A NOVEL SPECIFIC MARKER OF THYROID CANCER: IMMUNOHISTOCHEMICAL ANALYSIS AND BIOLOGICAL IMPLICATION OF RETROMER AS AN ONCOGENIC FUNCTION.

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[Background] Thyroid papillary carcinoma (TPC) comprises about 90% of all carcinoma originated from thyroid gland and is well known as a tumor frequently metastasizing to regional lymph nodes. Because other malignant tumors like pulmonary or breast carcinomas sometimes develop metastasis to such lymph nodes, immunohistochemical examinations would be required for the differential diagnosis. To date, antibodies against thyroglobulin and thyroid transcriptional factor-1 are commonly used to identify TPC. However it is occasionally difficult to assess signals by these antibodies on tissue sections, due to their heterogenous intensities or low specificities to TPC. Thus far a new antibody for specifically detecting TPC in histopathological examinations has been desired especially in a case of the differential diagnosis.

[Design] In this study we focused on a molecule (protein X) of retromer, which is recently reported to act as an intracellular active transporter of endosome. We initially employed quantitative PCR analysis of the expression of protein X in normal thyroid gland and TPC. Then a mouse 48C2 monoclonal antibody against protein X was established. Specificities of a 48C2 antibody were examined by immunoblot analysis of transformed cells with various retromer molecules. The expression of protein X was further studied in malignant tumors including 52 cases of TPC by immunohistochemistry with a 48C2 antibody. Transformed cells stably expressing protein X were also examined by WST-1 assay to investigate their proliferative activities.

[Results] Quantitative PCR analysis showed high levels of transcripts of protein X in

thyroid carcinoma rather than in normal thyroid gland. Immnohistochemical analysis revealed that a 48C2 antibody strongly reacted to TPC at high ratio (90.3%, 47/52 specimens). In contrast negative signals by immunostaining with a 48C2 antibody were observed in other papillary tumors such as pulmonary carcinoma (0%, 0/20), breast carcinoma (0%, 0/10) and ovarian carcinoma (0%, 0/5). Furthermore WST-1 proliferation assay showed high growth rate of transformed cells expressing protein X, when compared to control cells.

[Conclusions] The protein X of retromer would be a new reliable marker for the histopathological diagnosis of TPC. Given that protein X had a role in the growth advantage of TPC, downregulation of protein X might lead tumor regression of TPC.