A new animal model for the identification of novel signaling mechanisms mediating medullary thyroid carcinoma

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1. Introduction

Medullary thyroid cancer (MTC) is a neuroendocrine tumor representing over 14% of thyroid cancer-related deaths. MTC originates from calcitonin-producing parafollicular cells (or C-cells) of the thyroid gland and it metastasizes frequently to regional lymph nodes, lung, liver and brain. MTC has an indolent course and late detection is associated with a high rate of mortality. Total thyroidectomy is the only effective treatment for this disease. Some MTC (25%) are hereditary as component of multiple endocrine neoplasia-2 (MEN-2) and arise from well characterized mutations in the proto-oncogene RET, which encodes for a receptor tyrosine kinase. The majority of MTC cases are sporadic and the underlying causes are not known. Therefore understanding the molecular pathways mediating MTC is crucial for the development of novel therapies.

Cyclin-dependent kinase 5 (cdk5) is a proline-directed serine/threonine kinase that is activated by binding of its cofactor, p35. Cdk5 becomes dysregulated when calpain cleaves the first 88 amino acids of p35 to produce p25. The p25/cdk5 complex translocates to the cytoplasm and nucleus where it phosphorylates aberrant substrates. Although cdk5 is expressed ubiquitously, its physiological function has been predominantly studied in the central nervous system (CNS). Cdk5 is essential to the CNS development and to brain function. Growing evidence suggests that cdk5 plays a key role beyond the nervous system. For example, cdk5 is involved in modulating insulin secretion in pancreatic β cells and in regulating cell cycle and oncogenesis.

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 p25/cdk5 mediates MTC.

2. Cdk5 and p35/p25 are expressed in human thyroid and MTC samples

3. Cdk5 activity regulates growth and proliferation of cell lines derived from human MTC

4. An inducible, bitransgenic animal model for MTC

5. An inducible and arrestable animal model for MTC

6. p25-mediated Cdk5 activation in p250E mice causes MTC tumor growth

7. Retinoblastoma protein is inactive in MTC

8. Rb is a downstream target of Cdk5 in MTC

9. Conclusions

We thank Gabriel Metcalf for expert technical assistance. Dr. Stanley Siddiqui for providing thyroid and MTC specimens. The NIH (AB, PB, FM) and the NIEHS (AB) for the support of this research.

10. Acknowledgments

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We have developed a novel and clinically relevant animal model of MTC to study the mechanisms of tumorigenesis and to test new treatment strategies.