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REVIEW Open Access

Nitric oxide and cancer: a review

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Abstract

Nitric oxide (NO), is a ubiquitous, water soluble, free radical gas, which plays key role in various physiological as well as pathological processes. Over past decades, NO has emerged as a molecule of interest in carcinogenesis and tumor growth progression. However, there is considerable controversy and confusion in understanding its role in cancer biology. It is said to have both tumoricidal as well as tumor promoting effects which depend on its timing, location, and concentration. NO has been suggested to modulate different cancer-related events including angiogenesis, apoptosis, cell cycle, invasion, and metastasis. On the other hand, it is also emerging as a potential anti-oncogenic agent. Strategies for manipulating *in vivo* production and exogenous delivery of this molecule for therapeutic gain are being investigated. However, further validation and experimental/clinical trials are required for development of novel strategies based on NO for cancer treatment and prevention. This review discusses the range of actions of NO in cancer by performing an online MEDLINE search using relevant search terms and a review of the literature. Various mechanisms by which NO acts in different cancers such as breast, cervical, gastric,colorectal, and head and neck cancers are addressed. It also offers an insight into the dichotomous nature of NO and discusses its novel therapeutic applications for cancer prevention and treatment.

Keywords: Breast cancer, Gastric cancer, Lung cancer, Head and Neck cancer, H. Pylori, Human papillomavirus, Nitric oxide, Nitric oxide synthase

Review

Introduction

Nitric oxide (NO) is a short-lived, endogenously produced gas that acts as a signaling molecule in the body. Ignarro et al. and Palmer et al. simultaneously identified NO as the endothelium-derived relaxing factor in 1987 [1,2]. It is synthesized by nitric oxide synthase (NOS) enzymes; produced by mammalian cells at an appropriate magnitude and tempo, it serves as a key signaling molecule in various physiological processes. On the other hand, excessive and unregulated NO synthesis has been implicated as causal or contributing to pathophysiological conditions including cancer. Expression of NOS has been detected in various cancers such as cervical, breast, central nervous system, laryngeal, and head and neck cancers [3-7]. NO has been suggested to modulate different cancer-related events [8]. However, several lines of research have indicated that NO may have dual effects in cancer. At concentrations measurable in many different types of clinical samples, NO seems to promote tumor growth and proliferation. In contrast to this, NO is said to have tumoricidal effects;various direct and indirect mecl anisms have been proposed for its antitumor properties [9,10], although there is lack of data directly on cancer patients. Nevertheless, the tumoricidal properties of NO are being investigated for therapeutic purposes. NO is used alone or in combination with other cytotoxic agents. In order to obtain a better insight into the dichotomous nature of NO, an online search using proper search terms through MEDLINE was undertaken and the relevant literature was reviewed. This review discusses the diverse actions of NO in cancer and NO's novel applications in cancer treatment and prevention.

Biological and physiological aspects of NO

NO, a short-lived endogenously produced gas, is synthesized by a complex family of NOS enzymes. Mammalian cells are endowed with three genes encoding distinct isoforms of NOS– NOS1, NOS2, and NOS3 –with 51-57% homology between isoforms and different localizations, regulation, catalytic properties, and inhibitor sensitivity. NOS1, also known as nNOS (isoform first

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