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Focus on Immunohistochemistry – April 2001

Thyroid Transcription Factor-1 (TTF-1)

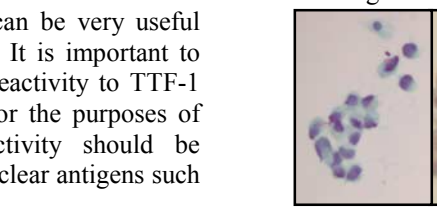
Transcription factors are nuclear proteins that have an important role in regulating gene expression, thereby determining and maintaining cellular phenotype. Thyroid transcription factor-1 (TTF-1) is a 38kDa protein (in the NKx2 family of DNA-binding proteins) that is expressed during embryonic development in the thyroid, diencephalon, and respiratory epithelium. Numerous studies have shown that antibodies to TTF-1 can be very useful reagents in diagnostic pathology. It is important to realize that only nuclear immunoreactivity to TTF-1 represents "true" reactivity, and for the purposes of diagnosis, any cytoplasmic reactivity should be ignored (similar to certain other nuclear antigens such as ER and PR).

TTF-1 as a marker of thyroid carcinoma

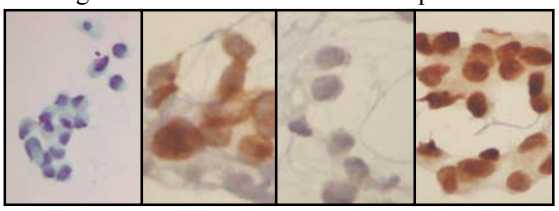
A high percentage (> 95%) of follicular, papillary, and insular thyroid carcinomas show expression of TTF-1. In addition, a similar percentage of medullary carcinomas of thyroid express this marker. Reactivity of Hurthle cell tumors with TTF-1 is somewhat less common (reported range from 20-75%). Anaplastic thyroid carcinoma is usually negative for TTF-1. Most authors report that parathyroid tissue is negative, and this agrees with our personal experience at ProPath.

TTF-1 as a marker of pulmonary adenocarcinoma

One of the most useful roles of TTF-1 is in the recognition of pulmonary carcinoma. Roughly 75% of primary pulmonary adenocarcinomas show expression of TTF-1, a feature that can greatly aid in the identification of lung carcinomas when they present as metastatic disease. Squamous carcinomas are almost always negative for TTF-1, although adenosquamous carcinomas of pulmonary origin may show reactivity in the glandular component. TTF-1 is not expressed in mesothelioma, so it also has utility in the differential diagnosis of mesothelioma vs. primary pulmonary adenocarcinoma. Pulmonary sclerosing hemangioma has also been found to express TTF-1.



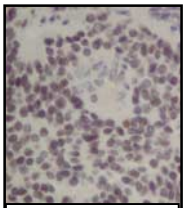
Lung ca, TTF-1



FNA smears of lung mass in a patient with previous colon ca. Only minimal material was obtained, with no cell block. The pap stain (left) shows carcinoma, which is cytokeratin 7 positive (second from left) and cytokeratin 20 negative (second from right). The TTF-1 stain shows strong nuclear reactivity. A conclusive diagnosis of pulmonary adenocarcinoma was rendered.

TTF-1 neuroendocrine tumors

In addition to its expression in medullary carcinoma of thyroid, TTF-1 may be expressed in other neuroendocrine tumors. Some authors have identified expression of TTF-1 in >80% of primary pulmonary small cell carcinoma, although our experience at ProPath is closer to 50-60%. Non-pulmonary small cell carcinoma may also be reactive, although the frequency of positivity is substantially less than with pulmonary small cell carcinoma. In addition, some authors have found that when pulmonary small cell carcinomas express TTF-1,



Medullary ca

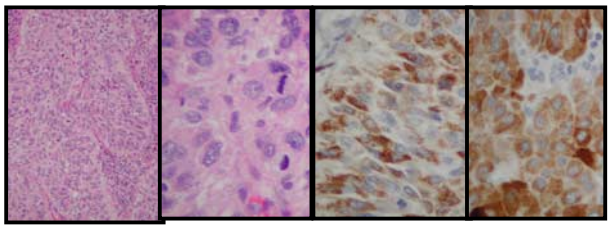
nearly 100% of cells stain, whereas non-pulmonary small cell carcinomas expressing TTF-1 usually show <50% of tumor cells staining. So-called "atypical carcinoids" of lung are frequently positive (80%). The reported rates of reactivity of typical lung carcinoids with TTF-1 range from 20%-95%, and there is some evidence to suggest that expression of TTF-1 may assist in the distinction of pulmonary (frequently positive) vs. non-pulmonary (usually negative). Due to its expression in neuroendocrine neoplasms, it is imperative that a neuroendocrine tumor be excluded, either by morphology or appropriate immunostains (in our opinion NSE is not an appropriate immunostain for this purpose) before using expression of TTF-1 as supportive evidence for primary pulmonary adenocarcinoma. One neuroendocrine tumor that has been found to be consistently negative for TTF-1 is Merkel cell carcinoma of the skin, so TTF-1 can assist in the distinction of Merkel cell tumor from metastatic pulmonary small cell carcinoma.

TTF-1 in miscellaneous tumors

TTF-1 has been reported in a small percentage of gastric carcinomas (1.5%) and endometrial adenocarcinoma (17%). At ProPath we have personally observed TTF-1 in a few endometrial carcinomas, and in very rare cases of breast and colorectal carcinoma, as well as a small percentage of pancreatic adenocarcinomas, and a case of desmoplastic small cell tumor.

Coarse granular cytoplasmic reactivity with TTF-1: a clue to hepatoma?

We have observed coarse granular cytoplasmic reactivity with some regularity in hepatoma, and we have had cases where this pattern of reactivity was the first hint that a particular tumor was indeed a hepatoma. (This reactivity does not represent endogenous biotin artifact, since it is even present when non-biotin based detection methods are used.) To my knowledge, this finding has not been reported in the literature, so it is best filed in the "personal observations awaiting further studies and hopefully confirmation by the literature" category, but we have found this pattern useful on a number of occasions. Nonspecific fine granular cytoplasmic reactivity may be observed in a number of other non-pulmonary carcinomas, including colorectal carcinoma, gastric carcinoma, prostate carcinoma, and cholangiocarcinoma.



H&E section (left two frames) of a supraclavicular mass on a 57 y.o. male. The patient had a prior history of hepatoma, although 4 experienced surgical pathologists felt the H&E suggested non-hepatocellular carcinoma. On the initial battery of stains, coarse granular cytoplasmic reactivity with TTF-1 was noted (second from right). Along with this finding and the intermediate filament phenotype, hepatoma was more seriously considered, and was confirmed by subsequent further immunophenotyping. TTF-1 on another hepatoma is shown in the far right panel.

Conclusion

TTF-1 is a very useful reagent in diagnostic pathology, and can assist in the identification of pulmonary adenocarcinoma, thyroid carcinomas, neuroendocrine tumors, and perhaps even hepatoma.

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