Gastric Cancer and Adenocarcinoma Tumorigenesis: cellular plasticity and metaplasia in cancer and repair

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Some Terms:

• Carcinoma/Adenocarcinoma
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- Carcinoma/Adenocarcinoma
- Metaplasia
Danish professor “Harry” Hirschsprung, obsessed with infantile intestinal disease, was on Le Comité d’organisation.
A. Conférences dans les séances générales.

1. Über Metaplasie.
   Sur la Metaplasie.
   On Metaplasia.
   Prof. Dr. R. Virchow, de Berlin.

2. Microbes pathogènes et vaccins.
   Über pathogene Mikroorganismen und Vaccinestoffe.
   Prof. Dr. L. Pasteur, de Paris.

Rudolph Virchow
• Basically founded the field of pathology
• Prolific in many fields (eg, Virchow’s node, Virchow’s triad)
• Coined many terms (leukemia, embolism, etc.) and started multiple fields
• Key theory (which he popularized from François-Vincent Raspail) was Omnis cellula e cellula
  • Thus, if you have weird cells arising in adults, then they must come from existing cells

• Thought Charles Darwin was an “ignoramus” and people who believed in evolution were “fools”
Take homes from his lecture introducing metaplasia:

• If all cells derive from existing cells, then how do you explain when normal-looking cells show up in the wrong place (not neoplasia, not hyperplasia)

• There are a lot of such “plastischen Prozessen” in the body

• He proposed calling these “Metaplasias”
George Adami: an earlier (reemerging) view on origin of metaplasia and cancer (1900)
Adami’s Laws on metaplasia and reversion (slightly paraphrased): 1900

1. “The fully differentiated cells of a tissue proper never arise from cells that are themselves fully differentiated.”

2. In normal adult tissues, differentiated cells arise by division from “mother” (stem) cells. However, more rarely, functional cells, “by reversion to a more embryonal type, take on the properties of mother cells.”

3. “Under abnormal conditions, the fully differentiated functioning cells of certain tissues are capable of proliferation and giving rise to cells of like nature, but this is only after a preliminary reversion to a simpler, more embryonic type.” The fully differentiated cell does not normally proliferate.

4. The “energy stored up by the [differentiated] cell may be expended in one of two directions...either in functional activity or in preparation for proliferation”. Changes in energy usage and differentiation state correspond to structural or morphological changes in the cell.

5. The more highly differentiated a cell, the more functional it is, the more complex its structure will be. And the more structure it has to scale down the less liable it will be to undergo reversion.
Adami proposed metaplasia/tumors came from:

1. Embryonic stem cell “rests” which remain latent until they are awoken
2. The mother cells, which remain undifferentiated and maintain active proliferation
3. “Differentiated cells which reverting to a simpler, more embryonic type, with this reversion gain the capacity for active and excessive proliferation.

Possibly, I may add, the tendency to the development of glandular cancer in later life bears some relationship to the reversion and degeneration of gland cells at this period. As the tissues become exhausted, the more highly differentiated cells tend to become structurally simpler, revert, that is to say, to a simpler type, and with this simplification of structure accompanying atrophy there may be, I would suggest, a greater liability for those cells to assume proliferative powers, along the lines already laid down.
Some Terms:

- Carcinoma/Adenocarcinoma
- Metaplasia
- Stem Cells/Differentiation
1930s-2005: Waddington Landscape predominates
Back to the present: Terms and Concepts OR the metaplasia field “reverts” back to Adami!
Key, re(!?)emerging concepts:

- Yamanaka: Differentiated postmitotic cells can reprogram to become proliferative, progenitor cells
- This happens following damage in organs without constitutive stem cells
- Or in organs with stem cells when the constitutive stem cell is insufficient for repair (stomach, intestines)
- The process may be the source of metaplasia, dysplasia, and cancer in adult cancers
Scaling: Even after the cell chooses its final fate, it scales up specific architectural features to perform its physiological function.

Dedifferentiation/Reversion: A differentiated cell downscales then reverts to an earlier, less differentiated phenotype (becomes a stem cell again)
Transdifferentiation: A differentiated cell downscales, then converts to another differentiated cell type.
Transdifferentiation: This might occur via dedifferentiation
Speculation:

I propose a Cyclical Hit Threshold Model of cancer initiation: Cycles of metaplasia may allow mutation storage and unmasking (label-retaining cells are mutation-retaining cells)
Cycles of dedifferentiation and redifferentiation may lead to accumulation of mutations that cause cancer in adult organs.

Mills and Sansom, *Science Signaling*, 2015
“Label-retaining”, reserve stem cells may be “mutation retaining cells” so that dedifferentiation and redifferentiation is a risk for neoplasia.
Pancreas: the case has become quickly established that metaplasia arises from differentiated cells that reenter the cell cycle

Reviewed in:
- Roy and Hebrok, *Dev Cell*, 2015
- Ziv et al., *Dev Cell*, 2013
Reprogramming/plasticity (by de/transdifferentiation) fuels acinar-to-ductal metaplasia and cancer.
“Downscaling” differentiated cellular features for cell to refocus energy on proliferation: Focus on a key scaling factor

Mills and Sansom, *Science Signaling*, 2015
"I wish to point out what a fruitful field awaits the investigator who wishes to study, with the aid of our present methods, the pathological conditions of the digestive organs and their treatment. Such an investigation is all the more desirable, because clinical study of the same subject (notwithstanding the zeal devoted to it during the last ten years and the results derived therefrom), has to contend with serious difficulties."

Stomach epithelial cell differentiation and disease

Acid-pumping cell

Digestive enzyme secreting cell
Stem Cells in the corpus/fundus of the Stomach: Canonical

Gastric Unit

Regions: Pit Isthmus Neck Base

Cell Type: Pit Cell Stem Cell Neck Cell Parietal Cell Zymogenic (Chief) Cell

MIST1 zone
Parietal cell atrophy causes regenerative metaplasia, a precursor lesion for gastric cancer.
Cell of origin for metaplasia?

Where do these metaplastic, proliferative basal cells come from?

Some new isthmal stem cell pattern?

Ablation of parietal cells

Mist1+

The chief cell lineage via dedifferentiation?

Mist1–

(there is evidence for both mechanisms)
Downscaling and Reversion in human metaplasia

Mouse knockouts are great, but what about humans?
Carcinoma of the Stomach
3% of cancer deaths in the USA

Epidemiology:
- Decline in incidence in US relative to colorectal CA and worldwide relative to lung CA
- Still a common cause of cancer death in US, especially male minorities, 3rd most common cause worldwide, and rates are rising again
- Third worst 5 year survival in US (much better in Japan)

Pathogenesis
- Dietary factors
- Genetic factors
- *H. Pylori*
- Low socioeconomic status
• *H. pylori* is often termed “necessary but not sufficient” for induction of most gastric CAs

• *H. pylori* is the most common cause of chronic atrophic gastritis

• Chronic atrophy (via HP or autoimmune gastritis) always associates with metaplasia and is a clear carcinoma precursor state

Potential Roles of *H. pylori* and Antecedent Gastritis and Metaplasia
H. Pylori is completely fascinating, but.... I know it can be confusing

- Most colonized people (>1/2 the world population) have no symptoms or occasional gastritis
- ~25% will have a peptic ulcer at some point, treatable by *H. pylori* eradication
- 1-10% will develop gastric cancer eventually
- (This is why *H. pylori* occurs multiple times in this lecture!)
Gastric Carcinogenic Pathway

H. pylori

Normal gastric mucosa → Chronic gastritis → Atrophic gastritis

Chronic gastritis → Atrophic gastritis → Intestinal metaplasia

Atrophic gastritis → Intestinal metaplasia → Adenoma/Dysplasia

Adenoma/Dysplasia → Intestinal-type gastric Adenocarcinoma

Sporadic E-cadherin mutations

Sporadic E-cadherin mutations → Adenoma/Dysplasia

Adenoma/Dysplasia → Diffuse-type gastric carcinoma

Hereditary E-cadherin mutations

Hereditary E-cadherin mutations → Atrophic gastritis

Hereditary diffuse-type gastric carcinoma

Intestinal Metaplasia from Autoimmune Gastritis or H pylori
Human metaplasias

Mills lab (Lennerz et al., 2010)
Gastric Carcinoma
Gross Pathology

Three major growth patterns (different etiologies)

Polypoid or fungating
  • Resemble right colon carcinomas
  • Most common in body and along greater curvature

Ulcerating
  • Most common in antrum and cardia
  • Can be difficult to distinguish from peptic ulcers

Infiltrative (different mechanisms)
  • Diffuse (linitis plastica)
Gastric Carcinoma
Ulcerated
Gastric Carcinoma
Polypoid/Exophytic/Fungating
Gastric Carcinoma
Infiltrative - Linitis Plastica
Gastric Carcinoma
Histological Types and Patterns, molecular mechanisms

Vast majority are adenocarcinomas (>90%)

Two major architectural patterns:

• Intestinal: cells look like colorectal cancer cells and often arises in association with intestinal metaplasia

• Diffuse: signet ring cells (E-cadherin mutations predominate, some familial forms)
Gastric Adenocarcinoma
intestinal type
Gastric Adenocarcinoma

intestinal type
Loss of E-cadherin junction proteins in Hereditary Diffuse Gastric Cancer (HDGC)

Humar et al., Cancer Res. 2007 67:2480
Model for DGC and HDGC development

Humar et al., Cancer Res. 2007 67:2480
Gastric Adenocarcinoma
Diffuse, poorly differentiated, signet ring cells

Normal mucous neck cells
Unleashing the WUCCI: FIB/SEM 3-D imaging and the tools we have to study metaplasia

Washington University Center for Cellular Imaging
(thanks, Paul! and thanks, Duy Tran for introducing FIB/SEM)
3D Nanoscale – FIB-SEM

Focused Ion Beam Milling Scanning Electron Microscopy (FIB-SEM)
FIB-SEM 3-D imaging reveals substantial architectural changes induced by MIST1
Disease: metaplasia (and cancer)

Where do metaplasias come from?

What is the cell-of-origin?

If cancers arise from metaplasia, then that cell might be the origin of cancer, too.
MIST1: is lost early in reprogramming
Cell reprogramming seems to be a conserved, cellular process, like apoptosis or mitosis with distinct stages.

Mills and Sansom, *Science Signaling*, 2015
H Pylori-infected Humans with chronic atrophic gastritis: MIST1+ chief cells seem to scale down and acquire TFF2 expression.

10/31 biopsy specimens showed focal MIST1/TFF2 colabeling.

~1% of gastric cancers are strongly MIST1+ (n=400 samples).

Lennerz et al., *Amer J Pathol* 2010
MIST1 and SPEM and Intestinal Metaplasia
Loss of MIST1 from chief cells undergoing metaplasia (downscaling)
MIST1 in intestinal metaplasia Paneth cells

Red MIST1
Brown CDX2
NOTE: in human stomach metaplasia, transitional forms are in the base, not isthmus.
The first stage of metaplasia
Back to mice: Normal gastric chief cells have abundant granules but few lysosomes

A

LAMP1
CathepsinD
PGC

B

Mills lab, Unpublished
As MIST1 is lost, lysosomes attack secretory granules.

% Cell cytoplasm occupied by lysosomes
At 12 hours after Tamoxifen: lysosomes “attack” secretory granules; 3-D projection: Crinophagy vs. Macroautophagy?
SPEM-type metaplasia requires functional lysosome trafficking.
Reprogramming of differentiated cells back into the cell cycle is a gene-dependent, conserved cellular process with distinct stages.
A note about Pavlov....
Pavlov Citations over time (Google nGram)

Lenin initiates secret funds for studies of how humans might be conditioned (brainwashed)

Digestive Disease Studies
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