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# Embryological signaling pathways in Barrett's metaplasia development and malignant transformation; mechanisms and therapeutic opportunities

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## Contents



**Abstract**

Barrett's metaplasia of the esophagus (BE) is the precursor lesion of esophageal adenocarcinoma (EAC), a deadly disease with a 5-year overall survival of less than 20%. The molecular mechanisms of BE development and its transformation to EAC are poorly understood and current surveillance and treatment strategies are of limited efficacy. Increasing evidence suggests that aberrant signaling through pathways active in the embryological development of the esophagus contributes to BE development and progression to EAC. We discuss the role that the Bone morphogenetic protein, Hedgehog, Wingless-Type MMTV Integration Site Family (WNT) and Retinoic acid signaling pathways play during embryological development of the esophagus and their contribution to BE development and malignant transformation. Modulation of these pathways provides new therapeutic opportunities. By integrating findings in developmental biology with those from translational research and clinical trials, this review provides a platform for future studies aimed at improving current management of BE and EAC.


*Keywords:* Barrett's metaplasia; Esophageal adenocarcinoma; Bone morphogenetic protein; Sonic hedgehog; WNT; Retinoic acid; Foregut

## 1. Introduction

Barrett's metaplasia of the esophagus (BE) is characterized by the presence of columnar epithelium in the distal part of the esophagus that is normally lined with squamous epithelium. The causative factors underlying the development

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of BE are debated, but persistent gastroesophageal reflux disease (GERD) is the main risk factor. The reported percentages of BE in GERD patients vary between 5 and 25% [1–4]. BE is the single known precursor lesion of esophageal adenocarcinoma (EAC) and can progress through a multistep process from metaplastic to low-grade, then high-grade dysplasia and eventually Esophageal Adenocarcinoma (EAC) [5].

The management of BE and EAC is hampered by the limited effectiveness of surveillance strategies and of current therapeutic regimens in EAC treatment. While the presence of BE increases the risk of EAC development by more than 10-fold, recent large cohort studies estimate the annual progression rate at less than 0.5% [6–8]. This low absolute rate of malignant transformation was the reason to question the relevance of current surveillance guidelines that recommend a gastroscopy every 3–5 years in BE patients [2,6,8,9]. Despite some promising results of acid suppressant medication and non-steroidal anti-inflammatory drugs (NSAIDs), no pharmacological interventions have been proven effective in eradicating established BE or preventing its progression toward malignancy [10–14]. Data from animal experiments and several cohort and case-control studies indicate that non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the rate of BE progression toward malignancy and the risk of EAC [15–22]. However, these findings are disputed by others [23] and the only available randomized controlled trial failed to show any benefit of Celecoxib in reducing progression toward malignancy [24]. The therapeutic options for patients with EAC are also limited. Despite neoadjuvant chemoradiation and surgery the overall 5-year survival of EAC patients is less than 20%, highlighting the need for new therapeutic targets [25,26].

Aberrant activity of embryological signaling pathways is often implicated in the development of metaplasia and cancer. Experimental data suggests that signaling pathways active during esophageal development can provide a new perspective on BE and EAC development and thus provide potential novel therapeutic targets. The Bone morphogenetic protein (BMP), Hedgehog (HH), Wingless-Type MMTV Integration Site Family (WNT) and Retinoic acid (RA) signaling pathways have a key role during embryological development of the esophagus and alterations in these pathways have been observed in both BE and EAC. In this review, we summarize the current knowledge regarding the role of BMP, WNT, HH and RA signaling pathways in esophageal embryology, their role in BE development and malignant transformation and discuss their potential as therapeutic targets in EAC treatment.

## 2. Signaling pathways in foregut embryology

The esophagus is derived from the embryological foregut. During embryological development the foregut lumen divides along the sagittal axis. The ventral half will become the trachea, lined with columnar epithelium

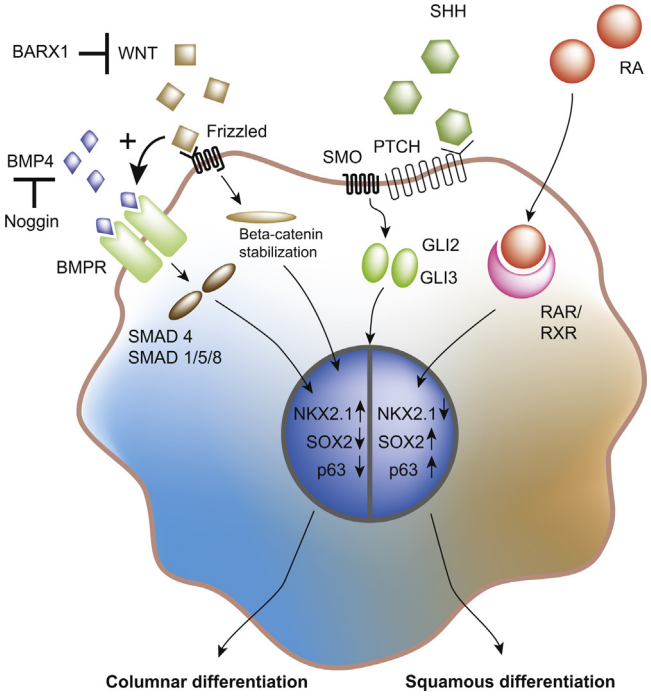


Fig. 1. Signaling pathways in foregut differentiation. Schematic representation of a foregut epithelial cell in which the BMP and WNT pathways contribute to columnar differentiation while RA signaling contributes to squamous differentiation. HH signaling plays a key role in foregut separation, but its effect on differentiation is currently unclear. BMP4, Bone Morphogenetic protein 4; BMPR, Bone Morphogenetic protein receptor; WNT, Wingless-Type MMTV Integration Site Family ligand; SMO, Smoothened; PTCH, Patched; SHH, Sonic Hedgehog; RAR, Retinoic Acid Receptor; RXR, Retinoid X Receptor; NKX2.1, NK2 homeobox 1; SOX2, Sex determining region Y-box 2

while the dorsal half will become the esophagus, lined with squamous epithelium [27]. Most of the understanding of the transcription factors and signaling pathways active in foregut separation and patterning comes from transgenic mouse models (Table 1). These models suggest that differentiation of foregut epithelium toward a squamous or columnar phenotype is regulated by the expression of three key transcription factors: NKX2.1, SOX2 and p63. NKX2.1 induces columnar differentiation of the foregut epithelium, while SOX2 and p63 expression is required for squamous differentiation. Knockout models showed that mice lacking NKX2.1 had impaired foregut separation and a common lumen lined with squamous epithelium [28], while in mice lacking SOX2 or p63 the esophagus was lined with columnar epithelium [28–30]. Further experiments identified four main signaling pathways active in the embryological foregut: the BMP, HH, WNT and RA signaling pathways. These pathways are required for proper development of the trachea and esophagus and influence differentiation by regulating the expression of NKX2.1, SOX2 and p63 [31–33,27] (Fig. 1).

Signaling through the BMP pathway contributes to a columnar differentiation of foregut epithelium. BMP ligands bind to type 1 and type 2 transmembrane BMP receptors (BMPR1 and BMPR2) that activate the SMAD transcription