Metabolic enzymes (IDH, FH, SDH) and mesenchymal tumor(syndrome)s

Judith V.M.G. Bovée
Department of Pathology
LUMC, THE NETHERLANDS

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Dr. Bovée declares she has no conflict(s) of interest to disclose.

Hallmarks of cancer

Tumours with somatic IDH1 or IDH2 mutations

- Glioma 80%
- Enchondroma, chondrosarcoma 40-60%
- Spindle cell hemangioma 70%
- Sinonasal undifferentiated carcinoma 55% (IDH2)
- Acute myeloid leukemia 20%
- Intrahepatic cholangiocarcinoma 20%
- Angio-immunoblastic T-cell lymphoma 20%
- Thyroid carcinoma 16%
- Melanoma 10%
- etc

Central cartilaginous tumours

- Enchondroma
  - In the medulla of bone
  - Small bones hands and feet

- Central chondrosarcoma
  - In medulla
  - Can be secondary to enchondroma
**Enchondromatosis; Ollier disease**
- Unilateral predominance
- Non hereditary
- Rare (1:100,000)
- Risk secondary chondrosarcoma 40%

**Enchondromatosis; Maffucci syndrome**
- Multiple enchondromas
- Multiple haemangiomas
- Unilateral predominance
- Extremely rare
- Associated with
  - Secondary central chondrosarcoma (~40%)
  - Angiosarcoma (3%)
  - Other malignancies (5%) including gliomas

**IDH1 and IDH2 mutations in central cartilage tumors**
- Ollier EC: 87%
- Secondary CS: 86%
- Primary central CS: 38-70%
- Periosteal CS: 15%
- Dedifferentiated CS: 54%

**Somatic mosaicism in Ollier disease / Maffucci syndrome**

**The role of mutant IDH in tumor formation**

**Increased D2HG and hypermethylation in enchondroma**

Adapted from K. Ichimura; Brain Tumor Pathol 2012

Pansuriya et al, Nat Genet 2011

Pansuriya et al, Int J Clin Exp Pathol 2010

Pansuriya et al, Osteoarthr Cartil 2011

Verdegaal et al, Oncologist 2011

Pansuriya et al, Int J Clin Exp Pathol 2010

Pansuriya et al, Nat Genet 2011

Cleven et al, Histoarchitecture 2015

Amary et al, J Pathol 2011

Amary et al, Nat Genet 2011

Pansuriya et al, Nat Genet 2011
From IDH mutation to enchondroma formation

**D2HG**  →  Epigenetic changes → Differentiation → Enchondroma

**D2HG inhibits osteogenic differentiation**

**in vitro**

Control  |  D-2-HG  |  D-2-HG  |  PBS

**in vivo**

Suijker et al, Oncotarget 2015

**Inhibition of mutant IDH1 in chondrosarcoma cell lines**

Cell viability after 72h  |  Migration  |  Colony formation

Suijker et al, Oncotarget 2015

**Usefulness at diagnosis**

- Chondrosarcoma versus chondroblastic osteosarcoma
- Dedifferentiated chondrosarcoma

**Spindle cell hemangioma**

- Benign vascular tumor
- Dermis and subcutis
- Wide age distribution; often children and adolescents
- Predilection for distal extremities
- Locally progressive over many years, but no true recurrence and distant metastases
- ~50% present as multifocal disease
- 5% arises in context of Maffucci syndrome
- 71% IDH1 mutations (IDH1 R132C)

Kurek et al, Am J Pathol 2012

**Spindle cell hemangioma: histology**

Suijker et al, Arch Pathol Lab Med 2013
SDH related tumours

- Extra-adrenal paraganglioma 40%
- Pheochromocytoma 3%
- Gastric GIST 5.75%
- Renal cell carcinoma 0.05-0.2%
- Pituitary adenoma 0.3%
- Hereditary paraganglioma
- Carney-Stratakis syndrome
- Carney's triad

- Germline inactivating mutations
- Autosomal dominant

paragangiomas

- Rare: 2–8 per million people
- Peak incidence 3rd to 4th decade
- Often benign
- High morbidity and mortality in case of production (catecholamines) or mass effect
- Autosomal dominant inheritance pattern

SDHB immunohistochemistry

SDHB IHC is negative when mutations are present in SDHA, -B, -C or -D

Loss of SDHA expression reliably predicts germline SDHA mutation

Berkant and Strauss. Internal Med 2009
**SDH deficient GIST**

- Exclusively gastric
- Children and young adults
- Estimated frequency ~7.5% of gastric GIST
- Female predominance
- Indolent clinical behaviour:
  - lymph node metastases 20-59%
  - Poor response to imatinib
  - Gastric recurrence is common

![Image](image1.png)

**Genetics of SDH deficient GIST; 2 groups**

67% SDHx mutations, 82% germline

- 62% female, median (range) age 23 (7-58) years
- ~30% presented with metastases (liver, peritoneal, lymph node)

22% methylation of the SDHC promoter leading to silencing of expression.

- young females, median [range] age, 15 [8-50] years
- ~40% presented with metastases (liver, peritoneal, lymph node).

![Image](image2.png)

**SDH deficient GIST; histology**

- Multinodular and plexiform growth pattern in muscularis propria
- Epithelioid morphology
- Lymphovascular invasion >50% (not prognostic!)
- Risk assessment not informative
- IHC:
  - KIT +++
  - DOG1 ++
  - SMA –
  - IGF1R

![Image](image3.png)

**Female 26 tumor stomach**

Female 26 tumor mediastinum

Calciﬁed lung nodule

Carney’s triad:
1. Epithelioid gastric GIST
2. Pulmonary chondroma
3. Extra-adrenal paraganglioma

- Young women, antrum
- Multifocal, epithelioid
- 47% metastases (lymph nodes)
- Unpredictable behaviour
- Loss of SDHB, no SDH mutations
- SDHC hypermethylation

![Image](image4.png)

**Male 50 years, paraganglioma, tumor stomach:**

Male 50 years, paraganglioma, tumor stomach:

- DOG1
- SDHB
- SDHA
Carney-Stratakis

- Epithelioid gastric GIST + paragangliomas
- Males = females
- IHC: loss of SDHB protein expression
- Germline mutations in SDHB, -C or –D
- Autosomal dominant

From SDH mutation to paragangioma development

- Loss of ShMC
- Increased H3K9me3

Similar mechanism in SDH deficient GIST

- Loss of ShMC

FH deficient tumours: HLRCC syndrome

1. Multiple cutaneous piloleiomyomas
2. Multiple early onset uterine leiomyomas
3. Type 2 papillary kidney cancer

- Germline inactivating mutations
- Autosomal dominant

HLRCC syndrome

- Extremely rare: ~150 families worldwide
- RCC is aggressive, early onset, propensity for early metastases
- Lifetime risk: ~15%

Early genetic testing and periodic renal imaging!
**FH deficient uterine leiomyoma**

- Symptomatic LM in up to 98% of female HLRCC patients
- Often hysterectomy before age 30

**FH deficiency:**

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected non-atypical LM</td>
<td>1.6%</td>
</tr>
<tr>
<td>Cellular LM</td>
<td>1.8%</td>
</tr>
<tr>
<td>Atypical LM</td>
<td>37.3%</td>
</tr>
<tr>
<td>Leiomyosarcomas</td>
<td>0%</td>
</tr>
</tbody>
</table>

- Somatic mutations in ~1% of all uterine leiomyomas


**FH deficient uterine leiomyoma**

Distinctive histological features:

- Distinctive hemangiopericytomatous vascular pattern
- Hypercellularity
- Small eosinophilic nucleoli with perinucleolar halo
- Stromal edema
- Chain-like arrangement of cells
- Atypia


**FH deficient uterine leiomyoma**

- Nuclear atypia
- Multinucleation
- Prominent nucleoli
- Mitoses including atypical mitoses
- Low biologic potential


**Immunohistochemistry to establish FH deficiency**

- S-(2-succino)-cysteine (2SC)
  - Sensitive, less specific
  - Not commercially available
- Fumarate hydratase
  - Less sensitive, more specific
  - Commercially available


**From FH mutation to LM formation: mechanism similar to SDH**

- Increased H3K9me3
- Loss of 5hmC

Harrison et al, Oncotarget 2015
Common mechanism of tumor formation

Inhibition of:
- TET2 DNA hydroxylase
- JmjC histone demethylase
- HIF Prolyl Hydroxylases

DNA hypermethylation → Inhibition of differentiation

Summary; implications for the pathologist

- Identify these patients
- Based on combination of different tumors
- Based on specific morphology
- Recommend genetic counseling
- Include this information at multidisciplinary tumor boards:
  - Surveillance and prevention
  - Therapy

Thank you