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Supplementary appendix

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Web Appendix:

A. Table: Characteristics of primary thyroid mesenchymal tumors.

B. Figure: A comparison of the molecular basis for the development of mesenchymal tumors and epithelial thyroid tumors:

A. Table: Characteristics of primary thyroid mesenchymal tumors. *

	Clinical features, treatment and prognosis	Imaging, FNA, and gross pathology features	Histopathology	Immunohistochemistry	Differential diagnosis[$]	Pathogenic genetic variants**
1. Paraganglioma	Reported cases: 76. Mean AODx: 50 years (range: 9 – 78 years); female predilection (~90% of cases); size: 2 – 10 cm. Could be a part of genetic syndromes such as SDHx. Unlike extrathyroidal paragangliomas, catecholaminergic symptoms are rare. About 30% of the tumors can be locally invasive. Surgery is usually curative, recurrence is rare.	US: hypoechoic/heterogenous nodules; cold nodules on scintigraphy. FNA: non-diagnostic/spindle cells. GP: reddish brown, well-circumscribed solid tumors consisting of sclerotic areas.	Principal (chief) cells and sustentacular cells, 'zellballen' pattern of cellular arrangement.	Principal cells: chromogranin A (+), synaptophysin (+), neuron specific enolase (+); sustentacular cells: S-100 (+).	MTC, Hurtle cell neoplasms, hyalinizing trabecular tumor, atypical follicular adenoma, metastatic carcinoid tumor.	*SDHB, SDHC, SDHD, SDHD, SDHA, SDHAF2 TMEM127,* and *VHL*.
2. Schwannoma	Reported cases: 37. AODx: usually 10 – 30 years (range: 11 – 80 years); 63% female; size: 2·5 – 6 cm. Usually asymptomatic but rarely present as rapidly enlarging neck masses. Benign PNST; surgery is curative, and recurrence is uncommon, excellent prognosis.	US: hypoechoic nodules (80%), rarely with cystic areas or as hyperechoic nodules. CT: homogeneous, soft-tissue lesions. FNA: paucicellular or spindle cells. GP: yellowish-tan to grey colored, well-circumscribed, firm masses with solid, grey-white cut-surface.	'Antony A pattern' (cell-rich areas), 'Antony B pattern' (cell-poor areas), 'Verocay bodies' (areas of nuclear palisading)	S-100 (+), neuron specific enolase (+).	Riedel's thyroiditis, MTC, ATC, spindle cell variant of thyroid carcinomas, neurofibroma, leiomyoma, malignant PNST.	*NF2, TTF1, SMARCB1, LZTR1, TSC1, TSC2, DDR1, ARID1A,* and *ARID1B.*
3. Granular cell tumor	Reported cases: 20. AODx: 11 – 53 years, about 90% female; size: 0·8 – 4·2 cm. Slow-growing neck masses. Mostly benign; surgery is most often curative, excellent prognosis. One patient with tumor invading the tracheal wall; was rendered disease free after surgery.	US: hypoechoic nodules (50%). FNA: large, polygonal cells with polymorphic nuclei and inconspicuous nucleoli, syncytial cell borders and prominent eosinophilic cytoplasmic granules. GP: firm, cream to white colored mass with a smooth cut-surface.	Tumor cells with abundant eosinophilic, granular cytoplasm; cells arranged in clusters/nests; also, presence of thick collagen bundles and large, pink epithelioid cells with bland nuclei.	S-100 (+).	PNSTs, Hurtle cell neoplasms, paraganglioma, melanoma, histiocytic neoplasms.	*ATP6AP1, ATP6AP2,* and *PTPN11*.
4. Neurofibroma	Reported cases: 6. AODx: 14 – 55 years, no sex predilection; clinical features similar to schwannomas; can occur as a part of neurofibromatosis 1. Benign PNST; surgery can be curative.	Imaging and FNA features are similar to schwannomas. GP: greyish, white, solid masses, with some areas containing mucoid degeneration.	Spindle cells, absence of Verocay bodies.	S-100 (+).	Schwannoma, leiomyoma, malignant PNST, MTC, ATC.	*NF1, RET*.
5. Hemangioma	Reported cases: 31. AODx: from 4 – 80 years, common in 4^{th} – 7^{th} decades of life; $2/3^{rd}$ cases in males; size: 1·8 – 22 cm. Slow-growing masses, intralesional bleeding can cause rapid increase in size. Benign; cured surgically, but potential risk for hemorrhage due to the vascular nature of the tumor.	US: hypoechoic lesion/multinodular goiter; CT/MRI: hypoenhancing lesion with occasional peri-tumoral calcifications; increased uptake on Tc-99 RBC scan or angiogram. FNA: non-diagnostic/bloody aspirate. GP: encapsulated mass with multifocal hemorrhagic areas with a spongy appearance on cut-surface.	Several dilated, anastomosed vessel lumens lined by flattened endothelial lining; lumens contain erythrocytes.	CD34 (+), CD31 (+), ERG (+).	Malignant vascular tumors, intrathyroidal vascular malformations, bloody FNA. Phleboliths in hemangioma can mimic thyroid carcinomas on physical exam.	*RAS, PIK3CA.*
6. Leiomyoma	Reported cases: 7. AODx: usually 40 – 60 years, (also reported in pediatric age group); 70% female; progressively enlarging neck mass; size: 1·5 – 9 cm. Benign; surgery is curative.	US: solid, hypoechoic lesions; RAIS: cold nodule. FNA: non-diagnostic/spindle cells. GP: greyish colored solid mass, sometimes with cystic regions.	Fusiform/spindle shaped cells with pale eosinophilic cytoplasm and blunt-ended, cigar-shaped nuclei, forming intersecting fascicles.	SMA (+), desmin (+).	Spindle cell variants of thyroid carcinomas, schwannoma, neurofibroma, leiomyosarcoma.	*HMGA2, PLAG1*.

7. Adenolipoma	Reported cases: 30. Average AODx: 53 years (9 – 79 years); 73% female; size: 1 – 25 cm. Asymptomatic neck swelling, occasionally causes compressive symptoms***. Could be associated with *PTEN* pathogenic variants. Benign; surgery is curative.	US: often isoechoic with the thyroid gland due to fat content, rarely hypo- or hyperechoic. CT: hypoenhancing lesion. MRI: hypointense lesion on fat suppression mode. GP: yellowish, soft mass on cut-section.	Mature adipose tissue with interspersed thyroid follicles containing benign follicular cells.	Thyroglobulin (+) in the follicular cells.	Thyrolipomatosis, amyloid goiter, dyshormonogenetic goiter, Hashimoto's thyroiditis, angiolipoma, hamartomatous nodule, liposarcoma.	Unknown.
8. Solitary fibrous tumor	Reported cases: 47 (including 9 cases of hemangiopericytoma). Mean AODx: 54 years (28 – 88 years); no sex predilection; size: 1·7 – 13·8 cm. Painless neck mass, sometimes causes compressive symptoms. Usually benign; surgery is curative in most cases, but malignant primary thyroid tumors with metastasis have also been reported in 2 patients.	US: solid lesion, rarely cystic regions, data on echogenicity is lacking. CT: heterogeneous enhancing lesion. RAIS: cold nodule. FNA: non-diagnostic/spindle cells with bland cytoplasm and collagenous stroma. GP: well-demarcated, tan-pink to tan-white, firm masses; tan to white cut-surface with occasional cystic areas	Spindle cells with bland cytoplasm, 'patternless distribution' of cells in the tumor stroma, with ectatic, branching thin-walled vessels.	STAT6 (+), CD34 (+), CD99 (+), bcl-2 (+).	MTC, ATC, PTC with desmoid-type fibromatosis, spindle-cell variants of thyroid carcinomas, SETTLE, malignant TMTs.	*NAB2-STAT6* gene fusion.
9. Malignant peripheral nerve sheath tumor	Reported cases: 6. AODx: 22 – 69 years; 85% female (one patient with neurofibromatosis 1). Clinical presentation is similar to benign thyroid PNSTs. Prognostic data is lacking, surgery and chemoradiation has been utilized with limited success.	Imaging and FNA features are similar to benign forms of PNST. GP: fleshy, grey-white mass with areas of necrosis and hemorrhage, sometimes with a dense fibrous capsule.	Spindle cells with large nuclei and prominent nuclei, frequent mitoses, areas of myxoid or hyalinized tissue and necrosis, cellular and acellular areas.	S-100 (+).	Schwannoma, spindle cell variants of thyroid carcinomas, rhabdoid variant of ATC, other malignant TMTs with spindle cell morphology.	*TP53*, *RB1*, and *CDKN2A*, *SUZ12* and *EED*.
10. Malignant vascular tumors	Reported cases: 68. Most common form of malignant TMT. Includes angiosarcoma, epithelioid hemangioendothelioma. Geographical predilection to Alpine regions. Risk factors: iodine deficiency, exposure to radiation, vinyl chloride. AODx: 6th decade of life; 80% female; size: 5 – 8 cm. Rapidly enlarging neck mass, compressive symptoms, weight loss. Treatment: surgery (potential risk for hemorrhage), chemoradiation, tyrosine kinase inhibitors. Poor prognosis, average survival of 5 months in 57% of patient.	US: hypoechoic/heterogenous nodule, occasional calcifications. CT scan: necrotic mass with invasion into adjacent structures. FNA: malignant cells mimicking undifferentiated carcinoma, epithelioid cells, or bloody aspirate. GP: encapsulated masses with hemorrhagic, necrotic and cystic areas.	Epithelioid endothelial cells containing abundant cytoplasm, large vesicular nuclei and prominent nucleoli, lining freely anastomosing channels.	CD31 (+), CD34 (+), Factor VIII-RA (+), FLI1 (+), ERG (+).	Other malignant TMTs, spindle cell variants of thyroid carcinomas, hemangioma, vascular malformations.	*MYC*, *FLT4*. *WWTR1-CAMTA1* and *YAP1-TFE3* gene fusions with epithelioid hemangioendothelioma.
11. Rhabdomyosarcoma	Reported cases: 4. AODx: 7 months – 68 years; all individual reported patients are males. Size: ~5 – 6 cm. Can be asymptomatic or can progressively enlarge and cause compressive symptoms. Surgery +/- chemoradiation. Lymph node metastases noted in one patient. Prognostic data is insufficient.	US: hypoechoic nodule. CT: hypoenhancing, heterogeneous mass, evidence of invasion into adjacent structures. GP: sparse data; one report described a white, solid mass with myxoid changes.	Small, round, oval, fusiform/spindle cells with sparse cytoplasm and hyperchromatic nuclei; Rhabdomyoblasts with abundant, eosinophilic cytoplasm.	Desmin (+), myogenin (+).	Malignant triton tumor, rhabdoid variant of ATC, Ewing sarcoma family of tumors, spindle cell variants of thyroid carcinomas, other malignant TMTs.	*PAX5-FOXO1* and *PAX7-FOXO1* gene fusion. Others: Genes in the RAS-MAPK pathway, *CTNNB1*, *FGFR4*, *IGF2*, *TP53*.
12. Leiomyosarcoma	Reported cases: 32. AODx: Median: 65 years (range: 32 – 90 years, one case reported in a 6-year-old with congenital immunodeficiency); 61% female. Size: 1·9 – 13 cm. Enlarging neck masses with compressive symptoms, weight loss. Distant metastases at diagnosis also has been reported. Treatment: surgery +/- chemoradiation, tyrosine kinase inhibitors. Poor prognosis, median survival of ~5 months.	US: hypoechoic or mixed cystic nodule with internal vascularity and calcifications. CT: bulky, necrotic masses with evidence of compression and invasion. RAIS: Cold nodule. FNA: non-diagnostic or undifferentiated malignant cells. GP: greyish colored, solid mass with cystic areas.	Spindle cells with hyperchromatic, blunt ended to pleomorphic nuclei, and with abundant, eosinophilic cytoplasm.	Desmin (+), MSA (+), H-caldesmon (+).	Spindle cell variants of thyroid carcinomas, other malignant TMTs with spindle cell morphology, leiomyoma.	*TP53*, *RB1*, *PTEN* and *ATRX*.
13. Liposarcoma	Reported cases: 16. Well-differentiated, myxoid, de-differentiated, and pleomorphic sub-types described in the thyroid. AODx: 23 – 82 years; 56% female. Size: 2·5 – 12 cm. Rapidly enlarging neck mass, compressive symptoms, weight loss. Treatment: surgery +/- chemoradiation. Disease is fatal in ~38% of the patients.	US: hypoechoic/hyperechoic or heterogeneous nodule. CT: hypo- or isodense lesion with compressive or invasive features. MRI: may reveal lipomatous nature of the tumor. RAIS: Cold nodule. FNA: non-diagnostic, suspicious for malignancy, or high-grade malignant cells. GP: soft or hard, often lobulated, greyish-white mass.	Spindle cells and/or lipoblasts with multivacuolization, often presence of myxoid stroma with capillary vessels.	S-100 (+), MDM2 (+).	Lipoma, angiolipoma, metastatic malignant phyllodes tumor, spindle cell variants of thyroid carcinoma, other malignant TMTs.	Well-differentiated forms: *MDM2*, *CDK4*, *HMGA2*. Myxoid forms: *FUS-DDIT3*, *EWSR1-DDIT3* fusions. Pleomorphic forms: *RB1*, *TP53*.

14. Osteosarcoma	Reported cases: 31. Average AODx: 60 years (21 – 97 years), 55% female; size: 9 – 10 cm. Rapidly enlarging neck mass with compressive symptoms. Treatment: surgery +/- chemoradiation. Poor prognosis, mostly fatal within a few months of diagnosis.	US: heterogeneous nodule with extensive calcification. CT: massive intra-tumoral calcifications, invasion into adjacent structures. Increase uptake on bone scintigraphy in one patient. FNA: non-diagnostic/fibrous tissue/spindle- to osteoblast-like cells/similar to ATC. FNA: data is sparse, rarely reported as poorly differentiated or anaplastic carcinoma. GP: hard, greyish mass with extensive calcification.	Spindle- to osteoblast-like cells with pleomorphic nuclei, multinucleated giant cells; Osteoid matrix/osseous metaplasia	Vimentin (+).	ATC, MTC, chondrosarcoma, other malignant TMTs, calcified goiter/cyst.	*CDKN2A*, *TP53*, *RB1*. Chromosomal aneuploidy is also observed.
15. Ewing sarcoma family of tumors	Reported cases: 12. Primary Ewing sarcoma and ALES have been described in the thyroid. AODx: 9 – 67 years; 60% male; size: 4 – 6 cm. Progressively expanding neck mass. Treatment: surgery +/- chemoradiation. Mostly favorable outcomes.	US: heterogeneous, hypervascular masses. CT: heterogeneously enhancing masses with compression of adjacent structures. FNA: small cell neoplasm/similar to hematologic malignancy or lymphoma. GP: data is lacking.	Uniform, medium to large cells, without prominent nucleoli; presence of 'Homer Wright' rosettes. ALES can have squamous pearls, peripheral palisading.	CD99 (+), FLI-1 (+). ALES: p40 (+), pankeratin (+)	MTC, primitive neuroectodermal tumors, hematopoietic malignancies, other malignant TMTs.	*EWSR1* and *ETS* family gene-related fusions.
16. Synovial sarcoma	Reported cases: 21. AODx: 12 – 72 years; 63% male; size: 6 – 7 cm (one case up to 17 cm). Rapidly enlarging neck mass, compressive symptoms, weight loss. Treatment: surgery +/- chemoradiation. Lung metastases are common. More than 58% of the patients were alive at the time of follow-up.	US: hypo-, hyper- or isoechoic, hypervascular lesions with rim calcifications. CT: heterogeneous mass compressing on adjacent structures. FNA: dedifferentiated/similar to ATC or MTC/spindle cell neoplasm. GP: greyish white, hard tumor, with or without a fibrous capsule, and with areas of hemorrhage and necrosis	Monophasic (spindle cells only) or biphasic (spindle cells and epithelioid cells) variants.	TLE-1 (+), CD99 (+), bcl-2 (+), CD56 (+), EMA (+).	Spindle cell variants of thyroid carcinomas, rhabdoid variant of ATC, other malignant TMTs, SETTLE, ectopic thymomas.	*SYT-SSX* gene fusion.
17. Fibrosarcoma	Reported cases: 12[#]. Two cases associated with history of radiation exposure. AODx: 5th – 7th decade of life; sex predilection data is lacking; size: 5 – 14 cm. Treatment: surgery +/- chemoradiation. Prognostic data is lacking.	US: heterogeneous masses with calcifications. CT: heterogeneous mass with cystic areas and calcifications. FNA: non-diagnostic/spindle cells. GP: soft or hard, often lobulated, greyish-white mass.	Spindle cells arranged in 'herringbone' pattern; pleomorphic cellular nuclei, prominent nucleoli and numerous mitotic figures.	Vimentin (+).	Spindle cell variants of thyroid carcinomas, other malignant TMTs with spindle cell morphology, fibromatosis.	Mostly unknown. Chromosomal abnormalities (aneuploidy) and several miRNA targets have been reported.
18. Chondrosarcoma	Reported cases: 4. AODx: 13 – 75 years; 2 male, 1 female, unknown sex in the 4th case; size: 2 – 7 cm. Myxoid and mesenchymal forms have been described in the thyroid (1 case each). Progressively expanding neck swelling with compressive symptoms. Treatment: surgery. Data on chemoradiation and follow-up is lacking.	Imaging data is sparse. US showed a hyperechoic nodule in one patient. CT showed hypoenhancing mass and RAIS revealed a cold nodule in another patient. FNA: non-diagnostic/follicular neoplasm. GP: solid, grey-white or grey-pink tumor with gritty, cartilage-like consistency.	Round to spindle cells, areas of hyalinized cartilage with pleomorphic chondrocytes.	S-100 (+).	Chondroma, chondroid metaplasia, osteosarcoma, other malignant TMTs.	*IDH1/2*, *TP53*, and *COL2A1*. Myxoid forms: Gene fusions involving *NR4A3*, *EWSR1*, *TAF15*, *TCF12* and *TFG*. Mesenchymal forms: *HEY1-NCOA2* fusion.
19. Undifferentiated pleomorphic sarcoma	Reported cases: 27 (including 2 cases of myxofibrosarcoma). AODx: 46 – 78 years; 74% female; size: 2·5 – 15 cm. Progressively enlarging neck mass with compressive symptoms. Treatment: surgery and radiation have been utilized' chemotherapy data is lacking. Poor prognosis, over 75% patients died from the disease.	US: hypoechoic nodule with coarse calcifications. CT: heterogeneously enhancing mass with extension into or compression of surrounding structures. FNA: non-diagnostic/hemorrhagic aspirate/suspicious for neoplasm. GP: greyish-white to greyish-yellow, often encapsulated, solid mass with areas of cystic degeneration, hemorrhage and necrosis	Pleomorphic, sometimes multinucleated to spindle cells arranged in 'storiform' pattern.	CD68 (+).	Metastatic phyllodes tumor, metastatic metaplastic carcinoma, spindle cell variants of thyroid carcinomas, other malignant TMTs.	*CCNE1*, *VGLL3*, and *YAP1*.

20. Carcinosarcoma	Reported Cases: 28; AODx: 43 – 80 years; 75% female; size data is sparse: usually ≤6 cm. Progressively expanding neck swelling, compressive features, and weight loss. Treatment: surgery +/- chemoradiation. Poor prognosis, regional and distant metastases are common and usual survival is a few months to 2 years in 93% of patients.	US: heterogeneous echogenicity, with coarse calcifications. FNA: carcinomatous component (PTC, ATC), and spindle cells suggestive of a sarcomatous component. GP: greyish-white mass with areas of hemorrhage and necrosis	Combined areas of carcinoma and sarcoma.	Carcinomatous regions: Pancytokeratin (+), thyroglobulin (+), PAX8 (+), TTF-1 (+); Sarcomatous regions: Vimentin (+).	PTC, ATC, MTC, spindle cell variants of thyroid carcinomas, other malignant TMTs.	*KRAS*, *PIK3CA*, *TP53*, and *CCNE* in gynecologic carcinosarcoma. One patient with thyroid carcinosarcoma had *DICER1* pathogenic variant in the neoplastic cells.
	TMT: Thyroid mesenchymal tumor. PTC: papillary thyroid carcinoma; MTC: medullary thyroid carcinoma; ATC: anaplastic thyroid carcinoma. AODx: Age of diagnosis. US: Ultrasound. CT: Computed tomography. MRI: Magnetic resonance imaging. RAIS: Radioactive iodine scintigraphy. GP: Gross pathology. PNST: Peripheral nerve sheath tumor. SETTLE: Spindle epithelial tumor with thymus-like differentiation. Tc-99: Technetium – 99. miRNA: micro-RNA. ALES: Adamantinoma-like Ewing sarcoma. * Data on certain TMTs such as rhabdomyoma (1 case), follicular dendritic cell sarcoma (3 cases), malignant triton tumor (2 cases), malignant glomus tumor (2 cases), Kaposi sarcoma (5 cases), alveolar soft part sarcoma (1 case), ameloblastic fibrosarcoma (1 case), and malignant mesenchymoma (1 case) are sparse, and these TMTs are not mentioned in the table. ** Molecular landscape of most TMTs is not entirely known. The genetic variants are provided from data based on both TMTs as well as extra-thyroidal mesenchymal tumors. *** Compressive symptoms include dysphagia, change in voice, shortness of breath, and neck pain. [#] Only includes cases published after 1970. Several cases on “thyroid fibrosarcoma” published prior to 1970 were identified, but the data on these cases were unavailable. It is likely that other forms of TMTs were grouped under the blanket term of “fibrosarcoma” in the older literature. [$] For all primary malignant TMTs, the likelihood of the TMT being a metastasis from an extrathyroidal primary tumor must be strongly considered during clinical evaluation.					

I. List of thyroid mesenchymal tumors and their references from the web appendix table:

1. Paraganglioma[1-22]
2. Schwannoma[23-34]
3. Neurofibroma[35-40]
4. Granular cell tumor[41-43]
5. Hemangioma[44-49]
6. Leiomyoma[50-56]
7. Adenolipoma[57-63]
8. Solitary fibrous tumor[64-76]
9. Malignant peripheral nerve sheath tumor[77-82]
10. Malignant vascular tissue tumors[83-93]
11. Rhabdomyosarcoma[94-98]
12. Leiomyosarcoma[99-113]
13. Liposarcoma[114-126]
14. Osteosarcoma[127-134]
15. Ewing sarcoma family of tumors[135-145]
16. Synovial sarcoma[146-154]
17. Fibrosarcoma[155-161]
18. Chondrosarcoma[162-169]
19. Undifferentiated pleomorphic sarcoma[170-175]
20. Carcinosarcoma[176-182]
21. Rhabdomyoma[183]
22. Follicular dendritic cell sarcoma[184-186]
23. Malignant triton tumor[187,188]
24. Malignant glomus tumor[189,190]
25. Kaposi sarcoma[191-194]
26. Alveolar soft part sarcoma[195]
27. Ameloblastic fibrosarcoma[196]
28. Malignant mesenchymoma[197]

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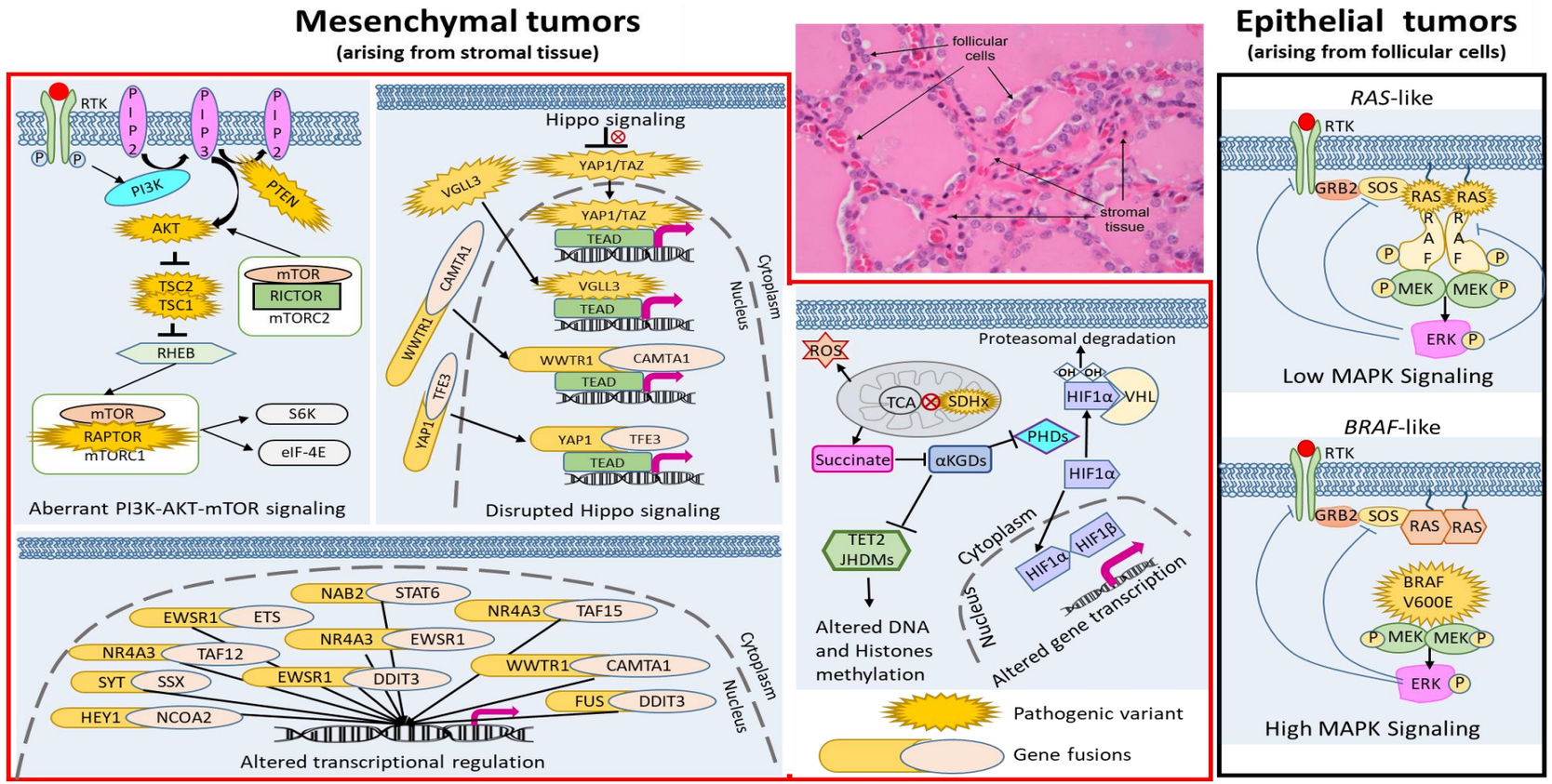
B. Figure: A comparison of the molecular basis for the development of mesenchymal tumors and epithelial thyroid tumors:



The figure illustrates and compares the molecular pathways driving the development of mesenchymal tumors and epithelial tumors.

Mesenchymal tumors: The exact molecular mechanism driving the formation of mesenchymal thyroid tumors is not fully elucidated, thus presented data are based on extrapolation from extrathyroidal mesenchymal tumors molecular signature. Altered PI3K-AKT signaling and hippo signaling have been reported in mesenchymal tumors. The hyperactive PI3K-AKT-mTOR signaling has been associated with the presence of pathogenic variants of the genes (*AKT, PTEN, TSC1, TSC2, RAPTOR*) that are involved in this pathway.[1] Similar presence of pathogenic variants of genes downstream of the hippo signaling promotes tumorigenesis.[1] The presence of *SDHx* pathogenic mutations within paragangliomas can lead to the disruption of the Krebs cycle (TCA) and thus resulting in the accumulation of succinate. The excess succinate competes with α-ketoglutarate and inhibits the activity of α-ketoglutarate dependent dioxygenases (αKGDs) like TET2, JHDMs, and PHDs which results in the alteration of DNA and histones methylation status and activation of HIFα pathway under normoxic conditions, thus leading to cancer progression.[2,3] In addition to this, gene-fusions also alter the normal signaling and disrupt the transcriptional regulation of various genes which play an important role in proliferation, survival and cell death, however, the exact mechanism is not understood.[4-12]

Epithelial thyroid tumors: MAPK signaling is the most common signaling pathway to be altered in thyroid cancer of epithelial origin and this alteration has been associated with the presence of mutually exclusive pathogenic variants: *RAS* and *BRAF* (p.V600E). The RAS-like thyroid cancers are driven by mutated RAS protein which activates the downstream signaling pathways leading to ERK activation. The activated ERK inhibits the RAS signaling through a negative feedback loop leading to low MAPK signaling. In contrary to this, the BRAF-like tumors lead to the constitutive activation of the MEK-ERK signaling pathway which does not respond to the negative feedback signaling from ERK and thus, resulting in high MAPK signaling activation.[13]

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