THE ROLE OF ENDOTHELINS IN CANCER PROGRESSION: RECENT INSIGHTS AND THERAPEUTIC OPPORTUNITIES

Cazacu Felicia[1], Sardari Veronica[1], Munteanu Roman[1], Rudic Ciprian[1], Tagadiuc Olga[1]
[1] Department of Biochemistry and Clinical Biochemistry, *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova.

Background. Endothelins (ETs) and their receptors (ETAR and ETBR) play a significant role in cancer progression, influencing processes such as proliferation, invasion, and metastasis. The endothelin axis contributes to modulating the tumour microenvironment (TME), affecting angiogenesis, immune evasion, and therapeutic resistance.
Objective of the study. To elucidate the role of endothelins in cancer progression, metastasis and treatment resistance, as well as the need for therapeutic targeting of the endothelin axis.
Materials and methods. A comprehensive review of scientific literature was conducted using peer-reviewed sources from databases such as PubMed, ScienceDirect, MDPI, Biomed Central, and Wiley Online Library, focusing on the studies published between 2019 and 2024.
Results. Endothelin-1 (ET-1) stimulates tumorigenesis via β-arrestin-mediated signaling, activating mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and Wnt/β-catenin pathways to induce pro-survival mechanisms and proliferation. It facilitates epithelial-mesenchymal transition (EMT) by upregulating matrix metalloproteinases (MMP-2, MMP-9) and suppressing tissue inhibitors of metalloproteinases (TIMPs), enhancing metastatic potential. Hypoxia amplifies ET-1 production, fostering angiogenesis through vascular endothelial growth factor (VEGF) upregulating and stabilizing hypoxia-inducible factor-1α (HIF-1α). ETBR expression correlates with immune evasion by recruiting M2-polarized macrophages and suppressing cytotoxic T-cell activity, observed in melanoma and gastric cancer. Despite promising preclinical results with ET receptor antagonists (bosentan, macitentan) in reducing tumor growth and metastasis, clinical trials have shown limited efficacy as monotherapies. Integrated strategies such as pairing ETAR inhibitors with paclitaxel or immune checkpoint blockers demonstrate enhanced antitumor effects by disrupting stromal-tumor crosstalk and vascular normalization. Emerging approaches, including polyphenols (quercetin, resveratrol) and extracellular vesicle-mediated gene silencing, offer novel routes to target ET-axis dysregulation. The endothelin axis is pivotal regulator of TME remodelling, influencing stromal interactions, immune suppression, and therapeutic resistance. Repurposing FDA-approved ET antagonists, represents a viable strategy to improve cancer outcomes. Further research should prioritize biomarker-driven patient stratification and dual-target therapies to address the complexity of ET signalling in malignancy.
Conclusions. The endothelin axis is central to cancer pathogenesis, influencing tumour processes and interactions within the tumour microenvironment. Targeting ET receptors offers promising therapeutic directions, particularly through repurposing approved ET receptor antagonists.
Keywords: endothelins, cancer progression, tumour microenvironment, angiogenesis, ET receptor antagonists.