# B-17

## YAP and TEAD form a transcriptional complex regulating neuroendocrine differentiation and tumorigenesis through a modular mechanism

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### BACKGROUND

Neuroendocrine tumors (NETs) are unusual tumors with neural and secretory morphology and loss of Yes-associated protein (YAP). YAP is a transcriptional co-activator of the Hippo pathway and canonical oncogene in numerous cancers, except NETs. Although YAP typically binds TEAD transcription factors to drive gene expression, we demonstrate that YAP-TEAD complex formation represses NET differentiation and tumorigenesis through targeted gene dysregulation.

### METHODS

Using lung (H727) and pancreatic (BON1) NET cells, we compared neuroendocrine markers (chromogranin A, INSM1), cell proliferation, and anchorage-independent cell growth after overexpressing constitutively active YAP (YAP-S127A) or mutant YAP (YAP-S127A/S94A) that disrupts YAP-TEAD binding. Subsequently, we mapped YAP-TEAD DNA-binding sites using ChIP-sequencing and evaluated gene expression using RNA-sequencing.

### RESULTS

Neuroendocrine marker expression, cell proliferation and anchorage-independent cell growth diminished with active YAP, but recovered with mutant YAP. ChIP-seq revealed 34,924 YAP-TEAD DNA-binding sites predominantly within distal enhancers. Following active YAP overexpression, RNA-seq uncovered 206 upregulated genes including known Hippo targets (CTGF, CYR61), and 137 downregulated genes comprising neural and secretory functions. Interestingly, ChIP-seq clusters correspond with modular roles for YAP/TEAD activation or repression of gene expression, including targeting histone components (cluster 1), classical signalling pathways like TGFβ and Notch (cluster 2 and 3), neuroendocrine differentiation (cluster 4) and general cell functions (cluster 5 and 6). In cluster 4, YAP/TEAD binds to distal enhancers regulating master neuroendocrine transcription factors (ASCL1, INSM1, NEUROD1, NKX2-2) and represses gene expression.

### CONCLUSIONS

YAP/TEAD complex formation represses NET differentiation and tumorigenesis through activation or repression of multiple transcriptional groups with differing functions, indicating a modular regulatory role. Specifically, YAP/TEAD regulates NETs through potential mechanisms including upregulation of TGF-beta and Notch signalling and downregulation of master neuroendocrine transcription factors.

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