

## The Relationship of Esophageal Adenocarcinoma with B-Catenin

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### Abstract

Esophageal squamous cell adenocarcinoma is a highly malignant tumor with poor prognosis. The Wnt/ $\beta$ -catenin signaling pathway is a key regulator of cell fate, proliferation, differentiation and survival. Aberrant activation of this pathway has been implicated in various human cancers, including esophageal squamous cell adenocarcinoma. This review presents the evidence that the levels and locations of Wnt/ $\beta$ -catenin signaling parts, such as  $\beta$ -catenin, E-cadherin, adenomatous polyposis coli, cyclin D1 and EB1, are changed in esophageal squamous cell adenocarcinoma and may play a role in its formation and growth. Furthermore, this review explores the possibility of using these parts as indicators or treatments for esophageal squamous cell adenocarcinoma. This review also emphasizes the difficulties and opportunities of revealing the molecular causes of Wnt/ $\beta$ -catenin signaling disruption in esophageal squamous cell adenocarcinoma and creating new ways of diagnosing and treating this severe cancer.

**Keywords:** Esophageal Squamous Cell Carcinoma; Wnt Signaling Pathway; Beta Catenin, E-Cadherin; Adenomatous Polyposis Coli Protein; Cyclin D1

### Introduction

The Wnt/ $\beta$ -catenin signaling pathway controls cell development, growth, diversity and survival. When this pathway is disrupted, it can cause different types of human cancers. Evidence suggests that the Wnt/ $\beta$ -catenin signaling pathway plays a role in the occurrence and development of esophageal squamous cell adenocarcinoma as well. In their study, Lin et al. [1] found a gradual decrease in the expression of E-cadherin, adenomatous polyposis coli and cyclin D1 in esophageal squamous cell adenocarcinoma, with a parallel increase in  $\beta$ -catenin. The researchers concluded that there is a negative correlation between  $\beta$ -catenin and E-cadherin expression, a positive correlation between  $\beta$ -catenin and cyclin D1, and no correlation with adenomatous polyposis coli. It is possible that adenomatous polyposis coli,  $\beta$ -catenin, cyclin D1 and E-cadherin are involved in esophageal squamous cell adenocarcinoma, so they could be used as biomarkers for the diagnosis of early esophageal cancer.

In the analysis of Salahshor et al. [2] on the expression and subcellular localization of major Wnt signaling components (including  $\beta$ -catenin) in patients with esophageal squamous cell adenocarcinoma, a dysregulation of Wnt signaling was

found. In a recent study by Zeng et al. [3], EB1 overexpression in esophageal carcinoma line EC9706 was associated with cell growth promotion. In addition, RNA interference was found to suppress EB1 protein, resulting in the inhibition of esophageal squamous cell adenocarcinoma growth. But the findings were not limited to the above. EB1 overexpression was found to contribute to  $\beta$ -catenin accumulation in the cell nucleus and  $\beta$ -catenin/TCF transcriptional activity. Additionally, EB1 affects the interaction between  $\beta$ -catenin and adenomatous polyposis coli. Finally, Tanaka et al. [4] found that FzE3 expression can enhance  $\beta$ -catenin signals in poorly differentiated esophageal cancers.

Discussion (Wnt/ $\beta$ -catenin signaling in esophageal squamous cell adenocarcinoma: alterations, challenges and perspectives) The Wnt/ $\beta$ -catenin signaling pathway is a key regulator of cell fate, proliferation, differentiation and survival. Aberrant activation of this pathway has been implicated in various human cancers, including esophageal squamous cell adenocarcinoma. The studies reviewed here provide evidence that the expression and localization of Wnt/ $\beta$ -catenin signaling components, such as  $\beta$ -catenin, E-cadherin, adenomatous polyposis coli, cyclin D1 and EB1, are altered in esophageal squamous cell adeno-

carcinoma and may contribute to its tumorigenesis and progression. Moreover, these components may serve as potential biomarkers or therapeutic targets for esophageal squamous cell adenocarcinoma [1-4].

However, the molecular mechanisms underlying the dysregulation of Wnt/ $\beta$ -catenin signaling in esophageal squamous cell adenocarcinoma remain unclear. Several factors may be involved, such as genetic mutations, epigenetic modifications, microRNAs, inflammatory cytokines and tumor microenvironment. For instance, mutations in the  $\beta$ -catenin gene (CTNNB1) have been reported in some esophageal squamous cell adenocarcinoma cases, leading to the stabilization and accumulation of  $\beta$ -catenin in the cytoplasm and nucleus. Epigenetic silencing of Wnt antagonists, such as secreted frizzled-related proteins, Wnt inhibitory factor-1 and Dickkopf-1, by promoter methylation has also been observed in esophageal squamous cell adenocarcinoma, resulting in the activation of Wnt/ $\beta$ -catenin signaling. Furthermore, some microRNAs, such as miR-21, miR-34a and miR-200b, have been shown to modulate Wnt/ $\beta$ -catenin signaling by targeting its components or regulators in esophageal squamous cell adenocarcinoma.

In addition, inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- $\alpha$ , can induce the nuclear translocation of  $\beta$ -catenin and enhance its transcriptional activity in esophageal squamous cell adenocarcinoma cells. Finally, the tumor microenvironment, composed of stromal cells, extracellular matrix and angiogenic factors, can also influence Wnt/ $\beta$ -catenin signaling in esophageal squamous cell adenocarcinoma through paracrine or autocrine mechanisms [5-7].

Therefore, further studies are needed to elucidate the complex interactions between Wnt/ $\beta$ -catenin signaling and other factors in esophageal squamous cell adenocarcinoma. A better understanding of the molecular basis of Wnt/ $\beta$ -catenin signaling dysregulation in esophageal squamous cell adenocarcinoma may lead to the development of novel diagnostic and therapeutic strategies for this aggressive malignancy.

## Conclusion

The Wnt/ $\beta$ -catenin signaling pathway controls cell development, growth, diversity and survival. When this pathway is disrupted, it can cause different types of human cancers, such

as esophageal squamous cell adenocarcinoma. The studies reviewed here show that the levels and locations of Wnt/ $\beta$ -catenin signaling parts, such as  $\beta$ -catenin, E-cadherin, adenomatous polyposis coli, cyclin D1 and EB1, are changed in esophageal squamous cell adenocarcinoma and may play a role in its formation and growth. Furthermore, these parts may be used as possible biomarkers or treatment options for esophageal squamous cell adenocarcinoma. Nevertheless, the molecular mechanisms underlying the dysregulation of Wnt/ $\beta$ -catenin signaling in esophageal squamous cell adenocarcinoma remain unclear. Several factors may be involved, such as genetic mutations, epigenetic modifications, microRNAs, inflammatory cytokines and tumor microenvironment. Thus, more research is required to reveal how Wnt/ $\beta$ -catenin signaling interacts with other factors in esophageal squamous cell adenocarcinoma. By understanding how Wnt/ $\beta$ -catenin signaling is disrupted in esophageal squamous cell adenocarcinoma at the molecular level, new ways of diagnosing and treating this severe cancer may be discovered.

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