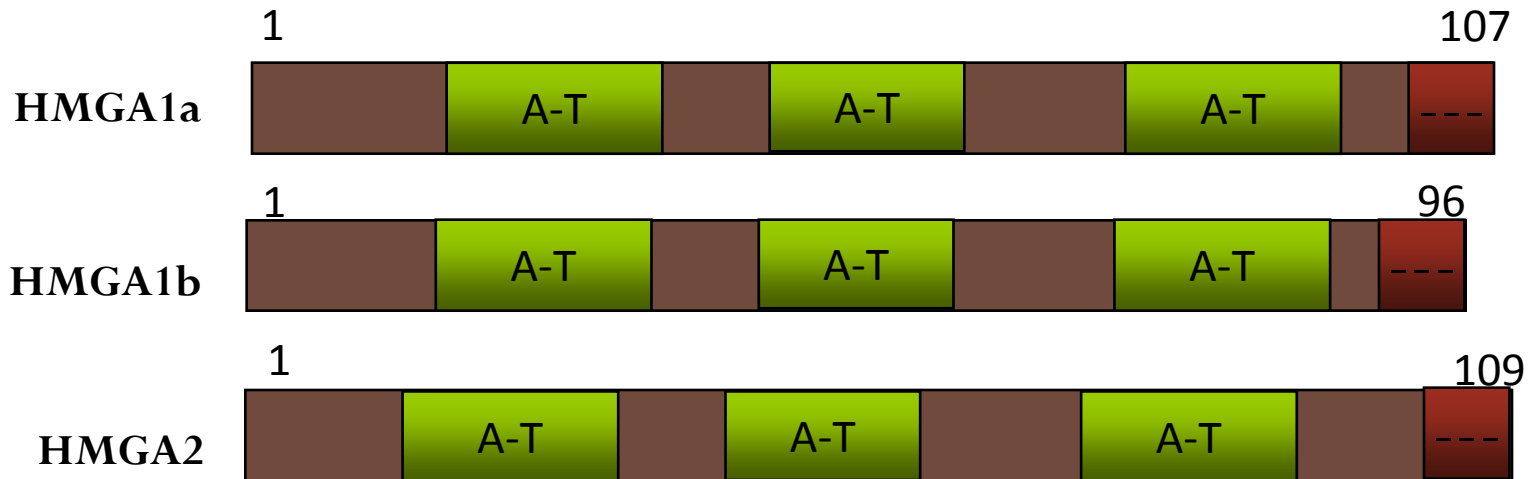


Regulation of *High Mobility Group A1* expression
by the Wnt β -catenin signaling pathway

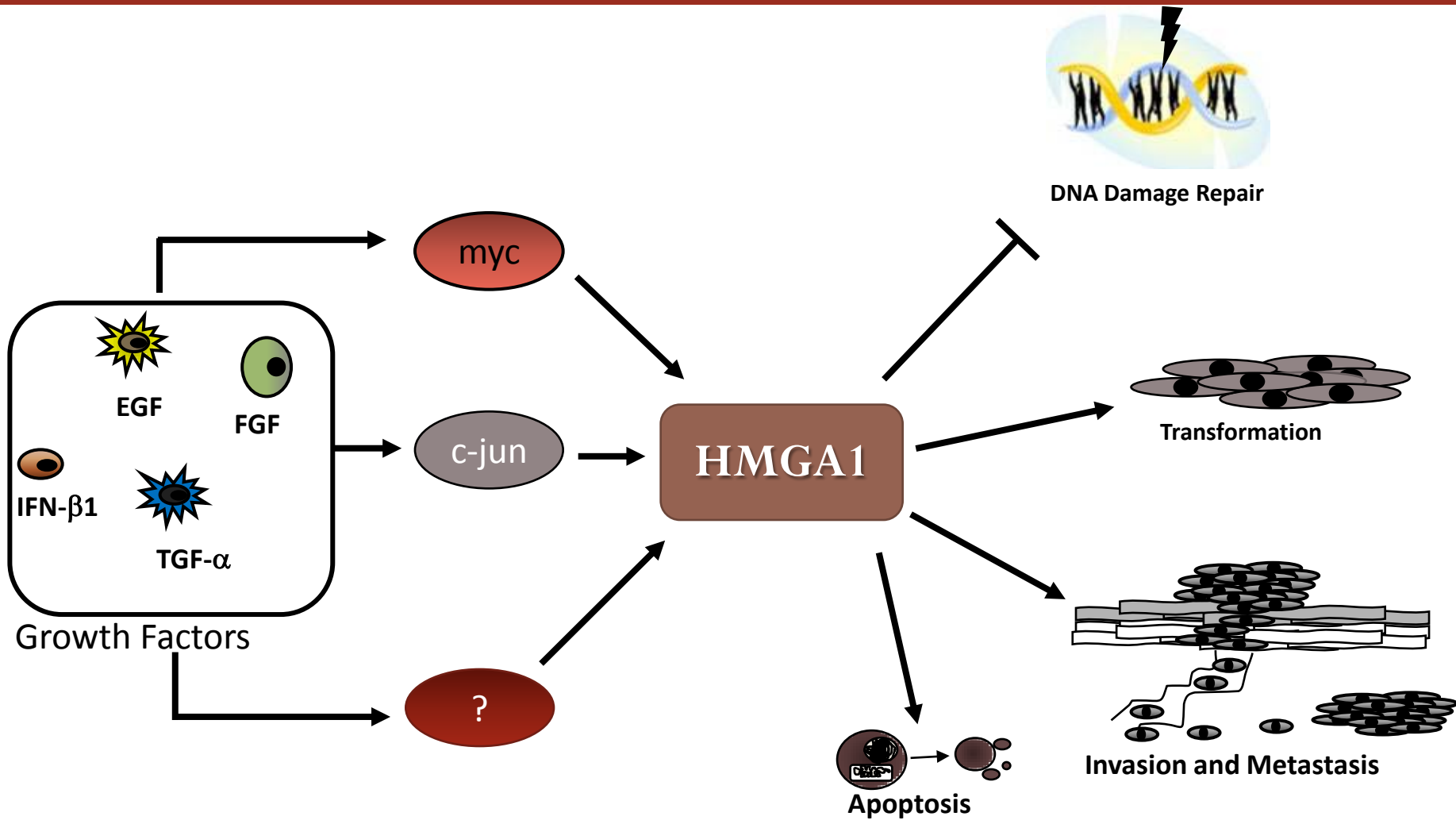
Takita Felder Sumter, Ph.D.
Associate Professor of Chemistry
Winthrop University

HMGA Gene Family

- The *HMGA1* gene encodes HMGA1a and HMGA1b which act as architectural chromatin binding proteins.
- HMGA2 is encoded by a separate gene.



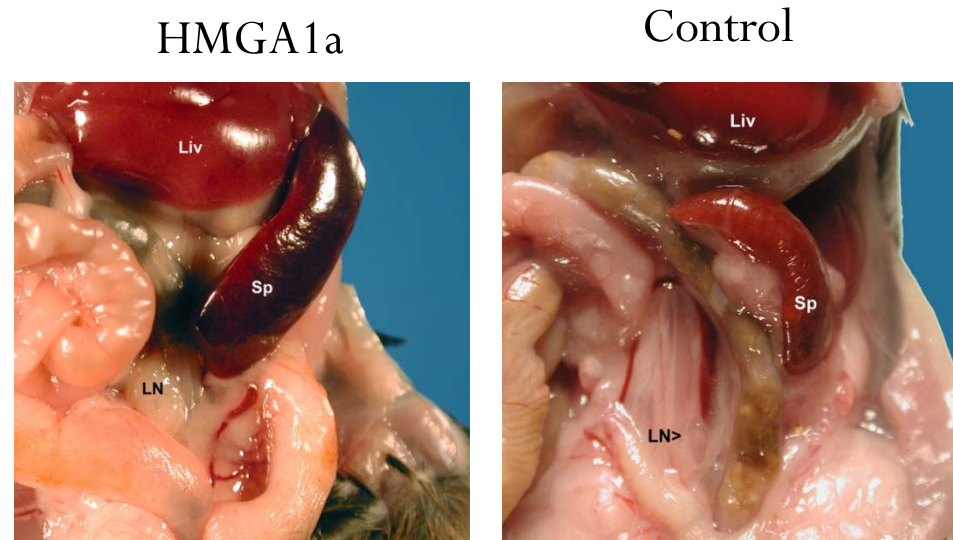
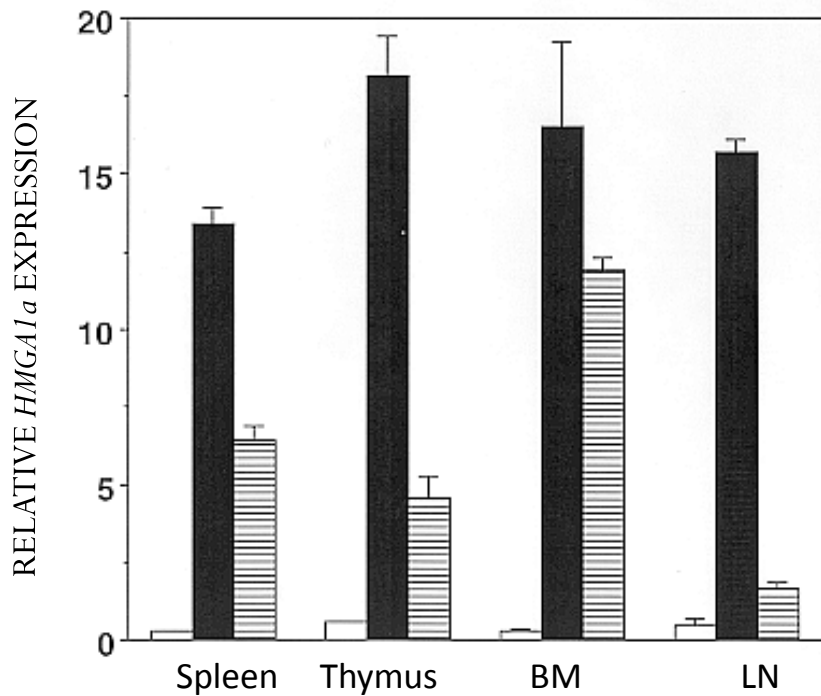
HMGA proteins participate in cell regulation



What are the processes that govern HMGA1 activation?

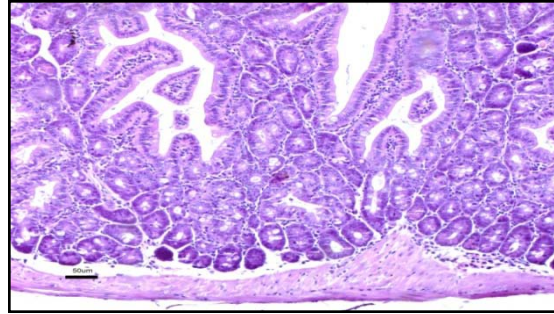
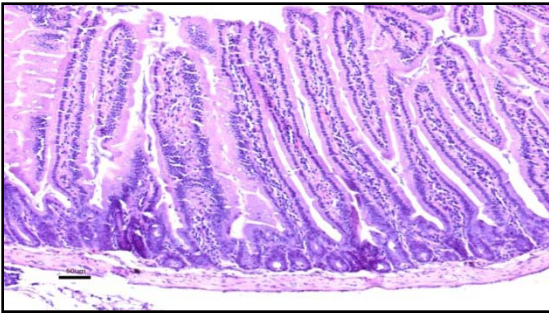
HMGA1a Transgenic mice develop lymphoid malignancy

➤ Transgenic Expression vector

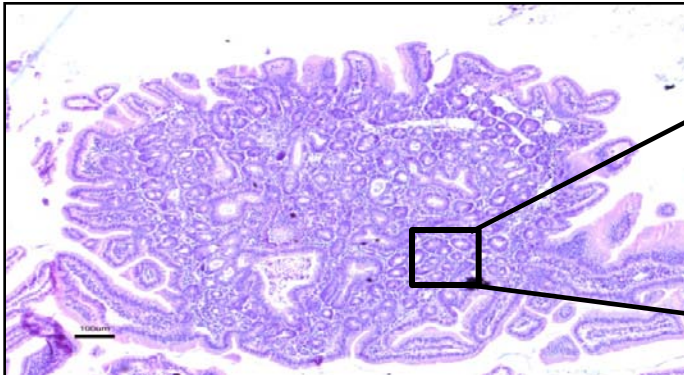


HMGA1a mice display proliferative changes in the small intestine

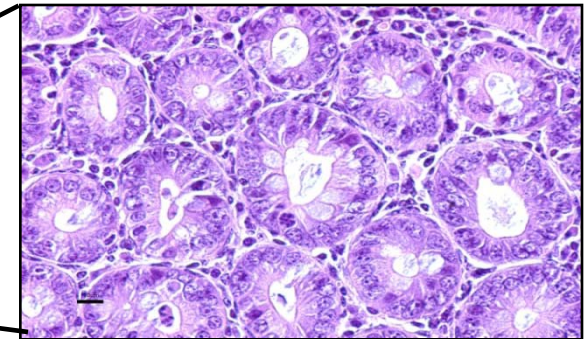
C57B6 crypt/villi structures HMGA1a Proliferative changes



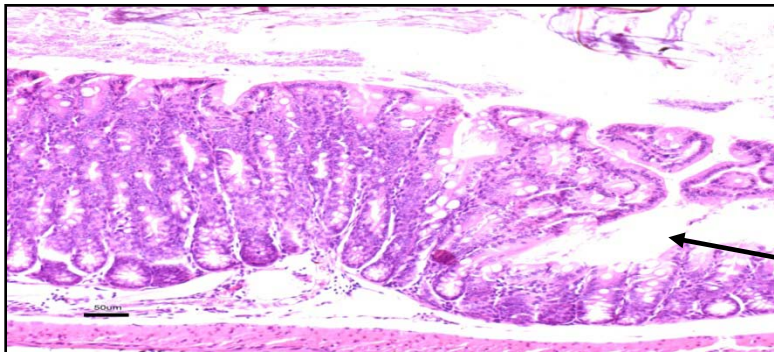
HMGA1a Polyp-like structure (2.5X)



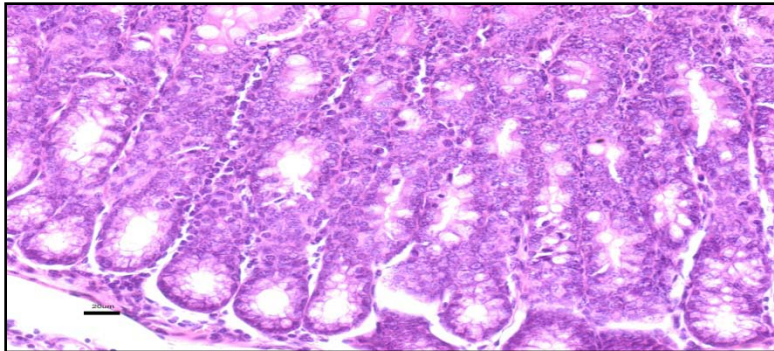
HMGA1a mitotic figures (40X)



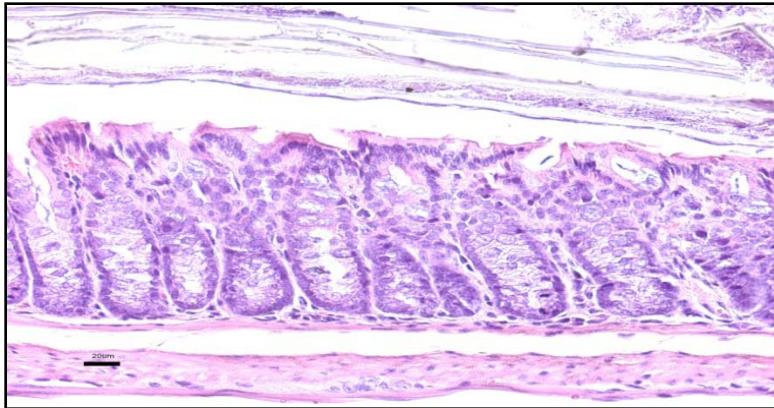
HMGA1a mice display proliferative changes in the colon



HMGA1a Colon: Flattened polyp-like growth (10X)



HMGA1a (20X)



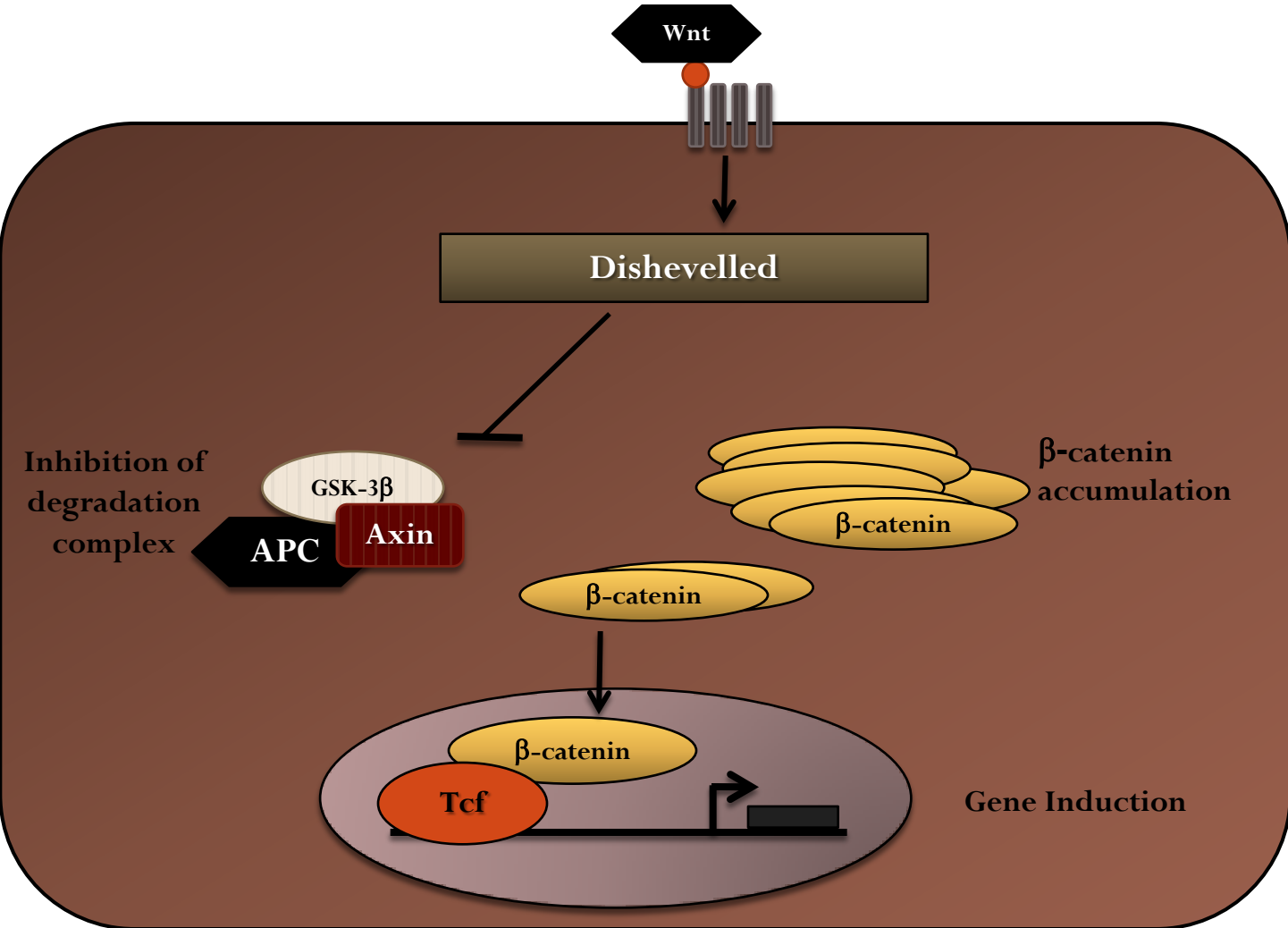
Control (20X)

What is the role of HMGA1 in colon cancer?

- HMGA1 is overexpressed in colorectal cancer
- Several HMGA1 target genes are important in colon cancer
 - COX-2, cyclin D, STAT3*

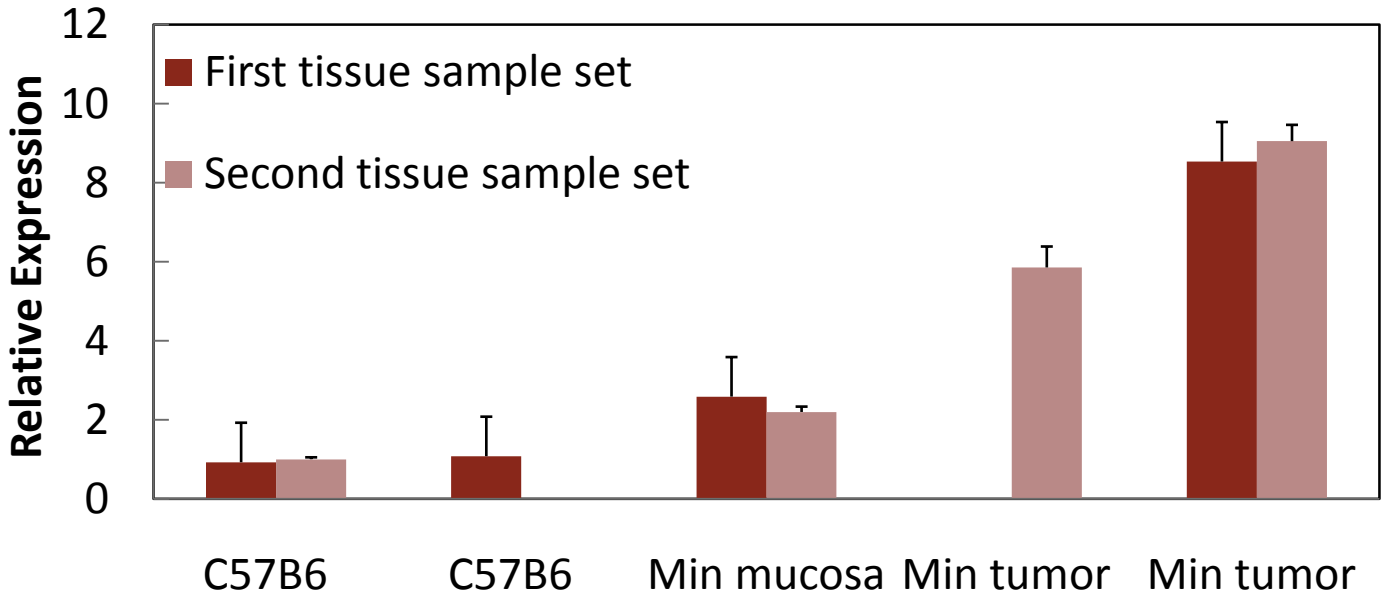
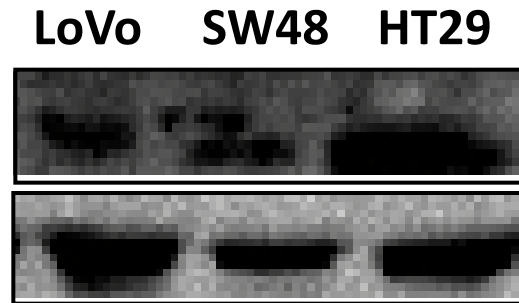
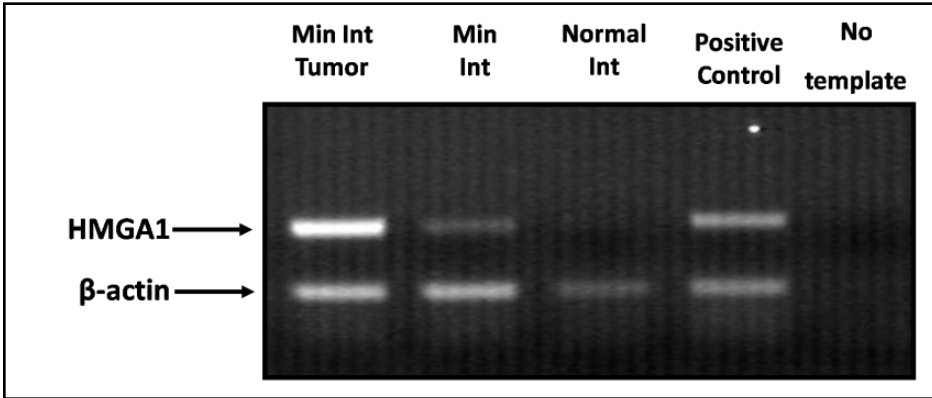
Hypothesis: HMGA1a is a target of Wnt signaling

The canonical Wnt signaling pathway

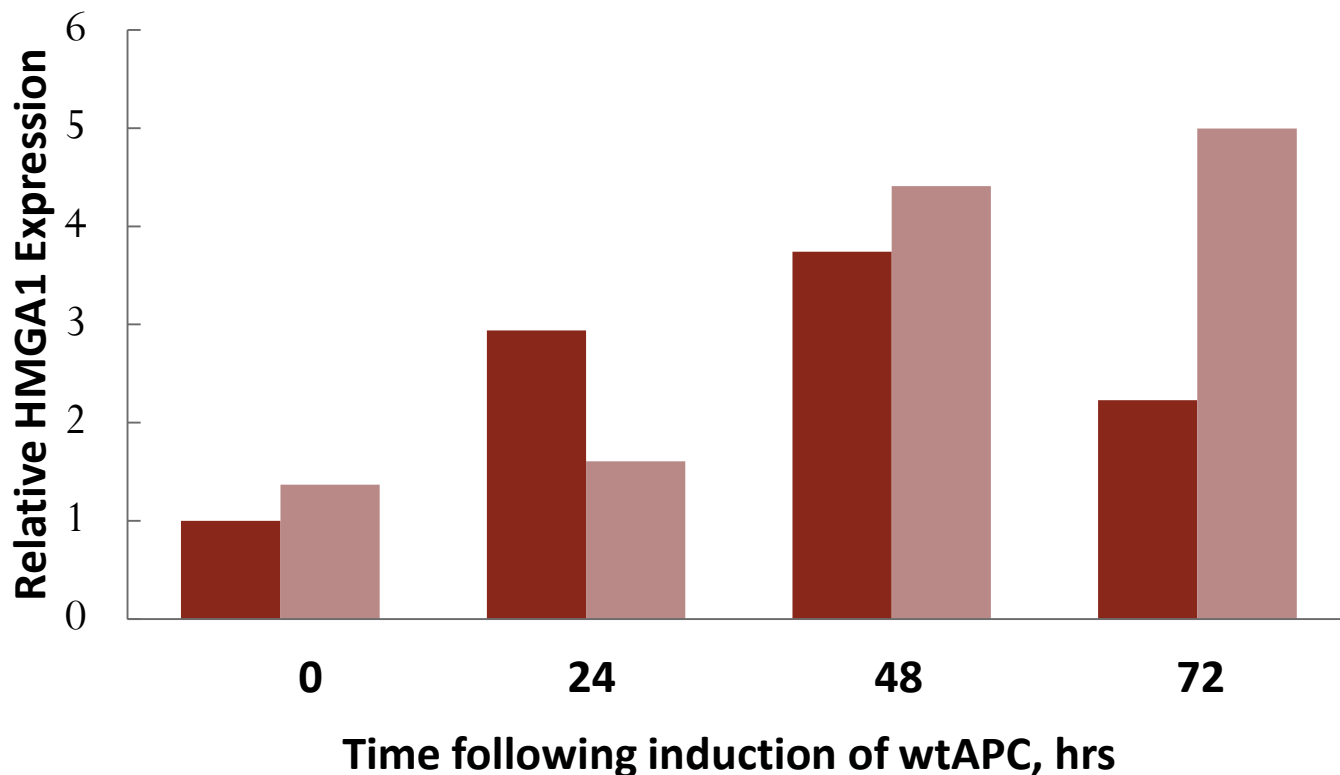
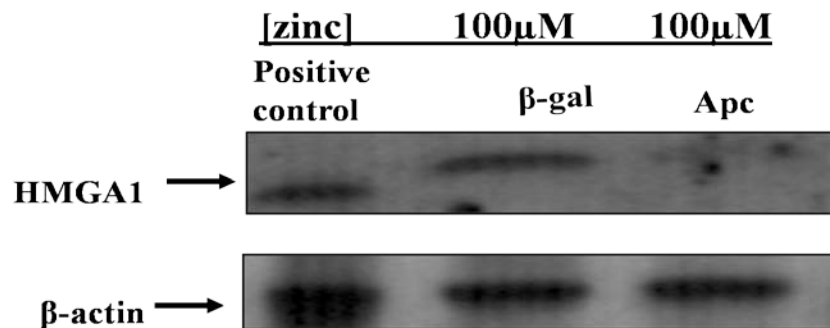


Mutations in components of the Wnt signaling pathway have causative roles in colon cancer.

Do *Apc* truncations affect HMGA1 expression?

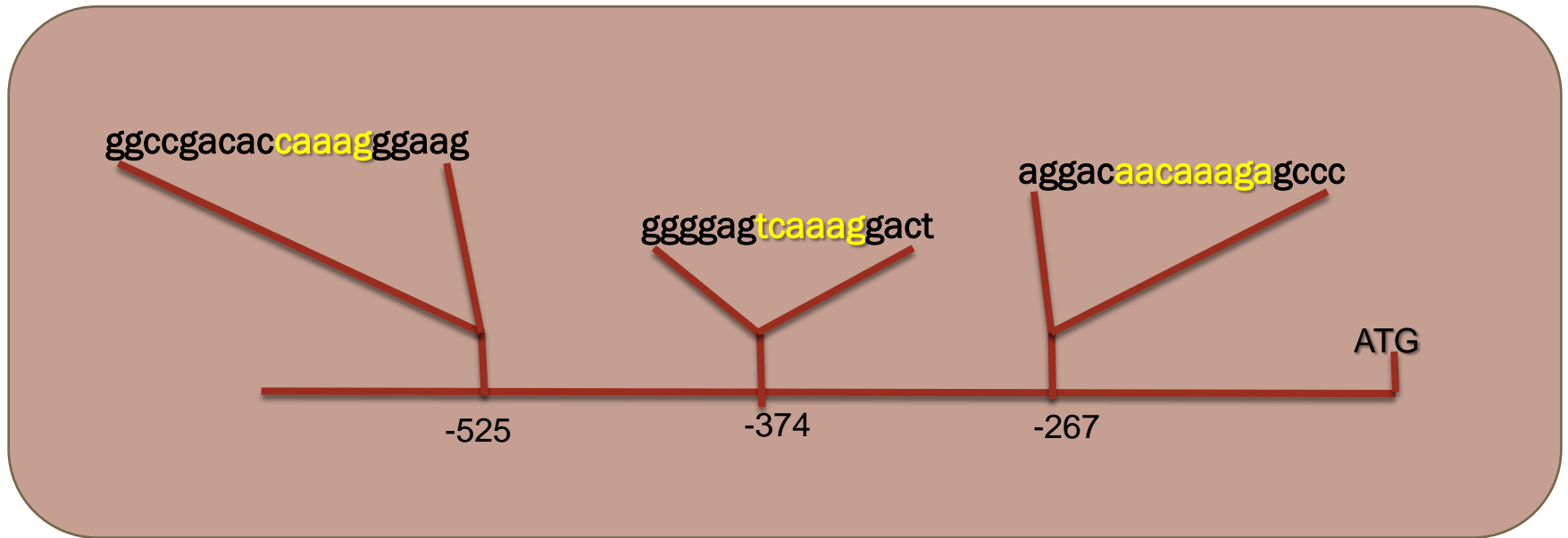


Will *Apc* recovery restore HMGA1 levels?



Is HMGA1 a direct target of TCF4?

Consensus TCF4 binding elements (TBEs) sequence: (A/T)(A/T)CAAAG



Summary

- *High Mobility Group A1 (HMGA1)* proteins are diverse biological mediators of viral integration, modification of chromatin structure, neoplastic transformation, and metastatic progression.
- We observed polyp-like structures in transgenic mice expressing *hmgal a*. To better understand the significance of HMGA1 in intestinal malignancies transformation, we explored the protein's involvement in Wnt signaling.
- In *Apc*^(Min/+) mice expressing truncated Apc, HMGA1 mRNA and protein levels were significantly elevated in *Apc*^(Min/+) intestinal tumors. Recovery of the full-length gene down-regulated HMGA1.
- Sequence analysis of the 5'-flanking sequence of *hmgal* identified three putative Tcf-4 binding elements and studies of the functional roles of these elements will further substantiate our findings.
- Our data implicates Wnt signal transduction in regulating HMGA1 and further expands the extensive regulatory network affected by Wnt/ β -catenin signaling.