Barrett's Esophagus and Esophageal Adenocarcinoma: An example of Malignant Transformation consecutive to Inflammatory Response due to Hydrochloric Acid Exposure. Revision

Elio A. Prieto González[1] and Pamela E. Lizondo[2]

1. Centro de altos Estudios en Ciencias Humanas y de la Salud. Universidad Abierta Interamericana. Argentina
2. Carrera de Licenciatura en Enfermería. Universidad Abierta Interamericana. Argentina

ABSTRACT

Introduction: A brief review aimed at presenting current knowledge on the mechanisms of progression from metaplasia to anaplasia at the molecular level and their possible implications for the prevention, classification, and treatment of this condition, from a Translational Medicine perspective. It focuses on the genetic and epigenetic alterations and the inflammatory phenotype underlying the onset and development of Barrett's esophagus (BE) resulting from exposure to gastric juice.

Objectives: To review the molecular and chromosomal aspects involved in the multistep malignant transformation process that links the changes characteristic of BE with dysplasia and esophageal adenocarcinoma (EAC).

Materials and methods: A literature review was conducted in PubMed and Google Scholar. Twenty English-language articles were analyzed, prioritizing publications from the last ten years, although classic foundational works were also included. The search encompassed both reviews and original articles.

Conclusion: In gastroesophageal reflux disease (GERD), the backflow of hydrogen ions and gastric components induces chronic inflammation and oxidative stress, promoting epigenetic modifications, chromosomal aberrations, mutations in tumor suppressor genes and oncogenes, as well as apoptosis inhibition and local immunosuppression, which drive progression toward adenocarcinoma. BE represents a paradigmatic model of carcinogenesis induced by a known acidic stressor, allowing the integration of molecular and histological changes into a progressive continuum and providing key evidence on the relationship between chronic inflammation and cancer.

Keywords: gastroesophageal reflux disease, Barrett's esophagus, inflammation, progression, epigenetics, mutation, esophageal adenocarcinoma.

Esófago de Barrett y adenocarcinoma de esófago: Un ejemplo de transformación maligna consecutiva a la respuesta inflamatoria por exposición al ácido clorhídrico. Revisión

RESUMEN

Introducción: una revisión breve orientada a exponer el conocimiento actual acerca de los mecanismos del desarrollo desde la metaplasia hasta la anaplasia a nivel molecular y sus posibles implicaciones en la prevención, clasificación y tratamiento de esta afección, desde la perspectiva de la Medicina Translacional. Un enfoque de las alteraciones genéticas y epigenéticas y del fenotipo inflamatorio que subyacen en la aparición y desarrollo del esófago de Barret (EB) a partir de la exposición al jugo gástrico.

Corresponding author: pamelalizondo@hotmail.com, Lizondo PE.

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Objetivos: revisar los aspectos moleculares y cromosómicos involucrados en el proceso de transformación maligna multietapas que conecta los cambios que caracterizan al EB con la displasia y el adenocarcinoma de esófago (ACE).
Materiales y métodos: se realizó una revisión bibliográfica en PubMed y Google Scholar. Se analizaron 20 artículos en inglés, priorizando publicaciones de los últimos 10 años, aunque se incluyeron trabajos clásicos de relevancia fundamental. La búsqueda abarcó tanto revisiones como artículos originales.
Conclusión: en la enfermedad por reflujo gastroesofágico (ERGE), la retrodifusión de hidrogeniones y componentes gástricos induce inflamación crónica y estrés oxidativo, favoreciendo modificaciones epigenéticas, aberraciones cromosómicas, mutaciones en genes supresores y oncogenes, además de inhibición de la apoptosis e inmunosupresión local, que promueven la transformación hacia adenocarcinoma. El EB es un modelo paradigmático de carcinogénesis inducida por un estrés ácido conocido, que permite integrar los cambios moleculares e histológicos en un *continuum* progresivo, aportando evidencia clave sobre la relación entre inflamación crónica y cáncer.

Palabras clave: enfermedad por reflujo gastroesofágico, esófago de Barrett, inflamación, progresión, epigenética, mutación, adenocarcinoma de esófago.

INTRODUCTION

Barrett's esophagus (BE) is a precursor condition associated with an increased risk of esophageal adenocarcinoma (EAC), one of the most aggressive forms of cancer. It is associated with several risk factors, including age ≥50 years, White race, male sex, obesity, and a family history in first-degree relatives of BE or EAC. This process is closely associated with gastroesophageal reflux disease (GERD), in which chronic exposure to gastric acid and bile salts leads to alterations in the esophageal mucosa that initially manifest as metaplasia, followed by dysplasia and, ultimately, progression to EAC[1,2].

Histologically, BE typically progresses from intestinal metaplasia (IM), characterized by the presence of columnar epithelium, to low-grade dysplasia (LGD), then to high-grade dysplasia (HGD), and finally to EAC. Throughout this progression, progressive alterations in cellular organization are observed, including loss of epithelial differentiation, increased cellular proliferation, and structural changes in esophageal glands[3].

At the molecular level, this process is driven by multiple epigenetic alterations, mutations in oncogenes and tumor suppressor genes, and the accumulation of chromosomal aberrations.

BE develops within a chronic inflammatory environment induced by persistent exposure to gastric reflux. This condition generates a vicious cycle in which inflammation –accompanied by increased production of reactive oxygen species (ROS)– promotes mutagenesis and genomic instability[4]. Chronic inflammation not only increases the risk of malignant transformation but also alters the tumor microenvironment, favoring cellular proliferation and immune evasion[5]. This article explores the molecular and chromosomal mechanisms involved in the progression from BE to EAC.

MATERIALS AND METHODS

We conducted a descriptive study. Electronic searches of the scientific literature were performed in PubMed and Google Scholar using keywords such as "gastroesophageal reflux disease," "inflammation," "mutation," "epigenomics," "chromosome aberrations," "aneuploidy," "oncogenes," "esophageal adenocarcinoma," and "transformation." Studies published within the last 10 years were analyzed, although earlier publications were included when considered relevant to the field. Searches were limited to open-access, full-text articles. Both review articles and original studies were included.

STATE OF THE ART

Molecular Mechanisms of Progression from BE to EAC

Chronic exposure to hydrochloric acid (HCl) and other gastric components induces a change in esophageal epithelial function, initially leading to intestinal metaplasia (IM). This change is largely mediated by proinflammatory factors, such as cytokines and chemokines, which are released during chronic inflammation[6]. Inflammation also results in increased release of reactive oxygen species (ROS), which induce DNA damage and cause mutations that lead to oncogene activation and inhibition of critical tumor suppressor genes involved in cell cycle regulation, genomic integrity, apoptosis, or malignant transformation, such as p53, TP16, and TP53[7].

These genetic alterations give rise to a pattern of chromosomal instability, which represents a fundamental feature in the progression from BE to dysplasia and, eventually, to EAC. Chromosomal abnormalities include loss of heterozygosity in tumor suppressor genes and chromosomal gains, creating an environment conducive to the development of invasive esophageal cancer[8,9]. For example, loss of chromosomes 4q, 18q, and 21, and more

frequently of the Y chromosome, has been documented in biopsy studies of patients with BE, whereas gains of chromosomes such as 14 and 20 are observed in more advanced stages of the disease[10,11].

Approximately 20% of these rearrangements correspond to interchromosomal translocations. In addition, the mutation frequency is estimated at 9.9 mutations/Mb (range, 7.1-25.2) per haploid genome. Structural aberrations affecting both the short (p) and long (q) arms of chromosomes from groups A (1p), B (3q), C (11p), and G (22p) have been frequently described[12]. Molecular cytogenetic techniques have allowed the identification, in BE, of aneuploidies involving chromosomes 4, 6, 7, 8, 9, 10, 11, 12, 17, 18, and Y. Importantly, these alterations have been detected from the earliest stages of dysplasia[8].

In another study using comparative genomic hybridization (CGH), a series of recurrent chromosomal gains and losses associated with both carcinoma and premalignant lesions was identified. The most frequent gains were observed in chromosomes 8q, 20q, 2p, 7p, and 10q, whereas losses were primarily located in chromosomes Y, 4q, 5q, 9p, and 18q. In premalignant stages, such as intestinal metaplasia (IM) and low- and high-grade dysplasia (LGD and HGD), similar chromosomal changes were observed, with an increasing number of alterations as lesion severity progressed. This represents a complex clonal evolution, likely driven by the emergence of divergent neoplastic subpopulations. These findings suggest that tumor evolution in BE is highly heterogeneous, posing a significant challenge for clinical surveillance of affected patients[13].

In esophageal biopsies from patients with BE and HGD without invasive EAC, loss of chromosome 9p has been shown to occur earlier than loss of 17p[11]. Loss of heterozygosity (LOH) at 17p is associated with the development of tetraploidy, confirming that loss of p53 contributes to genomic instability. Notably, LOH at 9p involved a larger proportion of the BE-affected area. These findings support a widely accepted model in which loss of CDKN2A represents an early event in BE progression, whereas alterations in TP53 occur at later stages[7].

The association between amplification of **c-MYC** and **EGFR** and progression from BE to EAC is well established; these genes play key roles in the regulation of cell proliferation, angiogenesis, and tumor invasion. Amplification of **c-MYC** and other loci becomes evident during the transitions from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and subsequently to EAC. These changes occur in the context of variations in ploidy, which become more pronounced as lesions progress toward anaplasia[7,14].

Chronic exposure to acid and bile has shown that cells subjected to these conditions experience an accumulation of chromosomal abnormalities that precede dysplastic changes[15]. Recurrent translocations –particularly those involving chromosomes (2;10;16)– have repeatedly been identified as chromosomal markers that become a key feature in the progression from BE to EAC. Such aberrations, identified by fluorescence in situ hybridization (FISH), occur at early stages of malignant transformation, even before significant histological changes become evident[16].

Within this context of BE progression, chromosomal instability has been linked to telomere shortening[3].

Chromosomal instability in BE is more pronounced in patients with shortened telomeres.

Alterations in Cell Cycle Control and Resistance to Apoptosis

Dysfunction in cell cycle control mechanisms plays a crucial role in the progression from BE to EAC. The accumulation of mutations in tumor suppressor genes, such as **p16^INK4a** and **TP53**, is common in EAC[11]. Disruption of cell cycle pathways promotes uncontrolled cellular proliferation. In addition, resistance to apoptosis is a key factor in tumor cell survival. In this context, mutations in genes such as **BCL-2** and **c-MYC** allow dysplastic cells to survive and progress toward invasive carcinoma. These tissue changes correlate with loss of heterozygosity (LOH), chromosomal translocations, and genetic amplifications[5].

Epigenetics and Regulation of Gene Expression

In addition to genetic mutations, epigenetic alterations play a crucial role in the progression from BE to EAC. Aberrant methylation of the promoters of tumor suppressor genes and genes involved in the regulation of inflammation, such as **NF-κB**, is a common phenomenon in the early stages of esophageal cancer[9]. Hypermethylation of **TP53** and hypomethylation of **EGFR** contribute to the activation of oncogenic pathways and inhibition of antitumor responses[17].

An important aspect to highlight is the role of microRNAs in epigenetic regulation. These small non-coding RNAs control the expression of genes involved in cellular proliferation and apoptosis. Alterations in microRNA expression –such as **miR-34a**, a negative regulator of **c-MYC**– have been associated with progression from dysplasia to invasive carcinoma[18].

Histone modifications and microRNA-mediated regulation are key tools for studying the molecular changes associated with BE and should therefore be considered potential early markers of disease progression, as they may be present at initial stages of BE, long before the development of dysplasia or cancer[19]. Chromosomal loss and hypermethylation of the promoter of the **CDKN2A–p16^INK4A** gene have been identified in BE, HGD, and EAC, suggesting their involvement throughout the esophageal carcinogenesis process. Likewise, promoter methylation of the Runt-related transcription factor 3 (**RUNX3**) gene has been described as an important independent risk factor for progression from BE to HGD, making it a clinically relevant predictive biomarker. In addition, aberrant methylation outside CpG islands, together with global hypomethylation, has been observed to favor malignant transformation.

Chromosomal loss and hypermethylation of the **CDKN2A-p16-INK4A** promoter have been identified in BE, HGD, and EAC, further supporting their role throughout the esophageal carcinogenesis process.

Likewise, methylation of the promoter of the Runt-related transcription factor 3 (**RUNX3**) has been proposed as an independent risk factor in the progression from BE to high-grade dysplasia (HGD), thus constituting an epigenetic biomarker with potential predictive clinical utility. On the other hand, hypermethylation of the promoter of the **APC** gene –known for its role in familial adenomatous polyposis (FAP) and colorectal cancer development– has also been associated with premalignant and malignant esophageal lesions such as BE and EAC[19,20].

In addition, it has been shown that both aberrant methylation outside CpG islands and global DNA hypomethylation may facilitate malignant transformation by promoting genomic instability and transcriptional dysregulation. In this context, the combination of multiple genetic and epigenetic alterations has demonstrated a relevant positive predictive value in assessing the risk of tumor progression. In particular, the concurrence of loss of heterozygosity (LOH) in **TP53** and **CDKN2A**, together with the presence of tetraploidy, has been associated with an approximately 39-fold increase in the risk of progression to EAC, underscoring the clinical relevance of these molecular alterations as important predictive markers. Aberrant expression (loss or overexpression) of **p53**, **Ki-67**, **p16**, **β-catenin**, **cyclin D1**, and **MCM2** has also been significantly associated with low-grade dysplasia (LGD), high-grade dysplasia (HGD), and EAC, indicating a high risk of malignant progression[19,20].

Tumor Microenvironment and Immune Evasion

The inflammatory microenvironment in BE favors the progression of esophageal cancer through a series of interactions between malignant cells and the immune system. Chronic inflammation increases the expression of molecules that promote angiogenesis and cell migration, while tumor cells develop mechanisms of immune evasion. The presence of regulatory T cells (Tregs) and the release of interleukin-10 (**IL-10**) are common features of this microenvironment, leading to a diminished immune response against tumor cells[2]. Studies of esophageal biopsies from patients with BE and EAC have demonstrated aberrant expression of programmed death-ligand 1 (**PD-L1**), suggesting that tumor cells may escape immune surveillance by inducing an immunosuppressive environment[21].

CONCLUSION

The progression from BE to EAC is a complex process mediated by a combination of epigenetic alterations –particularly hypermethylation and hypomethylation– in tumor suppressor genes and oncogenes, which may also undergo mutational events. The resulting chromosomal instability can lead to aneuploidy, which, together with genetic mutations, contributes to malignant transformation. These abnormalities arise within an inflammatory microenvironment in which immune surveillance may be impaired, thereby reducing the immune response against cells expressing tumor antigens. A deeper understanding of the molecular mechanisms involved in esophageal carcinogenesis may provide new diagnostic and therapeutic perspectives for EAC at early stages, with the potential to improve patient prognosis.

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