

FOCUS ON RESEARCH

MITOCHONDRIAL DNA DAMAGE IS A BIOMARKER OF AN AT-RISK ENVIRONMENT IN BARRETT'S OESOPHAGUS

Researchers

Mr RJE Skipworth, Dr JA Ross

Aim

DNA within mitochondria (intracellular structures) is 5-10 more likely to suffer damage in the presence of an inflammatory environment than DNA within the cell nucleus. We hypothesised that small changes (mutations) or losses of parts (deletions) of mitochondrial DNA (mtDNA) might be a marker of tissues abnormally affected by chronic inflammation in the oesophagus (gullet) and stomach and are thus prone to the development of cancer. We aimed to:

1. Determine the presence and number of mutations and specific deletions in the mtDNA of tissue samples from patients with conditions which predispose to oesophageal cancer, including Barrett's oesophagus, and conditions involving abnormal oesophageal cells to a lesser or greater degree (low grade and high grade dysplasia)(in order of risk from lower to higher).
2. Determine the presence and number of mutations and specific deletions of the mtDNA in patients with oesophageal and stomach cancer.

Project Outline/Methodology

Paired cancerous and non-cancerous tissue samples were obtained from patients with oesophageal and stomach cancer undergoing surgery in the Royal Infirmary of Edinburgh (RIE). Paraffin-embedded tissue samples of normal oesophagus, Barrett's oesophagus, low grade dysplasia and high grade dysplasia were also analysed. Mutations and deletions of the mtDNA were analysed by a molecular technique which amplifies the mtDNA. The sequences of amplified DNA were investigated to identify specific changes.

Key Results

In the 20 oesophageal and stomach cancer patients recruited, the percentage of samples harbouring mtDNA mutations was similar between cancerous and non-cancerous tissue (75% versus 80%). Within these samples, 23 mtDNA mutations were identified, 11 of which have not previously been described.

In contrast, the percentage of cancer cases in which a deletion of mtDNA was detected was significantly greater in non-cancerous tissue compared with cancerous tissue (75% versus 25%). Furthermore,

when all the results for oesophageal tissues were combined, it was apparent that only those samples with many abnormal cells (i.e. high grade dysplasia) but not cancer, or non-cancerous tissue from cancer patients, demonstrated presence of a specific deletion (termed $\Delta 4977$) in the mtDNA. These observations suggest that chronic inflammation contributes to the rate of mtDNA deletion. However, the lower percentage of mtDNA in cancerous tissue suggests that the final step of cancer development involves either the loss of cells containing mitochondria with large deletions, or only involves cells that do not have abnormal mitochondria (e.g. tissue stem cells).

Conclusions

The presence of $\Delta 4977$ mtDNA deletion or certain specific mutations in the tissue of patients with chronic inflammation of the oesophagus and stomach might be a useful marker of tissue at risk of becoming cancerous.

What does this study add to the field?

This study has demonstrated that mtDNA deletions/mutations can potentially be used as markers of at-risk tissue. Furthermore, it has discovered novel variants of the mtDNA sequence which have not previously been described.

Implications for Practice or Policy

Cancer of the oesophagus and stomach are increasing at the fastest rate of all tumours in Europe. Identification of markers for at-risk patients is a priority. This study, combined with ongoing work, will identify candidate markers.

Where to next?

The next stage will be to devise a longitudinal, prospective study investigating sequential biopsies from patients in screening programs for Barrett's oesophagus. In this way, we will be able to examine changes in mtDNA mutational status over time and correlate these with disease progression.

Further details from:

Dr James Ross, Tissue Injury and Repair Group, University of Edinburgh, EH16 4SB.

