Somatic Evolution of Barrett’s/Oesophageal cancer

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The problem: Overdiagnosis in Barrett’s oesophagus

Key issues

1. Oesophageal adenocarcinoma has a very poor survival rate
2. Most patients with Barrett’s oesophagus never get cancer
3. We cannot predict who will develop cancer

We do not fully understand the evolution of Barrett’s and its progression to cancer
Existing evolutionary model in Barrett’s oesophagus

Gland evolution?
Evolutionary dynamics?
Changes in clonal diversity?
Frequency and rate of clonal expansions?

Maley, Cancer Letters, 2007
Glands are the unit of selection

Phenotypes determine selection based on genotype and the microenvironment
Talk Overview

i. Analysis of the clonal structure of non-dysplastic Barrett’s mucosa

ii. Gland phenotype evolution within Barrett’s

iii. The gastric gland as the putative origin of Barrett’s

iv. Non-goblet cell glands and the progression to cancer

v. Classification and clonal analysis of dysplastic Barrett’s mucosa

iv. Diversity analysis as a cancer risk predictor?
mtDNA mutations as markers of clonal expansion in humans

- Poor DNA repair mechanisms
- No protective histones
- Oxidative stress means higher mutation rate than genomic DNA
- Somatic mutations are random
  - Over 40 yrs of age
  - No selective advantage
- Identifiable by histochemistry
mtDNA mutations as markers of clonal expansion in colonic crypts

- Stochastic loss of cytochrome c oxidase (CCO) activity is a reliable marker of clonal expansion
- Enzyme-histochemistry used to trace clonal lineages
- mtDNA sequencing by nested PCR Sanger sequencing

Taylor et al., JCI 2003
Greaves et al., PNAS 2006
Barrett’s glands are clonal

Nicholson et al., Gut 2012; 61(10):1380-89
Multilineage differentiation in Barrett’s glands

Nicholson et al., Gut 2012;61(10):1380-9
CDX2 and MUC6 label mutually exclusive compartments, while MUC5AC and CDX2 can label the same cell.
Foveolar cells and goblet cells are CLONAL in Barrett’s
Lineage relationships within the Barrett’s gland

Lavery et al., Gut 2014