Hereditary Diffuse Gastric Cancer: Past, Present and Future

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"Inoperable carcinoma of the stomach in a 21yr old is a tragic discovery.... This paper reports a Maori family in which gastric cancer is too common to be coincidental."

"The present survey (on stomach cancer) seems to have done little more than imbue the family with a deep sense of *makutu*. In the event of other members becoming affected, they may be more inclined towards their gods than their doctors."

*Ted Jones, NZ Med J. 1964*
Ngai Te Rangi 1995 ->
• Dominant inheritance of \textit{CDH1} mutation

• Diffuse gastric cancer
  - signet ring cell carcinoma
  - linitis plastica
  - multifocal disease
  - 70% penetrance

• Lobular breast cancer
  - 40% penetrance
Multifocal stage T1a signet ring cell carcinomas
E-cadherin ($CDH1$) and the adherens complex

- Cell adhesion
- Tissue integrity
- Differentiation
- Cell polarity
- Survival signaling
HDGC life history

- 2nd CDH1 hit
- Division out of the plane

Stage T1a

- Indolent
- Genetically simple

>Stage T1a

- EMT/additional mutations
Germline HDGC mutations

- >330 different CDH1 mutations
- No major hotspots
- >500 families worldwide
- Incidence 2-5/100,000
- ~5 known families with α catenin (CTNNA1) mutations

+ large deletions
HDGC Clinical Management International Consensus Guidelines

- Genetic testing, age >16yrs
  - CDH1 mutation positive
    - Surveillance endoscopy
      - Biopsy -ve
        - Repeat annually
      - Biopsy +ve
    - If unwilling for surgery, preferring to delay, or <20yrs
    - Age >20yrs
      - (Prophylactic) total gastrectomy
        - Close nutritional followup
        - Lobular br ca screening from 35yrs
What now?

*Very low mortality in known HDGC families*

But:
- Gastrectomy - high morbidity
- Surveillance still imperfect
- Poor understanding of individual risk
  - chance
  - frequency of 2\textsuperscript{nd} \textit{CDH1} hit
  - SRCC cell of origin
  - phenotype-genotype correlations

- VUS

- And the families just keep coming..
Is chemoprevention possible?
Vulnerabilities in *CDH1* mutant cells

Disruption of actin interaction with plasma membrane

Disruption of membrane partitioning, signal initiation and vesicle trafficking

Irreversible weaknesses in essential cellular functions
Druggable vulnerabilities in *CDH1*-mutant cells

Membrane partitioning and composition
- lipid raft formation

Vesicle formation and transport
- endocytosis, autophagy

GPCR/TK receptor signaling

Actin polymerisation

Nucleation of membrane-associated signaling proteins
- JAK2/PI3K/AKT/c-SRC/G proteins

PI3K/AKT signaling

*CDH1-/-* cells are more vulnerable to:

- RNAi inhibition of PI3K/AKT pathway genes
- Allosteric AKT inhibitors (eg. MK2206 and ARQ-092)

Godwin et al (2018); Nic Bougen-Zhukov
Megan Taylor
Mouse gastric organoids

CD44-Cre/\(Cdh1^{loxp/loxp/tdTomato^{loxP/loxP}}\)

- Air-liquid interface
- Stomachs from 2-4 day old mice
- ~50 organoids/stomach in 2-3 days

- Inducible \(Cdh1\) deletion and activation of red fluorescent marker gene

**Tanis Godwin**
**Tom Brew**
**Yasmin Nouri**

Green: E-cadherin
Red: \(Cdh1^{-/-}/\text{Tomato}^{+/-}\)
Gastric organoids with reduced *Cdh1* are more sensitive to AKT inhibition

Yasmin Nouri
HDGC mouse model

- CD44-Cre/\( Cdh1^{loxP/loxP/td-tomato^{loxP/loxP}} \)

- \( Cdh1 \) deletion and red fluorescence induced with tamoxifen in antrum

Augustine Chen
“The hill is beginning to heal”
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