A Novel Genetically Encoded Inhibitor of Hippo Signaling Pathway to Study YAP1/TAZ-TEAD Dependent Events in Cancer

Summary (1024-character limit)

The Hippo signaling pathway is one of the most frequently altered pathways in human cancer. Researchers at the National Cancer Institute (NCI) have developed a genetically encoded peptide inhibitor of the Hippo signaling pathway members YAP1/TAZ-TEAD, to dissect and study the specific TEAD-downstream regulatory gene expression networks of cell proliferation, tissue homeostasis, and stem cell functions in different cell types and pathologies. The DNA construct encoding this inhibitor may be delivered to cells using lentivirus, adenovirus, or adeno-associated virus, and is a valuable research tool. NCI seeks licensees for this peptide inhibitor and the encoding DNA construct.

NIH Reference Number

E-108-2019

Product Type

- Research Tools

Keywords

- Hippo Signaling Pathway, Peptide Inhibitor, Cancer Progression, Yes-Associated Protein 1, YAP1, TAZ, TEAD, Iglesias-Bartolome

Collaboration Opportunity

This invention is available for licensing.

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Description of Technology

The Hippo signaling pathway regulates a multitude of biological processes including cell proliferation, apoptosis, differentiation, tissue homeostasis, and stem cell functions. This axis has been recently listed as one of the top 10 signaling pathways altered in human cancer. Its role in modulating cell growth and proliferation is mediated by the activation of Yes-associated protein 1 (YAP1) and transcriptional co-activator with PDZ-binding domain (TAZ). Under low cell density conditions, YAP1/TAZ translocate to the nucleus, bind to various transcription factors including TEA domain (TEAD) family of transcription

factors, and drive the expression of genes associated with cell proliferation and differentiation. If hyperactivated due to disruptions in the Hippo pathway, this upregulation in gene transcription leads to uncontrolled cell growth, transformation, and cancer development.

Research into the Hippo pathway is limited due to technical difficulties in the precise study of the transcriptional networks downstream of YAP1 and TAZ. For example, simultaneous downregulation of YAP1 and TAZ is needed to observe an effect on cancer progression. Furthermore, there are numerous effectors to the Hippo pathway, not limited to transcription factors. To overcome these difficulties, researchers at the National Cancer Institute (NCI) have developed a genetically encoded, fluorescently labeled peptide inhibitor of YAP1/TAZ which specifically targets its interactions with TEADs (named TEAD-inhibitor or TEADi). TEADi consists of various TEAD binding domains, including those of YAP1 and TAZ, modified for efficient inhibition. Using this inhibitor, NCI researchers have studied the functions of the Hippo pathway in the epidermis and in squamous cell carcinoma.

Considering that the Hippo pathway constitutes one of the top signaling pathways altered in human cancer, disruption of YAP1/TAZ-TEAD complexes has become a main target to suppress oncogenic activity. TEADi can be used to dissect the TEAD-dependent and independent roles of YAP1/TAZ signaling and aid in the discovery of improved targeting strategies for this pathway. In conclusion, TEADi is a valuable research tool for studying YAP1/TAZ and the Hippo pathway in cancer and other pathologies, with improved advantages that include rapid and simple inhibition of TEAD transcription and specific blockage of nuclear events mediated by both YAP1 and TAZ without affecting structural or cytoplasmic functions of these proteins.

The NCI Laboratory of Cellular and Molecular Biology is seeking statements of capability or interest from parties interested in licensing this novel inhibitor of the Hippo signaling pathway.

Potential Commercial Applications

- TEADi DNA construct to study Hippo signaling pathway in different pathologies and cellular systems.
- TEADi DNA construct to selectively shut off Hippo signaling pathway for broader research purposes
- Delivery of TEADi DNA construct using lentivirus, adenovirus (AV), or adeno-associated virus (AAV) for broad research purposes

Competitive Advantages

- Rapid and simple inhibition of specific effectors of a signaling pathway frequently disrupted in cancer
- Inhibition of both YAP1 and TAZ factors that regulate the Hippo pathway
- Inhibition of YAP/TAZ interaction with a specific family of transcription factors
- Green fluorescent protein (GFP) label for easy tracking
- Nuclear localization signal to target hyperactivated YAP/TAZ

Inventor(s)

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Development Stage

- Pre-clinical (in vivo)

Publications

Jiao S, et al. A peptide mimicking VGLL4 function acts as a YAP antagonist therapy against gastric cancer. [PMID 24525233]

Patent Status

- **Research Material:** NIH will not pursue patent prosecution for this technology

Therapeutic Area

- Cancer/Neoplasm