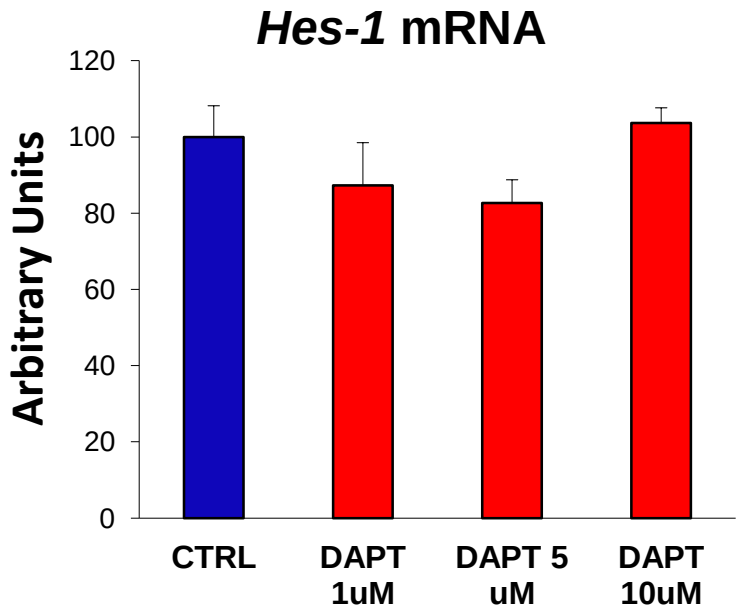


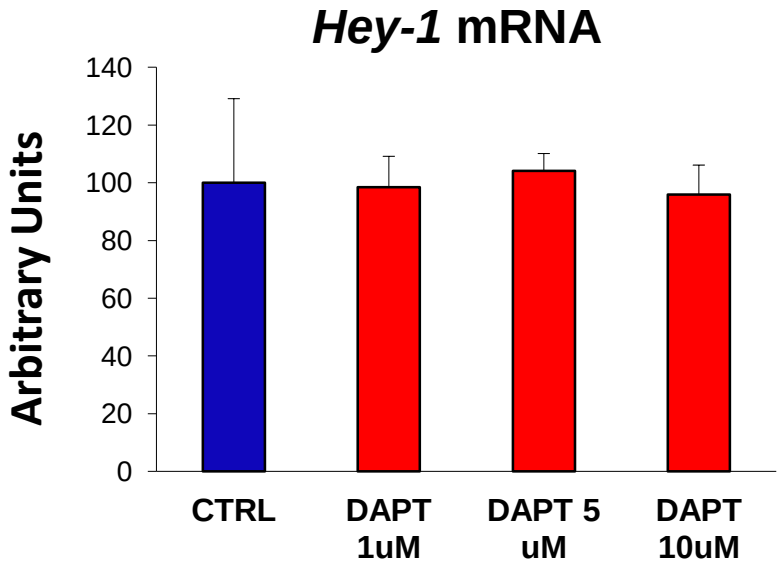




Effect of DAPT treatment for 48 hs on Notch pathway mRNA levels in GH3 cells in vitro.







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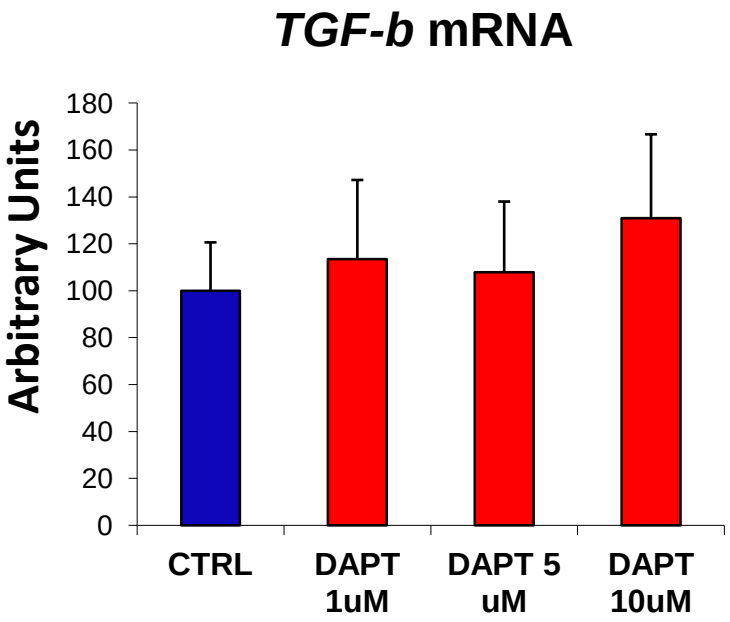
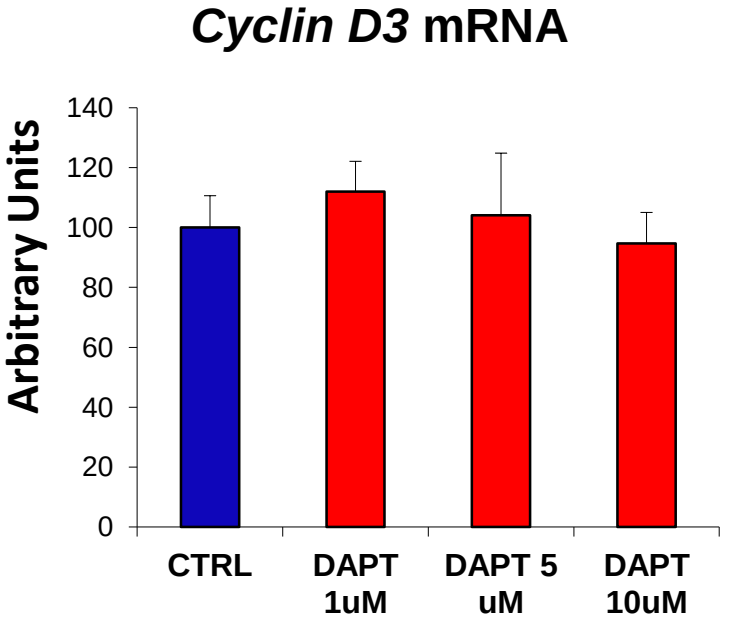
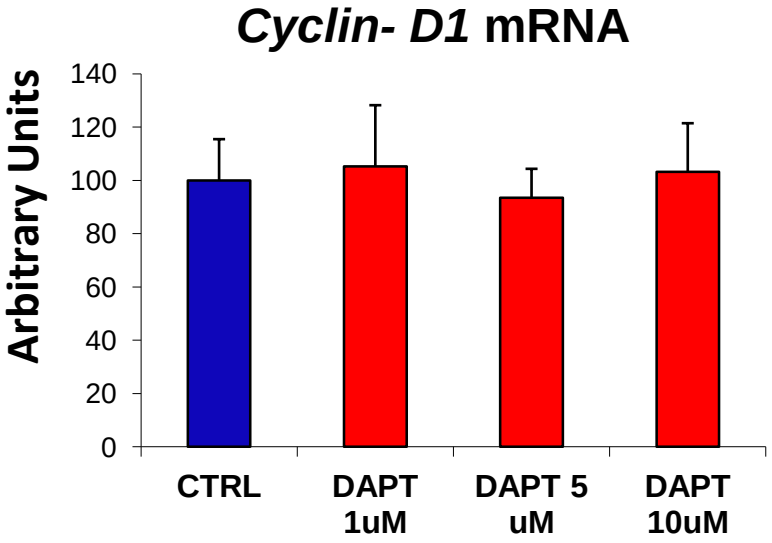
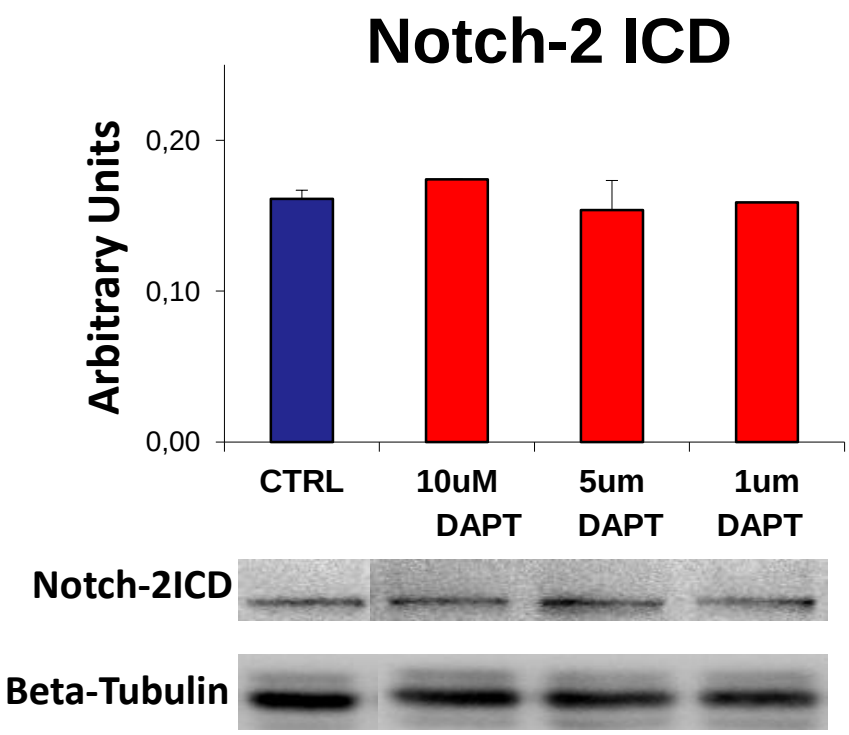
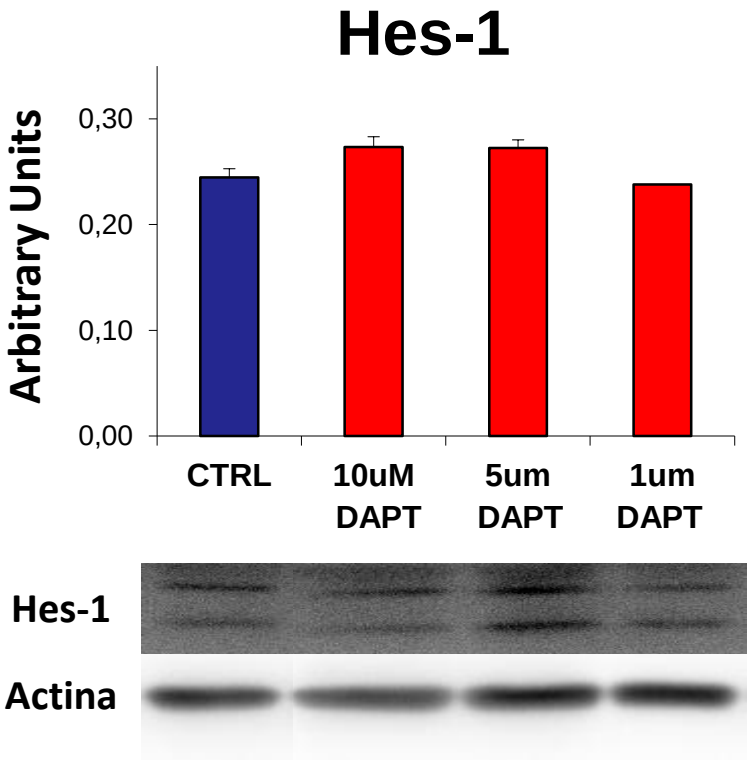






DAPT treatment did not modify Notch pathway protein levels in GH3 cells in vitro.





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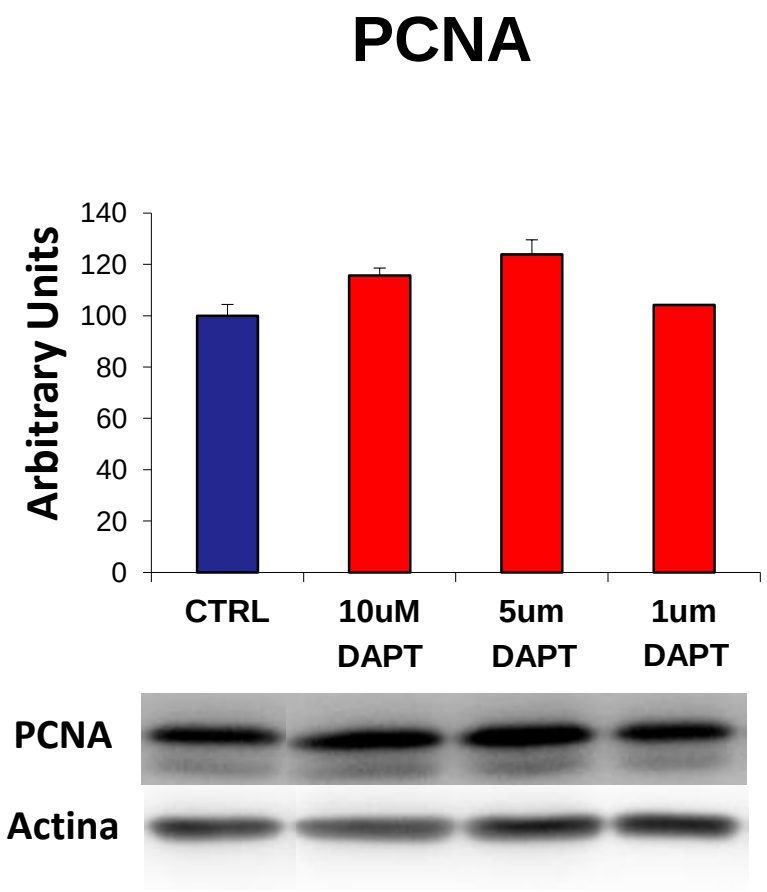
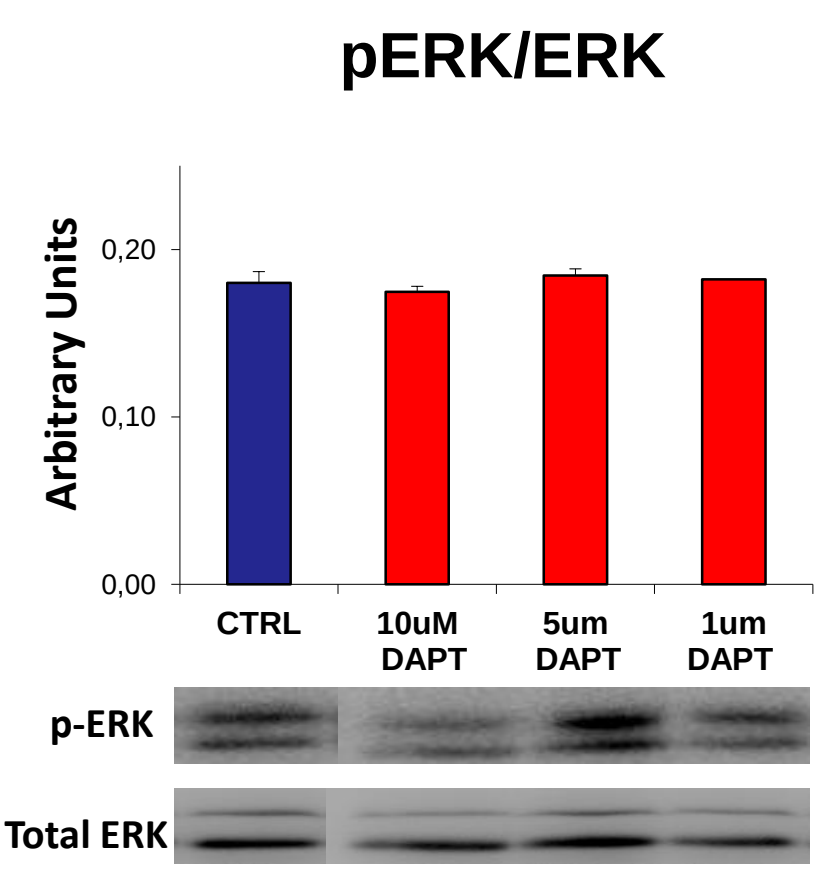
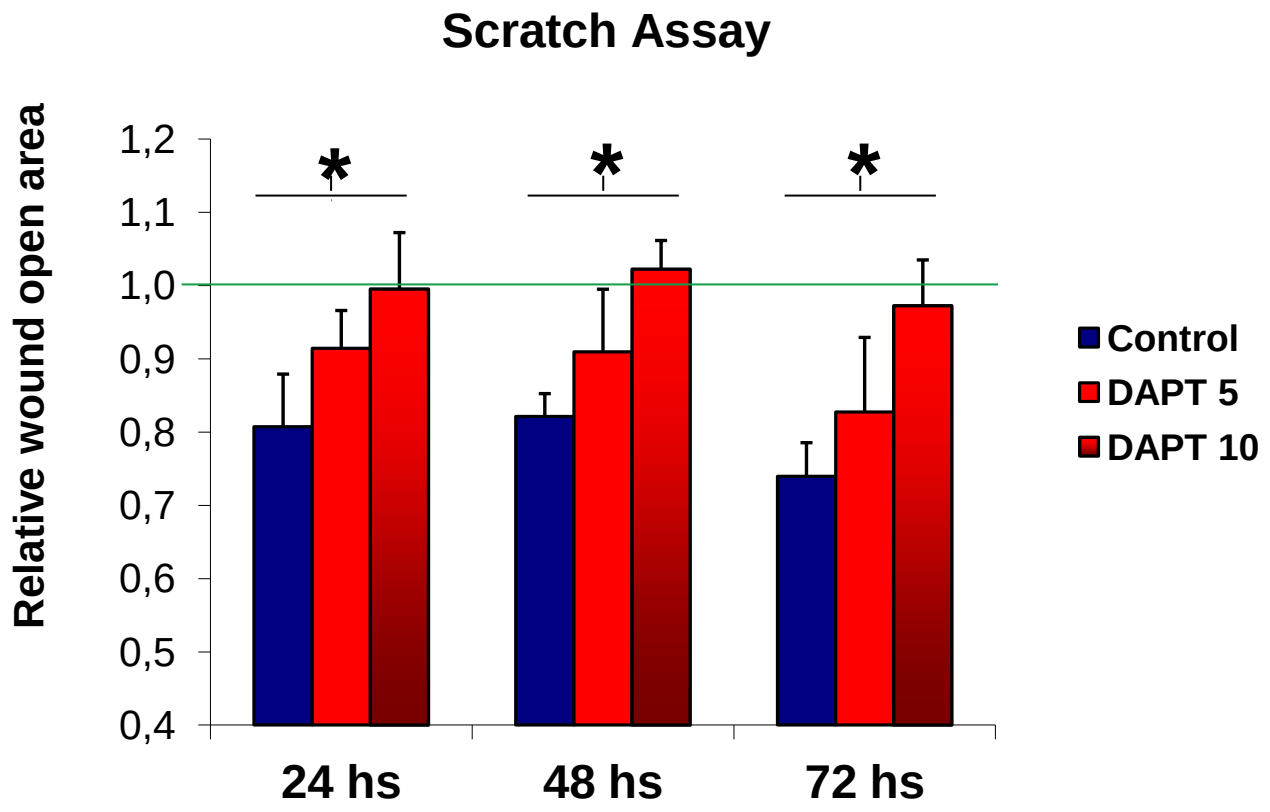
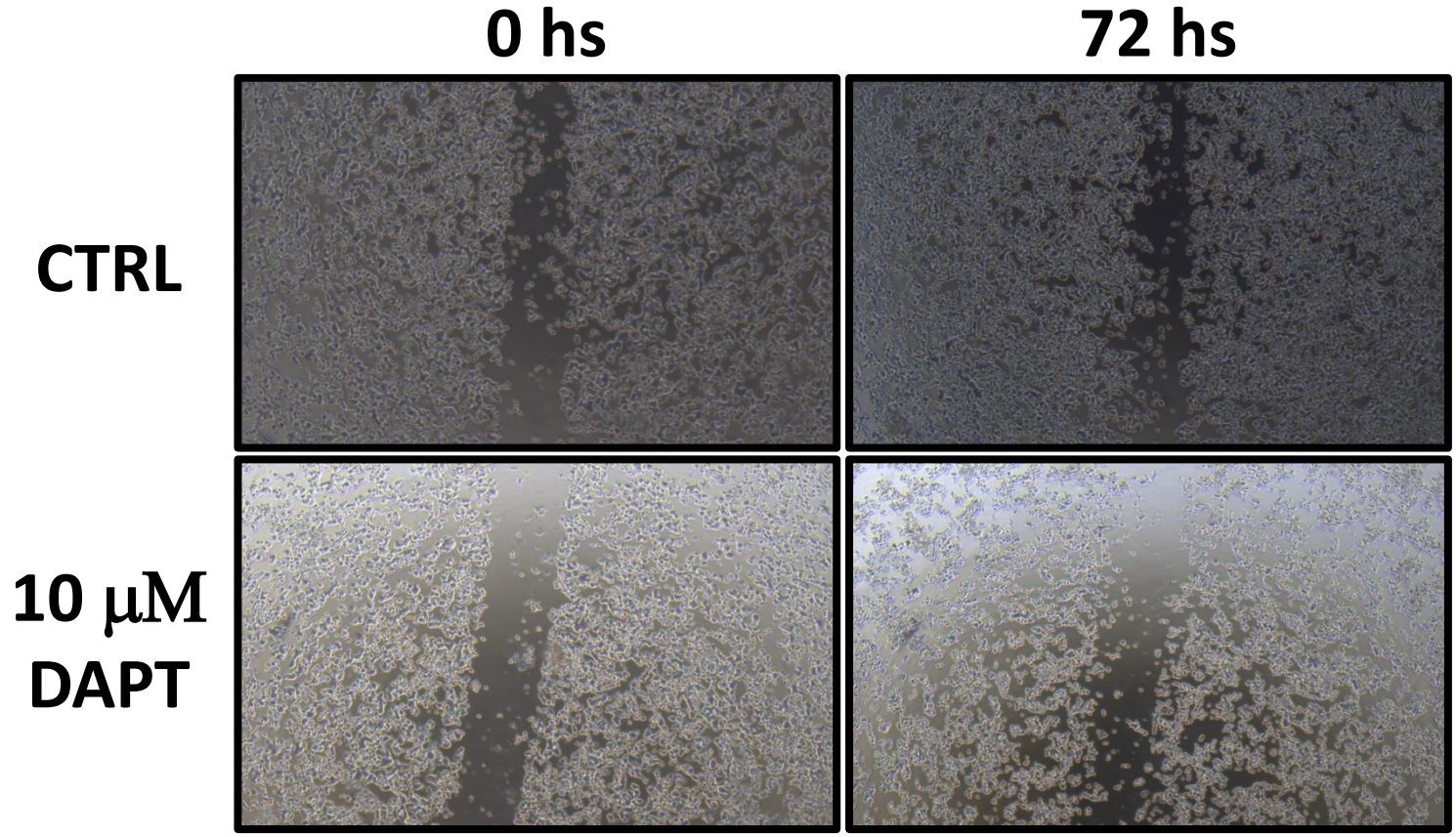




DAPT decreased migratory activity of GH3 cells in a Scratch assay.



DAPT blocks wound closure in GH3 cells in a Scratch assay.



Conclusions

In vivo Notch inhibition reduced:

- **Xenograft tumor growth.**
- **Hormone secretory activity.**
- **Cleaved Notch-2 and Hes-1 protein expression.**
- **And Hey-2 mRNA Expression.**

In vitro Notch inhibition reduced:

- **GH3 cell secretory activity.**
- **And wound healing, or migratory activity.**

These data highlight a fundamental role of Notch signaling in pituitary tumor generation.

¡¡Thank You Very Much!!