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INNOVATIVE DEVELOPMENT OF SCIENCE, TECHNOLOGY AND EDUCATION

PROCEEDINGS OF VIII INTERNATIONAL SCIENTIFIC AND PRACTICAL CONFERENCE MAY 9-11, 2024

VANCOUVER 2024

INNOVATIVE DEVELOPMENT OF SCIENCE, TECHNOLOGY AND EDUCATION

Proceedings of VIII International Scientific and Practical Conference

Vancouver, Canada

9-11 May 2024

Vancouver, Canada

2024

UDC 001.1

The 8th International scientific and practical conference "Innovative development of science, technology and education" (May 9-11, 2024) Perfect Publishing, Vancouver, Canada. 2024. 775 p.

ISBN 978-1-4879-3792-8

The recommended citation for this publication is:
Ivanov I. Analysis of the phaunistic composition of Ukraine // Innovative development of science, technology and education. Proceedings of the 8th International scientific and practical conference. Perfect Publishing. Vancouver, Canada. 2024. Pp. 21-27. URL: https://sci-conf.com.ua/viii-mizhnarodna-naukovo-praktichna-konferentsiya-innovative-development-of-science-technology-and-education-9-11-05-2024-vankuver-kanada-arhiv/.

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УДК 616.34-002-092:612.015.11

THE INVOLVEMENT OF THE MITOCHONDRIAL REDOX HOMEOSTASIS IN THE ESOPHAGEAL AND GASTROINTESTINAL DISEASES

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Abstract This review article synthesizes recent advancements related to the understanding of the role of reactive oxygen species in gastrointestinal pathologies based on the analysis of scientific publications. The global feature of gastrointestinal diseases is inflammation as a complex biological response of the body to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is essential for the elimination of the cause of injury and the initiation of tissue repair and healing. The involvement of the imbalance between the production of oxidants and antioxidant defenses resulted in oxidative stress and underlying tht inflammation of the gastrointestinal tract is presented. The findings in the field of mitochondrial redox regulation disorders in the context of esophageal and gastrointestinal inflammation are shown. This review highlights the mitochondrial dysfunction in the features of the gastrointestinal diseases, offering novel insights into their pathogenesis and pointing towards innovative therapeutic strategies.

Keywords: esophageal and gastrointestinal pathologies, inflammation, oxidative stress, mitochondrial homeostasis.

Introduction. Gastrointestinal diseases refer to pathologies involving the gastrointestinal tract including the esophagus, stomach, small intestine, large intestine and rectum. Despite significant advancements in identifying the causes of

inflammation the biochemical and molecular mechanisms underlying mucosal disorders remain elusive. They are a major site for the generation of reactive oxygen species (ROS), chemically reactive molecules that can cause oxidative stress (OS) when produced in excessive amount. The specific signaling pathways through which OS influences the development of the gastrointestinal inflammation are not fully understood, Mitochondria, the energy-generating organelles in cells, play a crucial role in maintaining redox homeostasis. Disruption of mitochondrial redox homeostasis can lead to increased ROS production, contributing to tissue damage and inflammation disorders. The importance of maintaining redox balance within the gastrointestinal diseases is becoming increasingly apparent, suggesting that interventions aimed at restoring this balance could have therapeutic potential. This gap in knowledge underscores the need for further research to elucidate these mechanisms, which is essential for developing effective preventive and therapeutic strategies. This study aims to investigate the role of mitochondrial redox homeostasis in oesophageal and gastrointestinal pathologies particularly in the context of inflammation.

Methods. To investigate the role of inflammation mitochondrial redox homeostasis in the pathogenesis of various gastrointestinal diseases, we performed a systematic review of the literature using the databases: PubMed, Web of Science, Scopus, and Google Scholar using the above-mentioned keywords. In the process of studying the published material 15 articles selected for citation.

Results. Gastrointestinal diseases, such as gastroesophageal reflux disease **(**GERD), Barrett's esophagus, esophageal adenocarcinoma, gastritis, peptic ulcer, gastric cancer, and inflammatory bowel disease are characterized by chronic or recurrent inflammation of the gastrointestinal tract, which affects the structure and function of the mucosal barrier, the epithelial cells, the immune cells, and the microbiota. Inflammation in the gastrointestinal tract is mediated by various factors, such as genetic susceptibility, environmental triggers, cytokines, chemokines, growth factors, adhesion molecules, and transcription factors [1]. When inflammation is excessive, persistent, or inappropriate, it can lead to tissue damage and dysfunction,

and contribute to the development and progression of various diseases, including gastrointestinal diseases.

GERD is a chronic, progressive, and relapsing condition which is characterized by multifactorial pathogenesis. The pathophysiology involves the interaction of chemical, mechanical, psychologic, and neurologic mechanisms. GERD occurs due to chronic abnormal reflux of gastric contents into the esophagus. This disorder resulting from the retrograde flow of gastric acid promotes symptoms and signs. The clinical presentation is highly heterogeneous including esophageal syndrome consisting of heartburn, regurgitation, and extra-esophageal syndrome. Complications of GERD are peptic stricture, erosive esophagitis which characterized by the metaplasia of esophageal stratified squamous epithelium into columnar epithelium with goblet cells due to long-standing, repetitive injury from acid-bile reflux and development of Barrett's esophagus which is a leading known risk factor and a pathologic precursor for esophageal adenocarcinoma [2, 3].

A key and central event in the development and progression of many inflammatory disorders, including those involving the gastrointestinal tract is production of ROS [4]. ROS modulate the expression and secretion of inflammatory mediators, such as cytokines, chemokines, adhesion molecules, and growth factors, which recruit and activate inflammatory cells, such as neutrophils, macrophages, lymphocytes, and mast cells [5].

The human body has several mechanisms to preventing and repairing damages caused with ROS by producing endogenous antioxidants which act as free radical scavengers[6]. Excessive or prolonged ROS production can cause an imbalance between the oxidants and antioxidant defenses and leads to oxidative stress (OS) which can exacerbate inflammation, tissue damage and plays a pivotal role in the pathogenesis of various gastrointestinal diseases [7].

The important center for the metabolic activities of the body that involves ROS production is mitochondria. Due to the chronic excessive ROS in mitochondria resulted from inflammation, the affection of mitochondrial DNA starts as well as direct damage to cell structure and function [8]. Mitochondrial ROS can activate

various signaling pathways, such as NF-κB, MAPK, NLRP3 inflammasome, and STAT3, which are involved in the inflammatory response and tissue injury [9]. Mitochondrial ROS can also induce mitochondrial-mediated cell death, such as apoptosis, necrosis, and autophagy, which can affect the fate and turnover of inflammatory cells and tissue [10].

Mitochondria are not only the main sites of ROS production but also important organelles in the antioxidant system. The major ROS detoxifying enzyme of cells localized in mitochondria is superoxide dismutase which is a metalloenzyme and hence, requires a metal cofactor for its activity named manganese superoxide dismutase (MnSOD) [11].

In the gastrointestinal tract important source of ROS is the mitochondrial respiratory chain, which generates ROS as a by-product of oxidative phosphorylation. Mitochondrial redox homeostasis is a key regulator of inflammation in the gastrointestinal tract, as mitochondria are both sources and targets of ROS and reactive nitrogen species, which modulate the activation and function of inflammatory cells and molecules.

Mitochondrial dysfunction and oxidative stress are involved in the pathogenesis of GERD and its complications. N.J. O'Farrell1 et al. demonstrated that increased mitochondrial instability and markers of cellular and mitochondrial stress are early events in the Barrett's disease sequence. [12]. These findings suggest an increase in mitochondrial biogenesis at the Barrett's metaplastic stage. Under combination of GERD and autoimmune thyroiditis the tendency to overexpression of MnSOD and depression of total antioxidant activity has been revealed [13]. The assessed imbalance between decline of extracellular antioxidants and activation of mitochondrial antioxidants which is more pronounced in combination of diseases and that this may cause the deterioration of mitochondrial function. The increase of biomarkers of mitohondrial antioxidant defense system with non-specific citoprotection mechanism in patients with GERD provides the basis to consider MnSOD as prognostic indicator of clinical outcome of disease in young age.

In human intestinal diseases, the intracellular ROS levels are increased,

generating cell stress and a reduction in the diversity of microbial community in the gut [14]. Esophageal adenocarcinoma cells have enhanced mitochondrial ROS generation, increased mitochondrial biogenes, oxidative metabolism and adaptive antioxidant response [15].

Conclusion. Mitochondrial redox homeostasis is a crucial factor in the pathogenesis of esophageal and gastrointestinal diseases, and its dysregulation can lead to chronic and unresolved inflammation, which can promote tissue injury, fibrosis, metaplasia, dysplasia, and carcinogenesis. Understanding the molecular mechanisms and interactions between mitochondrial redox homeostasis and inflammation in the gastrointestinal tract may provide new insights into the etiology, diagnosis of such pathologies.

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