Title: FLYWCH1, a novel transcription factor with tumor suppressor activity

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Background

Wnt/β-catenin-signaling pathway is the principal force of intestinal hemostasis and morphogenesis. Aberrant activity of this pathway is highly implicated in cancer development, particularly in colorectal cancer (CRC). Although Wnt/β-catenin pathway is a well-studied pathway, the precise molecular mechanisms involved in the nuclear interactions of β-catenin with DNA-binding transcription factors (other than TCF4) are still under debates. Human FLYWCH1 has been first characterized and identified in our lab as a novel transcription factor, which interacts with nuclear β-catenin and modulates its transcriptional activity (Muhammed *et al.,* under publication).
FLYWCH1 differentially expressed between normal as well as between different stages of colorectal cancers. However, we have just started exploring the biological functions and mechanisms of FLYWCH1 in colon/ intestinal development, homeostasis and tumor formation.

Methods

Loss- and gain-of-function analysis, CRISPR-Cas9, RNA-Seq, Western blotting, Immunoprecipitation, qRT-PCR, and immunofluorescence techniques.

Results

1. Endogenous β-catenin physically interacts with the C-terminal domain of FLYWCH1 protein in human CRC cell lines.
2. FLYWCH1 overexpression negatively regulates the expression of some but not all β-catenin/TCF4 target genes in CRC cell lines.
3. R-spondin1 synergizes with Wnt-3A in repressing of *FLYWCH*1 in CRC cell lines.

Conclusions

a) FLYWCH1 protein binds to the endogenous β-catenin protein while negatively regulates the transcription of a specific-subset of β-catenin /TCF target genes, regardless of Wnt signaling status.
b) Activation of Wnt signaling forms a negative feedback loop during FLYWCH1 repressed β-catenin/TCF4 target gene in carcinogenesis.
c) Our current and future studies with focuses on the *in vivo* role(s) of FLYWCH1 will provide insights on a novel molecular mechanism mediated by FLYWCH1 and the

canonical Wnt/β-catenin pathway in CRC carcinogens, where may offer a new potential approach(s) and implications for future therapeutics.