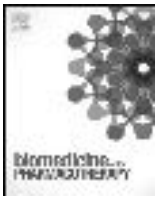
Biomedicine & Pharmacotherapy 176 (2024) 116873

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Review

Therapeutic implications of signaling pathways and tumor microenvironment interactions in esophageal cancer

Inamu Rashid Khan [a], Hana Q. Sadida [b], Sheema Hashem [c], Mayank Singh [d], Muzafar A. Macha [e], Ammira S. Al-Shabeeb Akil [b], Ibraq Khurshid [a,*], Ajaz A. Bhat [b,*]

[a] Department of Zoology, Central University of Kashmir, Ganderbal, Jammu and Kashmir 191201, India
[b] Department of Human Genetics-Precision Medicine in Diabetes, Obesity and Cancer Program, Sidra Medicine, Doha 26999, Qatar
[c] Department of Human Genetics, Sidra Medicine Doha 26999, Qatar
[d] Department of Medical Oncology (Lab), Dr. B. R. Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India
[e] Watson-Crick Centre for Molecular Medicine, Islamic University of Science and Technology, Awantipora, Jammu and Kashmir 192122, India

ARTICLE INFO

Keywords:
Cancer
Esophagus
Signaling
TME
Metastasis
Drug
Resistance
Therapy

ABSTRACT

Esophageal cancer (EC) is significantly influenced by the tumor microenvironment (TME) and altered signaling pathways. Downregulating these pathways in EC is essential for suppressing tumor development, preventing metastasis, and enhancing therapeutic outcomes. This approach can increase tumor sensitivity to treatments, enhance patient outcomes, and inhibit cancer cell proliferation and spread. The TME, comprising cellular and non-cellular elements surrounding the tumor, significantly influences EC's development, course, and treatment responsiveness. Understanding the complex relationships within the TME is crucial for developing successful EC treatments. Immunotherapy is a vital TME treatment for EC. However, the heterogeneity within the TME limits the application of anticancer drugs outside clinical settings. Therefore, identifying reliable microenvironmental biomarkers that can detect therapeutic responses before initiating therapy is crucial. Combining approaches focusing on EC signaling pathways with TME can enhance treatment outcomes. This integrated strategy aims to interfere with essential signaling pathways promoting cancer spread while disrupting factors encouraging tumor development. Unraveling aberrant signaling pathways and TME components can lead to more focused and efficient treatment approaches, identifying specific cellular targets for treatments. Targeting the TME and signaling pathways may reduce metastasis risk by interfering with mechanisms facilitating cancer cell invasion and dissemination. In conclusion, this integrative strategy has significant potential for improving patient outcomes and advancing EC research and therapy. This review discusses the altered signaling pathways and TME in EC, focusing on potential future therapeutics.

1. Introduction

The poor prognosis and growing incidence of EC pose a serious global health concern. It is the sixth most common cancer worldwide [1]. Over 500,000 people die from this disease every year, which makes it deadly [2]. In 2020, this type of cancer claimed more than 544,000 lives globally [1]. Nearly 80 % of occurrences of this malignant tumor occur in less developed regions, where the burden of the disease is notably higher. Men account for around 70 % of cases, and the incidence and mortality rates differ between the sexes by two to five times [3]. The

Abbreviations: BE, Barrett's esophagus; CAFs, Cancer-associated fibroblasts; CAR, Chimeric antigen receptor; EAC, Esophageal adenocarcinoma; EC, Esophageal cancer; ECM, Extracellular matrix; ECM, The extracellular matrix; EGFR, Epidermal growth factor receptor; EMMPRIN, Extracellular matrix metalloproteinase inducer; EMT, Epithelial mesenchymal transition; ESCC, Esophageal squamous cell carcinoma; FDA, Food and Drug Administration; HGFR, Hepatocyte growth factor receptor; HIFs, Hypoxia-inducible factors; ICI, Immune checkpoint inhibitor; IFN-γ, Interleukins and Interferon-gamma; LATS1/2, Large tumour suppressor kinase 1/2; MMPs, Matrix metalloproteinases; MST1/2, Mammalian STe20-like kinases 1/2; NAC, Neoadjuvant chemotherapy; NK, Natural killer cells; PLK 1, Polo like kinase 1; PLK1, Polo-like kinase 1; RUNX, Runt-related transcription factor; TAM, Tumour associated microenvironment; TEAD, Transcriptional enhanced associate domain; TIME, Tumor immune microenvironment; TKs, Tyrosine Kinases; TME, Tumour microenvironment; VEGFR, vascular endothelial growth factor receptor; YAP, Yes associated protein.

* Corresponding authors.
E-mail addresses: dr.ibraq@cukashmir.ac.in (I. Khurshid), abhat@sidra.org (A.A. Bhat).

https://doi.org/10.1016/j.biopha.2024.116873
Received 24 March 2024; Received in revised form 21 May 2024; Accepted 3 June 2024
Available online 5 June 2024