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Review Article

B-Catenin and its Connection with Oesophageal Adenocarcinoma and Barrett's Oesophagus

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Abstract

Oesophageal Adenocarcinoma (OAC) and Esophageal Squamous Cell Carcinoma (ESCC) are the two principle histopathological subtypes of Oesophageal cancer (OC). OAC is the predominant EC subtype in western countries whist in most cases considered to progress from a precursor lesion named Barrett's Esophagus (BE). β-Catenin belongs to the catenin family in tandem with alpha-catenin and gamma-catenin. Abnormal expression of β-catenin causes carcinogenesis. Lack of balance in the signaling and structural properties of β-catenin usually leads to deregulation of cell growth and disease associated with cancer and metastasis. Esophageal adenocarcinoma can be developed within the consecutive change of ordinary epithelium into metaplastic epithelium which is called Barrett's esophagus which leads to dysplasia and then cancer. β-catenin (CTNNB1) regulates cell-cell adhesion and gene transcription. The aim of the current review is to evaluate and clarify the association among beta-catenin expression in patients with esophageal adenocarcinoma and Barrett's Esophagus.

Keywords: Beta-catenin; Oesophageal Adenocarcinoma; Barrett's Esophagus; Cancer; Patients

Introduction

Oesophageal Cancer (EC) is ranked as the ninth most common cancer type as well as the sixth prime cause of cancer-related death worldwide [1]. The only curative treatment that can be provided to a patient is surgery. Neoadjuvant therapy that patients undergo before esophagectomy comprises radiochemotherapy and/or chemotherapy [2]. EC starts when abnormal cells initiate to develop in the esophagus muscular tube. Men have got 2-fold to 3-fold higher mortality and incidence of esophageal cancer in comparison to women. The two principle histopathological subtypes are Oesophageal Adenocarcinoma (OAC) and Esophageal Squamous Cell Carcinoma (ESCC) [3]. OAC is the predominant EC subtype and, in most cases, it is considered to progress from a precursor lesion named Barrett's Oesophagus (BO). Barrett's Esophagus (BE) is defined by the distal oesophagus that is covered with metaplastic columnar epithelium, rather than the normal squamous epithelium which is actually anticipated anatomically [4]. Esophageal adenocarcinoma (EAC) is the most common EC subtype in the Western world and the majority of patient cases are believed to progress from a precursor lesion called Barrett's oesophagus. BE and EAC risk factors are body weight, gastrooesophageal reflux disease (GERD), low level of education, and hiatal hernia whilst cigarette smoking and alcohol consumption indicate inconsistent conclusions in observational studies [5, 4].

β-Catenin (Beta-Catenin) belongs to the catenin family in tandem with alpha-catenin and gamma-catenin. It is actively entailed in cell adhesion via cadherin-catenin complexes (CCCs) and the Wnt (Wingless-related integration site) signaling pathway. Deregulation lets β-catenin gather in the nucleus, which might be beneficial in helping the differential diagnosis process of chosen neoplasms [6]. In addition, β-catenin adhesion complex defect is connected with an undifferentiated phenotype

and invasive carcinomas with increased frequency. The vast majority of the adenocarcinomas occurring in Barrett esophagus become clinically visible at a moderately advanced stage, leading to a poor prognosis [7]. The purpose of the present review is to evaluate and clarify the association among beta-catenin expression in patients with esophageal adenocarcinoma and Barrett's Esophagus.

What is B-Catenin

As a multifunctional protein and encoded by the CTNNB1 gene, β-Catenin was recognized at first as an integral structural segment of cell–cell adhesion (ability of a cell to adhere to some other cell or an extracellular matrix, affecting and controlling cell function and behavior) [8]. In mammals, there are 19 Wnt molecules that are already known. In case of a non-activated signaling pathway, an intracellular destruction perplex that comprise glycogen synthase kinase 3 beta (GSK3β), Axin2 and adenomatous polyposis coli and Axin2 is constructed and results in phosphorylation and ubiquitination of βeta-catenin. Consequently, βeta-catenin is recognized and moved away by the proteasomal degradation complex [2].

Implementing control over developmental process, β-Catenin-mediated signaling could act as a possible link mechanism between cancer and inflammation, as it is a significant segment of intercellular junctions [9]. Pretty essential is the role that it plays in cadherin-based adherens junctions which make cell–cell contacts stable as it sequesters the greatest percentage of β-catenin in epithelial cells [10]. As a transcriptional factor of vital importance in Wingless–Int (Wnt) signaling that puts control on human embryonic development as well as adult tissue homeostasis, it has also a profound impact on organ regeneration and stem cell renewal [11]. Abnormal expression of β-catenin causes carcinogenesis (transformation of normal cells to malignant cells) and tumor progression of many types of cancer through quashing the T-cell factor responses [12]. Lack of balance in the signaling and structural properties of β-catenin usually leads to deregulation of cell growth and disease associated with cancer and metastasis [13].

Barrett's-associated adenocarcingenesis in Tambunting et al., research can also be connected with the WNT/b-catenin pathway, as it is an important constituent of complex intestinal homeostasis and the intestine-like phenotype and a restricted expression pattern that underly EAC and BE progress [14]. This study also indicated that in familial adenomatous polyposis (FAP), the deprivation of APC function mutation gene led to overactive b-catenin signaling. TNFa (Tumor Necrosis Factor a) levels increase step by step on account of metaplasia-dysplasia-carcinoma while early findings proved to up-regulate the c-myc (protein that controls cell proliferation and apoptosis) oncogene via β-catenin activity regardless of NF-kB (ancient protein transcription factor) in esophageal cells [15].

Oesophageal adenocarcinoma - Barrett's oesophagus

Oesophageal adenocarcinoma depicts one of the fast-growing cancer cases in countries with high income. Barrett's oesophagus is a known premalignant precursor as regards to oesophageal adenocarcinoma. Despite the estimated prevalence of more than 5% to 6% in the population owing to Barrett's oesophagus, only a small number of patients who live with Barrett's oesophagus are in the position to develop adenocarcinoma making more difficult clinical management owing to the lack of valid predictors [16].

Esophageal adenocarcinoma is one of the deadliest forms of cancer that ranks eleventh in terms of mortality among all malignant neoplasmatic diseases. Even if the development of new treatment strategies and contemporary multi-modal therapies have enhanced survival rate, patients that live with oesophageal adenocarcinoma still have not got a good prognosis. Barrett's oesophagus is defined by the change of the normal esophageal squamous epithelium to metaplastic esophageal columnar epithelium. The principal risk factor concerning Barrett's oesophagus is abiding gastro-oesophageal reflux (GERD), as gastric acid constantly does damage to the epithelium of the distal oesophagus. In spite of the evolution of medicine and technology, the absence of valid predictors does not assist in explaining the rare transition from Barrett's oesophagus to oesophageal adenocarcinoma, and as a result, efficinent surveillance and intervention strategies cannot get developed [17]. It is suggested that mucosal defences in the majority of patients with Barrett's oesophagus depict adaptations to the stiff intra-oesophageal environment of long-term gastroesophageal reflux disease [18].

Risk factors such as GERD, smoking, obesity and malnutrition could be responsible for most of the oesophageal adenocarcinomas. The consequences of obesity may affect all stages of neoplastic progression and biological interactions with GERD, even if obesity is probably also influenced by other pathways. Neoplastic progression to oesophageal adenocarcinoma is represented by unstable genome (including chromosomal instability), disturbance of regulatory pathways and temporal clonal evolution which may be adjusted by host, environmental hazards and protective factors. Appropriate measuring complexity of these changes could create difficulties and opportunities for enhancing risk stratification, early detection and proper protection [18]. Oesophageal adenocarcinoma and Barrett's oesophagus are characterized by component inheritance with significant overlap in the genes that participate in the development of the risk of each condition [17].

The association between Barrett's oesophagus and oesophageal adenocarcinoma is of great importance for public health. OAC continues to grow at a breathtaking pace for at least four decades in many areas of the Western world and especially in Asian countries, such as Mongolia, China, Pakistan, Japan, Bangladesh, Afghanistan, Yemen, Azerbaijan and Myanmar, a situation that used to be extremely rare based on the above countries' health profiles [19]. Nevertheless, 95% of people with oesophageal adenocarcinoma diagnosis still do not have a previous diagnosis of Barrett's Oesophagus [18]. The usual frequency of BE as precancerous disease in individuals is 2.4–4%; thus, the issue of diagnosis, early and continuous BE detection as well as observation patient are absolutely significant owing to the high risk of malignities [20]. Furthermore, esophageal cancer corresponds to 3% of patient cases and ranks 6th of all malignant diseases and is the 3rd most frequent type in tumor list of the gastrointestinal tract. The neoplastic progression of BE is showed by the development of metaplastic areas of metaplasia and an expanding degree of epithelial dysplasia, starting from low-grade dysplasia (mild to moderate) and high-grade dysplasia (severe to carcinoma in situ) [21].

The continuing impact of gastric reflux on the esophageal mucosa, leads to esophageal adenocarcinoma development. It is

almost impossible to be detected in the first stages of the disease on account of delaying onset of clinical symptoms that involve pain dysphagia, respiratory problems (paroxysmal cough, irritation after eating food and aggravation in supine position. Probability for surgical treatment during diagnosis time does not usually surpass 50%. The frequency of EAC towards the long history of BE is raising steadily, reaching more than 5% of patients with BE every year, whilst the 5-year survival rate of EAC patients is very low fluctuating no more than 15%. Prediction of malignancy will probably lead to track the course of BE, predict the transition to EAC, and, therefore, make easier early detection and treatment [21]. β-catenin may serve as a molecular biomarker of progression from BE to OAC. Biomarkers play a significant role as both symptomatic and prognostic markers, and expanding prove recommends that a set of markers gives much more precise and unsurprising comes about than a single marker [22]. Markers that complement current histological assessment anticipate dysplasia and encourage metastatic changes in BO (Barrett's Oesophagus) cells, stratify and evaluate the need for proceeded observing recurrence and the need for more obtrusive medications may demonstrate valuable [23].

Association of B-Catenin with Esophageal adenocarcinoma and Barrett's Esophagus

Current care guidelines are focus on the approach of endoscopy which should be used for detecting early warning signs and monitoring patient's deterioration due to Barretts' esophagus; but its efficiency still remains unclear. To prevent the rising mortality and morbidity from Esophageal adenocarcinoma, it is essential that early detection and active surveillance biomarker assays be developed and have high predictive accuracy, cost-effective, and clinically feasible to get implemented [24].

Many remarkable advances have taken place in the last 10 years in the development of minimally invasive molecular biomarkers-an effort led in large part by the Early Detection Research Network (EDRN). Research in molecular biology, which has started last decade, is anticipated to solve the "paradox" of Barrett's esophagus as well as to identify and control patients with BE. Based on efforts of EDRN several promising biomarkers have been discovered; nevertheless, only a small number of them are in the position to assist both in evaluation and identification of patients with BE and in great danger of progression to EAC [25,24]. Progress in multi-omics technologies (i.e., proteomics, epigenomics), have led to several potential diagnostic and prognostic biomarkers that are identified at the level of RNA, DNA, RNA, and proteins, such a beta-catenin [22]. In addition, the advancement of swallowable cytology proper collection devices as well as the development of emerging technologies have resulted in promising assessments that could probably be implemented into health care in the next 10 years [24].

The parallel study of active β-catenin as well as DKK1 in human esophageal tissues verified a concurrent DKK1-overexpression with abnormal activation of β-catenin signaling in EAC in contrast to healthy mucosa and Barrett's and healthy mucosa. The promising role of new molecular markers that restrain cell cycle and promote progression of lymph node metastases or induce tumor growth, might bring in advanced targeted therapies. Dickkopf-1 (DKK1) as a secreted Wnt/β-catenin pathway competitor entailed in embryogenesis. It prevents the carcinogenic Wnt/β-catenin signaling and its abnormal presence is observed in several malignancies, containing EAC [26]. In EAC the aberrant β-catenin transcriptional activity is caused by growth factors that are associated with Wnt-axis. This activity consequently leads to DKK1-overexpression which can accelerate tumor growth as well as metastasis according to secreted glycoproteins and particular receptors [26].

β-catenin was essentially overexpressed compared to other biomarkers (such as P53, cyclin D1, cyclin A, Cox2, Sox2, P16, Ki67) in several scientific studies [27,28]. Signaling pathways related with β-catenin altogether advance the separation of cancer stem cells, the forebears of developing cancer cells. β-catenin may not only be utilized for the needs of high-risk BE patients but also be valuable as a prognostic marker [23]. It is known that Esophageal adenocarcinoma is created within the consecutive change of ordinary epithelium into metaplastic epithelium called Barrett's esophagus, which leads to dysplasia and then to cancer. β-catenin (CTNNB1) has two functions, to regulate cell-cell adhesion as well as gene transcription [29]. This single molecule performs multiple tasks through precise subcellular compartmentalization and tight control. A major viewpoint of its regulation is the capacity of β-catenin to make reciprocally exclusively protein complexes with three distinctive accomplices: adenomatous polyposis coli (APC) and lymphocyte enhancer factor 1 (LEF1) and E-cadherin.

The competitive nature of these interactions guarantees that transcriptionally active β-catenin does not undergo degradation and as a result, β-catenin, which is part of the intercellular adhesion complex, is not transcriptionally active. APC, which downregulates β-catenin, is a segment of crucial significance of the Wnt signaling pathway. Due to lack of Wnt signaling, APC brings about perplex degradation of β-catenin, deterring its gathering within the cytoplasm. Specifically, in Kalatskaya's research [29], in typical esophageal squamous epithelium, β-catenin is primarily present at the plasma membrane, with some cytoplasmic staining, but does not accumulate in the nucleus. As for BE, it was shown that the majority of β-catenin is membrane localized [30]. In 3–13% of EAC samples, no β-catenin was detected, leading to the hypothesis that loss of E-cadherin expression releases β-catenin into the cytoplasm, while 7–38% of OAC samples maintain normal β-catenin distribution and expression patterns [29]. The relationship of β-catenin with BE and OAC in Kalatskaya's research is well-illustrated as aggregation of β-catenin in cell cores demonstrates tissue progression [29,31]. The most important repercussion of β-catenin aggregation within the nucleus is its transcriptional action. Surprisingly, the appearance of irregular β-catenin, involving deprivation of membranous staining and presence of nuclear staining, is connected with better chances of survival [32].

In addition, Gokulan et al. underlined the importance of some EACs which indicated activity of the WNT/β-catenin pathway via mutations or deprivation of the following APC, AXIN1, and CDH1 genes, even if de-regulation of that particular pathway was not so regular in comparison to other tumor types. Mutations of the CTNNB1 gene, which actually encrypts β-catenin, turned up to be rather unusual [33]. In the same research, deviant activity of the Wnt/β-catenin signaling is a usual incident throughout the last phases of BE neoplastic transformation. This procedure lies beneath tumor possess [7]. Intense nuclear expression of beta-catenin, typical characteristic of its activation, was actually found in 61-63% of EAC. Nuclear accumu-

lation of β-catenin is not common in regular esophageal tissues as well as in Barret's metaplasia [34,33].

Accurate diagnosis and proper therapy for any patient are issues of utmost importance. As far as the contemporary technology, computer-aided detection (CADe) systems (developed by Barrett's Oesophagus Imaging for Artificial Intelligence (BONS-AI) consortium) that are concentrated on detecting primary Barrett's neoplasia based on images and video can help endoscopists a lot. In this way, endoscopists on the one hand can ameliorate and increase their detection rate, while on the other hand they could avoid missing an important number of high-grade dysplasia (HGD), a critical step before EAC, as 53% of endoscopists previously referred that they could miss at least 25% of lesions [35].

Conclusion

Barrett's esophagus is considered to be the only known precursor of esophageal adenocarcinoma. Regular endoscopic surveillance is absolutely necessary for patients with Barrett's metaplasia, as it predisposes adenocarcinoma while leading them to get a better prognosis. β-catenin may serve as a molecular biomarker of progression from Barrett's esophagus to esophageal adenocarcinoma. Consequently, it is necessary that future research examine thoroughly the association of β-catenin with BE and EAC in order to improve cancer diagnosis and upgrade treatment, due to the fact that BE and EAC are still poorly treatable diseases.

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