In Brief: The (Molecular) Pathogenesis of Barrett´s Oesophagus

Michaela Aichler, Axel Walch*

Affiliation

Research Unit Analytical Pathology, Institute of Pathology, Helmholtz Zentrum München – German Research Centre for Environmental Health, Neuherberg, Germany

Corresponding Author:

* A. Walch, Research Unit Analytical Pathology, Institute of Pathology, Helmholtz Zentrum München – German Research Centre for Environmental Health, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany. E-mail: axel.walch@helmholtz-muenchen.de

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Abstract

Barrett's oesophagus is a metaplastic change, such that the normal squamous epithelial lining of the oesophagus is replaced by specialised columnar lined epithelium. Barrett´s oesophagus is clinically significant and has a high health economic impact as it is associated with heightened risk of progression to oesophageal adenocarcinoma. This review discusses the pathogenesis of Barrett´s oesophagus with an emphasis on the underlying molecular events.

Keywords: Barrett´s oesophagus, pathogenesis, oesophagus

Introduction

Barrett´s oesophagus (columnar-lined oesophagus; CLO) is the replacement of the lining epithelium of the oesophagus, a metaplastic conversion of normal oesophageal squamous epithelium to specialised intestinal columnar epithelium. The prevalence in the population is estimated as 1 in 50 – 100 people, based on upper endoscopy and histopathological data. CLO has a well-established risk of progressing to intraepithelial neoplasia and oesophageal adenocarcinoma, a cancer with a rapidly increasing incidence and poor prognosis (about 10% 5 year survival) and, in this context, has a high impact for health economics.

Molecular pathogenesis

CLO is regarded as a complication of gastro-oesophageal reflux disease (GORD), reflux of gastic contents to the oesophagus and erosive oesophagitis, and is associated

with hiatus hernia. Reflux episodes result in denuding the oesophagus of normal epithelium, allowing repopulation with columnar epithelium. The exact mechanisms underlying these changes are controversial. Beside gastric acid, bile acids might also be involved in the pathogenesis of CLO through an increase in reactive oxygen specis (ROS) leading to oxidative DNA damage and cell death. However, ROS associated with inflammation in CLO may also be involved. The risk of CLO in men with GORD is 1.5 – 3-fold higher than in women. Obesity and high BMI are also associated with the risk of GORD complications, whereas alcohol and smoking are not strongly associated. Epidemiological studies suggest a familial contribution to GORD and BO, but no specific genetic basis for a hereditary disease has been identified.

It is thought that continuous cycles of injury and repair in CLO that accompanies chronic inflammation predisposes to alterations in gene expression by the epithelial cells. Metaplasias occur when such alterations affect homeotic genes, like the caudal-type homeobox transcription factors (Cdx), that control tissue phenotypes. The changes from columnar to squamous epithelium are associated with a decline in levels of morphogenic factors that regulate the expression of these genes. Reduced methylation of the *CDX1* gene promotor occurs in the intestinal metaplasia of CLO compared to normal oesophageal epithelia, which may underlie CDX1 expression and the columnar phenotype in CLO. CDX2 is also expressed in most CLO lesions and expression in normal squamous epithelium is suggested as a risk factor for the development of CLO and may precede expression of other intestinal markers within the inflamed oesophagus. There is evidence that CDX2 is induced directly by components of refluxate such as acid, bile and pepsin, suggesting a causative effect.

These circumstantial events suggest that CDX gene expression underlies the development of CLO, but actually this condition is probably more a polygenic trait.

In the early stages of disease, basal dysplastic changes are seen in the crypts in CLO, but the upper crypts and surface epithelium associated with these dysplastic crypts show the definitive morphology of a differentiated epithelium. Recent data demonstrated that dysplastic cells at the crypt base and the morphologically differentiated cells in the upper crypt and surface epithelium contain the same oncogenic mutation, showing definitively that the surface epithelium is derived from the dysplastic crypt epithelium (*i.e.* the early lesions are clonal). Therefore, the dysplastic phenotype is not fixed by the early genetic events and dysplastic cells seem able to respond to differentiation signals early in their development, implying that further events are required for disease progression.

Cytokines, ROS and reactive nitrogen species (RNS) are produced by inflammatory cells in CLO and play a crucial role in the progression to oesophageal cancer. Cytokine activated pathways drive tumour growth by inhibiting apoptosis while stimulating tumour cell proliferation, angiogenesis and tissue remodelling. Additionally, ROS and RNS directly damage DNA and therefore induce genetic mutations leading to malignant transformation. Major inflammatory pathways associated with cancer are NF-κB and IL-6/STAT3 and these pathways may be activated by bile acids and gastric acids in oesophageal carcinogenesis. Furthermore, genomic instability (e.g. chromosome instability/abnormality) seems to be fundamental for neoplastic progression in CLO. For example, spatial data in CLO epithelium led to the hypothesis that 9q LOH and mutations of *CDKN2A* are early events that precede 17p LOH and *TP53* mutation, and later DNA tetraploidy and

aneuploidy. Intriguigingly, array based studies have not been able to identify consistent genetic changes, indicating molecular diversity in CLO.

Involvement of stem cell activation

Recent studies on the development on CLO focused on a potential progenitor cell population. Such candidates include cells resident in the oesophageal gland ducts or the interbasal layer of the epithelium, bone-marrow-derived stem cells or transdifferentiated squamous cells. Recently, a molecular link between reflux syndrome and stem cell activation has been proposed. Gastric and bile acids acid as proinflammatory factors may lead to the upregulation of sonic hedgehog (SHH) in the squamous oesophageal epithelium, leading to the induction of bone morphogenetic protein 4 (BMP4) in oesophageal mesenchyme. BMP4 and downstream targets (*e.g. SOX9*) are present in CLO and squamous epithelium in the area of oesophagitis, but not in normal non-inflamed oesophageal mucosa. BMP4 can activate stem cells, which can then lead to the development of CLO. However, substantial debate exists about the cell(s) of origin of CLO and the underlying mechanisms. Recent data indicated a p63-positive stem cell population at the squamocolumnar junction in mice and human. Upon programmed damage to the squamous epithelium, these embryonic cells migrate toward adjacent specialised squamous cells in a process that may recapitulate early CLO.

Clonal evolution

The levels of genetic and molecular diversity in CLO and the resulting extensive heterogeneity might be important in the evolution of oesophageal adenocarcinoma

and the development to treatment resistance. Clonal evolution is the progressive morphological and genetic change of somatic cell populations from normal homeostatic cell division and death within tissues to abnormal neoplastic growth and cancerous spatial expansion within and across tissues. *CDKN2A* mutation and methylation, 9q LOH, *TP53* mutations and 17p LOH are drivers for clonal expansion, and the size of clones with 17p LOH or tetraploidy/aneuploidy increased the risk of progression from CLO to oesophageal adenocarcinoma. Currently, periodic endoscopic biopsies are used to assess the risk of progression to oesophageal adenocarcinoma in patients. However, with regard to clonal evolution, this approach poses substantial challenges for patient care as well as research due to sampling error.

Conclusions and perspective

CLO is clinically significant and has a high health economic impact as it is associated with heightened risk of progression to oesophageal adenocarcinoma. Currently, the clinical management of CLO is hampered by the lack of reliable predictors of progression. The knowledge of molecular mechanisms underlying the pathogenesis of CLO can help in the development of new therapeutic strategies and might have a clinical impact on cancer risk and screening.

Author contribution statement

MA and AW contributed to preparing the manuscript and figure.

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Suggested further reading

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Fig.1: Pathogenesis of Barrett´s oesophagus. Gastro-oesophageal reflux causes a dissociation of tight junctions between squamous cells, causing an increased permeability in the sqamouse epithelium. Cells in the basal layer are exposed to acid, bile salts and inflammatory mediators. Factors as CDX, BMP4 and other morphogenic factors are expressed. This might direct the squamous-to-columnar cell metaplasia characteristic of Barrett´s oesophagus.