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A New Animal Model for the Identification of Novel Signaling Mechanisms Mediating Medullary Thyroid Carcinoma

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Background: Medullary thyroid carcinoma (MTC) is a neuroendocrine cancer, which originates from calcitonin-producing C-cells. Surgical resection is the only effective treatment available. Understanding the molecular pathways mediating MTC is crucial for the development of novel therapies. Cyclin-dependent kinase 5 (Cdk5) and its activators, p35 and p25, have recently been implicated in MTC etiology. P25 is a cleavage product of p35 and the binding of p25 to Cdk5 leads to aberrant Cdk5 activity. Here we present a new mouse model in which conditional expression of p25 in thyroid C-cells leads to tumorigenesis and lethal MTC. Furthermore, we use this animal model to identify the signaling pathways by which Cdk5-p25 mediates MTC.

Methods: Transgenic expression of p25-GFP in C-cells was driven by a neuron-specific enolase promoter via a tetracycline-controlled transactivator system. p25 overexpression (p25OE) was induced by withdrawing dietary doxycycline. Re-administration of doxycycline repressed p25OE. Mouse thyroid tumors were characterized histologically; their gene and protein expression patterns were analyzed using DNA microarrays and immunoblotting. Cdk5 activity was assayed in vitro using histone H1 as a substrate. MTC cell lines were utilized to further delineate the role of Cdk5-p25 in MTC malignancy.

Results: p25OE mice developed calcitonin-positive bilateral thyroid tumors that metastasized to the lungs. Repressing p25OE arrested tumor growth. Cdk5 activity was consistently enhanced in growing compared to arrested tumors. Accordingly, inhibiting or knocking-down Cdk5 slowed-down MTC cells proliferation. Furthermore phosphorylation of retinoblastoma protein, which was identified as a downstream target of Cdk5, was necessary for MTC proliferation.

Conclusion: We present the first conditional animal model for MTC and show that aberrant Cdk5 activity promotes MTC. Therefore, targeting Cdk5 or its downstream effectors is a potential strategy for MTC treatment. Furthermore, our animal model may be used to identify novel therapeutic targets and to test newly discovered drugs.