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Review

Targeting arachidonic acid pathway by natural products for cancer prevention and therapy

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ABSTRACT

Arachidonic acid (AA) pathway, a metabolic process, plays a key role in carcinogenesis. Hence, AA pathway metabolic enzymes phospholipase A_2s (PLA_2s), cyclooxygenases (COXs) and lipoxygenases (LOXs) and their metabolic products, such as prostaglandins and leukotrienes, have been considered novel preventive and therapeutic targets in cancer. Bioactive natural products are a good source for development of novel cancer preventive and therapeutic drugs, which have been widely used in clinical practice due to their safety profiles. AA pathway inhibitory natural products have been developed as chemopreventive and therapeutic agents against several cancers. Curcumin, resveratrol, apigenin, anthocyans, berberine, ellagic acid, eugenol, fisetin, ursolic acid, [6]-gingerol, guggulsteone, lycopene and genistein are well known cancer chemopreventive agents which act by targeting multiple pathways, including COX-2. Nordihydroguaiaretic acid and baicalein can be chemopreventive molecules against various cancers by inhibiting LOXs. Several PLA_2s inhibitory natural products have been identified with chemopreventive and therapeutic potentials against various cancers. In this review, we critically discuss the possible utility of natural products as preventive and therapeutic agents against various oncologic diseases, including prostate, pancreatic, lung, skin, gastric, oral, blood, head and neck, colorectal, liver, cervical and breast cancers, by targeting AA pathway. Further, the current status of clinical studies evaluating AA pathway inhibitory natural products in cancer is reviewed. In addition, various emerging issues, including bioavailability, toxicity and explorability of combination therapy, for the development of AA pathway inhibitory natural products as chemopreventive and therapeutic agents against human malignancy are also discussed.

1. Introduction

Cancer has been considered as a global health burden by World Health Organization (WHO) and it represents one of the leading causes of mortality and morbidity worldwide, with approximately 14.1 million new cases and 8.2 million cancer related deaths annually [1,2]. The number of new cases is expected to rise by about 70% over the next two decades. Thus, the global action plan (2013–2020)

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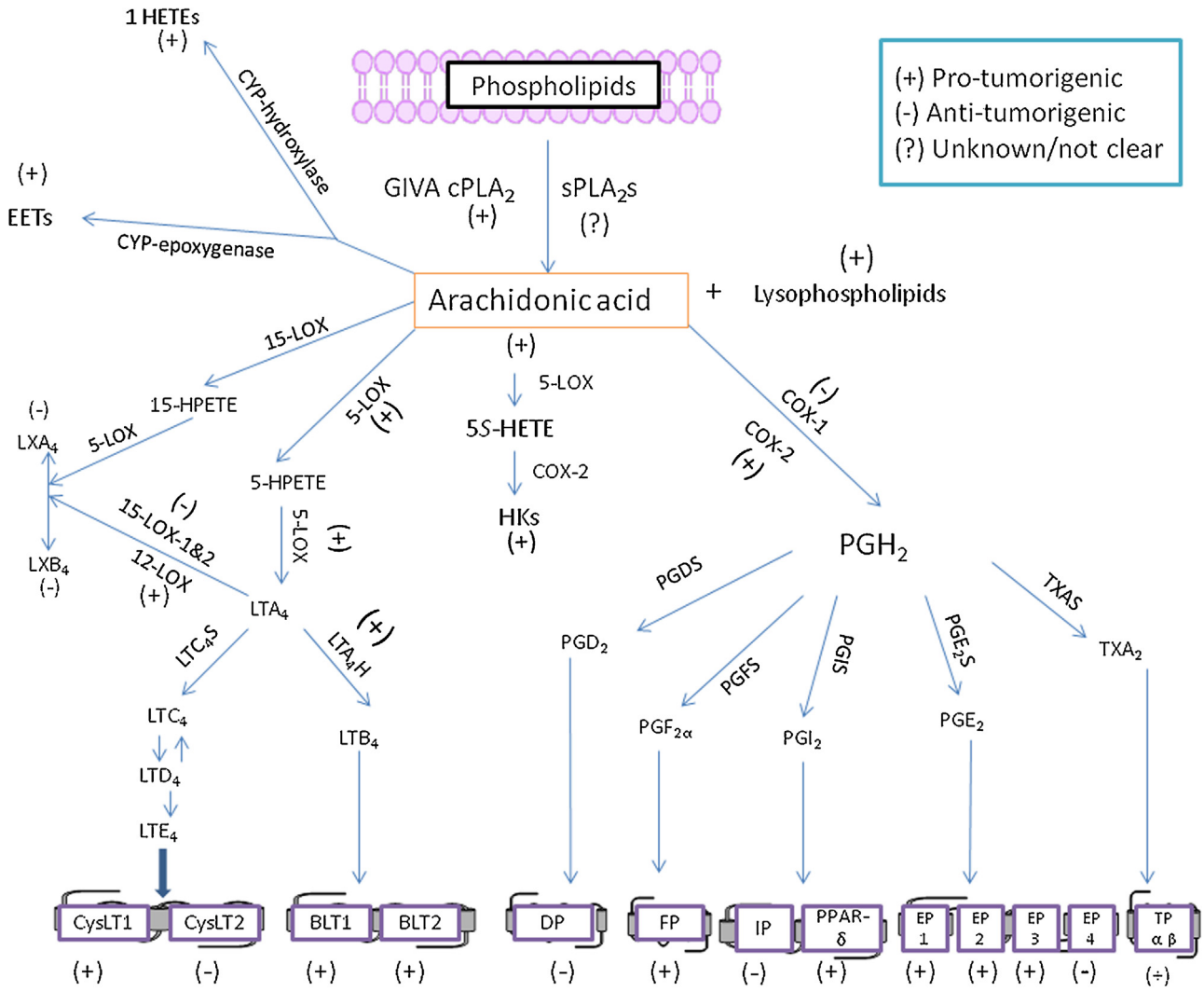

Fig. 1. General biochemical events of arachidonic acid (AA) pathway. Phospholipase A_2s (PLA_2s) act on membrane bound phospholipids and convert in to AA and lysophospholipids (LPLs). $cPLA_2$ is an intracellular enzyme, exhibits pro-tumoigenic property. Roles of extracelluar $sPLA_2$s in cancer are controversial or not clear. The liberated LPLs are also involved in carcinogenesis. Further AA is catalyzed by cyclooxygenases (COXs) and lipoxygenases (LOXs) into prostaglandins (PGs) and leukortiens (LTs) respectively. COXs initially convert AA to PGH_2 and specific downstream enzymes isomerize PGH_2 to prostacyclin (PGI_2), prostaglandins D_2, E_2, or $F_2\alpha$, or thromboxane (TX) A_2. COX-1 is a constitutive enzyme and non-carcinogenic in nature. Role of COX-2 has been characterized as pro-carcinogenic. PGE synthases convert PGE_2 into PGH_2. PGE_2 exerts its physiological effects by binding to E prostanoid (EP) family of GPCR, which differentiated into four subtypes EP1-4. The roles of EP2, EP3 and EP4 have been characterized as pro-tumorigenic but the role of EP1 in tumorigenesis is not clear. TXA synthase (TXAS), a downstream enzyme of COX, catalyzes PGH_2 to TXA_2. Roles of TXAS, TXA_2 and its TXA receptors TPα and TPβ has been characterized as pro-tumorigenic in cancers. PGI synthase, PGI_2 and PGI receptor IP exhibit anti-tumorigenic properties. In some cases, PGE_2 and PGI_2 exert their functions via activation of nuclear peroxisome proliferator-activated receptor delta (PPARδ). PGE_2 promotes carcinogenesis by indirect activation of nuclear PPARδ but role of PGI_2/PPARδ in cancer is unknown. PGD_2 is derived from PGH_2 by activity of two distinct PGD synthases (PGDS), exerts its functions *via* activation of two distinct PGD_2 receptors DP and exhibit anti-tumorigenic properties. $PGF_2\alpha$ formed from PGH_2 by the activity of PGF synthase and exert its function *via* binding to the FP receptor and exhibit pro-tumorigenic properties. 5-LOX converts AA to 5-HPETE and subsequently to LTA4. Moreover, LTA_4 hydrolase and LTC_4 synthase convert LTA_4 into LTB_4 and cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) respectively. Each of the leukotrienes exerts its physiological effects by binding to its cognate G protein-coupled receptor (GPCR). LT receptors are also involved in carcinogenesis. CysLT1 functions as tumor promoter while CysLT2 exhibits anti-mitogenic property. Lipoxins (LXs) are formed by successive oxygenation of AA by two LOX enzymes, one of which is usually 5-LOX. LXs are also produced from LTA_4 by the activities of 12 or 15-LOX. LXs and LXR are anti-inflammatory, anti-cancer and anti-angiogenic mediators. In addition, 5*S*-HETE, a 5-LOX metabolite, serves as a substrate for COX-2 to form pro-angiogenic mediators hemiketals (HKs). Cytochrome P450-dependent epoxygenase and hydroxylase are cytochrome P450 monooxygenases levels exert their pro-tumorigenic actions by producing respective epoxyeicosatrienoic and hydroxyeicosatrienoic acids from AA.

was formed by WHO and the International Agency for Research on Cancer in collaboration with other adhering bodies of the United Nations (UN) organization, such as UN Noncommunicable Diseases Interagency Taskforce (2014), to prevent and control the incidence of non-communicable diseases, including cancer [2,3]. These efforts are aimed to coordinate and conduct research on the causes of human cancer and the mechanisms of carcinogenesis, develop scientific strategies for cancer prevention and control, generate new knowledge, and disseminate existing knowledge to facilitate the delivery of evidence-based approaches to cancer control [2,3]. In this scenario, several research groups all over the world have been working to understand the mechanism involved in carcinogenesis and cancer progression, and developing many strategies for prevention and therapy of cancer [4].

Cancer initiation and progression are multistep processes and are regulated by different internal factors, including growth factors and their receptors, cytokines, chemokines, transcriptional factors, nuclear receptors, as well as arachidonic acid (AA)-derived lipid mediators [5–10]. Moreover, several external factors, such as cigarette, dietary carcinogens, environmental factors and certain chemicals, induce various types of cancers by activating several pro-tumorigenic factors, including AA metabolites [9,10].