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Genomics, Epigenetics and Molecular Considerations in Esophageal Adenocarcinoma: What You Need to Know?

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Abstract

Esophageal malignancies are usually encountered in patients over 50 years old and are associated with significant morbidity and mortality. Efforts to improve patient outcomes are slowly shifted towards unravelling the molecular basis of esophageal cancer as this approach could lead to designing individualized treatment protocols and implementing precision medicine paradigms. Our aim was to present recent advances in esophageal adenocarcinoma genomics, epigenetics and molecular biology with regards to their role on disease pathophysiology, patient outcomes and applications to clinical care. Disease progression is correlated with missense mutations and in-frame deletions of EGFR, as well as with upregulation of a variety of genes (*CXCL1 CXCL3, GATA6* and *DMBT1*), microsatellite instability and telomerase overexpression. On the other hand, p53 loss of heterozygosity as well as *HER2* and *c-MYC* amplifications tend to develop in later stages of the disease and are associated with poor prognosis. Downregulation of *CDKN2A*, e-cadherin, *SMAD4, RUNX3* and aneuploidy/tetraploidy are also correlated with unfavorable outcomes. Lastly, p53 immunohistochemistry and methylation panels are already being applied in clinical practice.

Keywords: Esophageal cancer; Esophageal adenocarcinoma; Genomics; Epigenetics

Introduction

Esophageal malignancies are mostly seen in patients over 50 years old and constitute the eighth leading cause of cancer-related deaths worldwide [1,2]. Esophageal cancer (EC) is classified in two major histologic types, namely esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) [3]. Gastroesophageal reflux disease is the main risk factor for development of Barrett's esophagus which is a precursor lesion of EAC, while tobacco smoking and alcohol abuse have been found to predispose to ESCC [2]. In recent years, significant progress has been made in increasing our understanding regarding the genetic aberrations that contribute to the development of esophageal carcinomas and account for their unfavorable prognosis. Interestingly, efforts to improve patient outcomes are slowly shifted towards uncovering the molecular basis of EC as this approach could lead to designing individualized treatment protocols and implementing precision medicine paradigms [4]. The aim of this short review article was to present recent advances in EAC genomics and epigenetics with regards to their role on disease pathophysiology, patient outcomes and applications to clinical care.

First of all, it has been long known that genetic mutations at the receptor level result in dysregulation of cell signaling pathways and aberrant cellular proliferation. The most common receptor mutations seen in early stages of EAC are activating missense mutations and in-frame deletions of the Epidermal Growth Factor Receptor (EGFR) [5]. On the other hand, *HER2* and *c-MYC* amplifications tend to develop in later stages of the disease and are associated with poor prognosis [6,7]. Interestingly, recent data seem to suggest that *HER2* and *EGFR* are frequently amplified synchronously and preferentially dimerize with one another [8]. As a result, it is not surprising that target therapy with *HER2* and *EGFR* inhibitors have showed promising results as adjuvant treatment options in EC [9,10].

Furthermore, EAC have been associated with inactivating mutations and under-expression of the *TGF-β1* receptor type II, which prevent cell cycle arrest and promote tissue invasion [11]. Notably, downregulation of specific members of the *TGF-β* family, namely the *SMAD4* and *RUNX3* genes, has been correlated with high tumor recurrence and observed mortality rates [12,13].

Similarly, to numerous other malignancies, inactivation of the tumor suppressor *TP53* gene is also seen in EC leading to dysregulated cell cycle checkpoints and subsequent accumulation of unrepaired DNA damages. Although mutations resulting in p53 loss of heterozygosity (LOH) may develop even in premalignant stages of esophageal carcinoma, whole-genome and amplicon sequencing have revealed that these genetic aberrations occur more frequently in high grade tumors [14,15]. Interestingly, the British Society of Gastroenterology currently recommends p53 immunohistochemistry as part of routine assessment of Barret esophagus and EAC as this has been shown to diminish diagnostic variability between pathologists [1,16]

EC has also been associated with loss of function of the *CDKN2A* gene, which encodes the regulator p16. These molecules inhibit the cyclin-dependent kinases *CDK4* and *CDK6* which in turn regulate progression from phase G to phase S of the cell cycle. *CDKN2A* under-expression seems to mainly occur through epigenetic modifications, particularly hypermethylation; while inactivating mutations tend to develop less commonly [17]. E-cadherin silencing usually occurs due to epigenetic changes as well, and is associated with high tumor grade and poor survival rates [18]. Furthermore, activation of the Wnt signaling pathway, which downregulates e-cadherins, usually occurs due to

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over-expression of *cyclin D1, Sox-9, c-MYC* and the *WNT2* ligand [19]. Considering that e-cadherins are required for the maintenance of the adherens junction, under-expression of these molecules through the aforementioned mechanisms leads to the disruption of the adherens junction, loss of contact inhibition and, ultimately, aberrant cellular proliferation [18].

In addition to point mutations, large-scale chromosomal alterations also occur in EAC and influence their prognosis. Firstly, flow cytometry studies have showed strong correlation between aneuploidy/tetraploidy and low survival rates in patients with EAC [20]. Secondly, microsatellite instability appears to be a significant mechanism favoring progression from Barrett esophagus to invasive adenocarcinoma and seems to be encountered in approximately 7% of EAC cases [21]. Furthermore, the expression of telomerase, the enzyme responsible for telomere maintenance, is intensified as the disease progresses from metaplasia to full-blown EAC. Considering that telomere shortening is correlated with apoptosis, overexpression of this enzyme enables cancer cells to escape programmed death and provides unlimited replicative and proliferative potential [22].

Discussion

Upregulation of certain homeostatic genes, such as *CXCL1* and *CXCL3* (chemokine ligands), GATA6 (transcription factor) and DMBT1 (regulator protein of the immune system) has also been associated with progression from Barrett esophagus to invasive adenocarcinoma. Furthermore, methylation of number of other genes including *p16*, *RUNX3, HPP1, NELL1, TAC1, SST, AKAP12*, and *CDH13* has also been linked with progression to malignancy. Notably, methylation panels of the aforementioned genetic loci are currently being clinically used as biomarkers of EAC in certain high volume centers [23]. Interestingly, hypomethylation of noncoding DNA regions have been correlated with disease progression as well [24]. Last but not least, investigations regarding the role of microRNAs (miRNAs) in EC are also gaining traction. Particularly there are data suggesting that miR-25, miR-99a, miR-133a, and miR-133b have diagnostic potential, while miR-21, miR-27b, miR-126, miR-143, and miR-145 as a panel may be valuable as both diagnostic markers and predictors of disease progression [25].

Conclusion

In conclusion, genetic research in EC has yielded several promising results, with p53 immunohistochemistry and methylation panels already being applied in clinical practice. Future studies should focus not only on identifying more biomarkers, but also need to thoroughly assess target therapy as a means of improving patient outcomes.

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