Prostaglandins, Leukotrienes and Essential Fatty Acids 86 (2012) 3–11

Contents lists available at SciVerse ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

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

Review

Radiation resistance, invasiveness and metastasis are inflammatory events that could be suppressed by lipoxin A_4

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ARTICLE INFO

Article history:
Received 27 September 2011
Accepted 30 September 2011

Keywords:
Prostaglandins
Polyunsaturated fatty acids
Lipoxin A_4
Radiation
Drug resistance
Metastasis
Cancer

ABSTRACT

Radiation induces overexpression and activity of the MET oncogene that, in turn, enhances the production of prostaglandin E_2, a pro-inflammatory molecule. Prostaglandin E_2 promotes tumor cell invasion, prevents apoptosis, enhances their metastasis and causes radioresistance. It is proposed that lipoxin A_4, a potent endogenous anti-inflammatory molecule, opposes the actions of prostaglandin E_2 and thus, could promote radiosensitivity, suppress tumor cell proliferation, invasiveness and suppress metastasis. Thus, methods designed to enhance endogenous lipoxin A_4 formation or its synthetic analogs may be useful in the management of cancer.

1. Introduction

Tumor cell drug resistance and metastasis are major issues in oncology. It is desired that strategies are developed that selectively kill tumor cells, reverse or block tumor cell drug resistance and inhibit metastasis. In this context, the effect of radiation on eicosanoid metabolism: influence of eicosanoids on tumor cell proliferation, invasion and metastasis and possible relationship among metabolism of polyunsaturated fatty acids (PUFAs), NF-kB signaling pathway and tumor cell apoptosis is interesting.

2. Ionizing radiation and UV radiation and eicosanoid metabolism

Ionizing radiation and UV radiation have profound effects on eicosanoid metabolism, though the degree of effects could be variable. One to 7 days after whole body exposure of mice to a single dose of 700 R of x-rays, little or no change was detected in prostaglandin-like activity in the brain, blood and seminal vesicles, while lung and spleen showed significant increases on the fourth day (from 62 ng/g to 145 ng/g) and from fourth day to seventh day (from 13.2 ng/g to 259 ng/g by fourth day and was still by seventh day 184.4 ng/g). This prostaglandin-like activity measured has been identified as prostaglandin E_1 (PGE_1) and $PGF_{2\alpha}$. Splenic tissue from mice exposed to radiation inactivated PGE_1 less potently than did tissue from non-irradiated mice [1]. These changes in the PG levels could be attributed to alterations in the activity of 15-hydroxy prostaglandin dehydrogenase (PGDH) that fell within 4 h of radiation exposure in the spleen with a transient recovery between 4 and 72 h followed by a second reduction in PGDH activity till the end of the seventh day. In contrast, both the jejunum and kidney showed lesser falls in the activity of PGDH, while it was increased in the lung. Thus, changes in the activity of PGDH may contribute to the increase in prostaglandin concentrations in the spleen and jejunum, and thereby to some features in radiation sickness [2]. Similar, if not identical, results were reported by Trocha and Catravas [3], who noted that whole-body irradiation of rats, resulted in the release of hydrolases from lysosomes, an increase in lysosomal enzyme activities, and changes in the prostaglandin levels in spleen and liver tissues. A transient increase in the concentration of PGE and PGF and leakage of lysosomal hydrolases occurred in both spleen and liver tissues 3–6 h after exposure to radiation that attained maximal values for hydrolase activities, PGE and PGF content and release of lysosomal enzymes by day 4 post-irradiation in rat spleens whereas in liver showed only slight increases in PGF at this time. By day 7 post-irradiation, significant increases in PGE and PGF in the spleen and PGF in the liver associated with leakage of hydrolases from the lysosomes was noted that reverted to near

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doi:10.1016/j.plefa.2011.09.008

normal by day 11 [3]. Steel and Catravas [4] reported similar increases in PGE and PGF_2 in guinea pigs exposed to 0×5, 1×5 or 3×0 Gy of gamma-radiation at 1–3 h but also detected significant increases in thromboxane B_2 (TXB_2) in parenchymal lung tissues that reverted to normal by 24 h. On the other hand, 1 h to 14 days after total-body exposure of guinea pig to 3.0 Gy of Cobalt 60 showed significant changes in PG concentrations in bronchial airway tissues. At 3 h post-exposure, tissue levels of PGE were significantly elevated, while at 48 h transiently elevated levels of $PGF_{2\alpha}$ were noted that returned to control by 72 h, with little or no change in the airway synthesis of TXB_2 [5]. These results suggest that, in general, radiation enhances PGE_1, PGE_2, PGI_2, PGF and TXB_2 levels [6]. This is supported by the observation that COX-2 protein is upregulated after irradiation resulting in elevated levels of PGE_2 in PC3 cells [7]. The ability of radiation to enhance PGE_2 synthesis could be attributed to increased COX-2 mRNA stability through p38 mitogen-activated protein kinase [8]. These results coupled with the observation that 16,16-Dimethyl prostaglandin E_2 ($DiPGE_2$), a stable analog of PGE_2, increases the LD50/30 survival in CD2F1 male mice when given prior to ionizing radiation [9] indicate that enhanced PG production following radiation imparts a survival advantage to the cells/tissues/whole organism.

Similar increases in the production of prostacyclin (PGI_2) by various tissues, especially vascular endothelial cells, have been reported. For instance, exposure of endothelial cells to gamma-radiation results in an enhanced production of PGI_2. The increased PGI_2 synthesis is due to the increase in arachidonic acid release and an activation of cyclooxygenase [10] due to radiation-induced damage (5000 rad), while metabolically active cells, which remained confluent and firmly attached to the culture dish following single, low and intermediate doses (200–1200 rad) radiation, exhibited a marked decrease in their capacity to synthesize PGI_2 upon exposure to various stimuli of the AA cascade such as AA, melittin, ionophore A23187 and PGH_2. The amount of PGI_2 produced by the endothelial cells decreased as a function of the dose of radiation and time interval between irradiation and subsequent stimulation [11–13].

Even ultraviolet (UV) B radiation has similar action (compared to gamma-radiation) on prostanoid synthesis in inducing the production of various eicosanoids that are ultimately responsible for the inflammation seen following sunburn [14]. It was noted that UVB exposed skin produced PGE_2, $PGF_{2\alpha}$ and PGE_3 that accompany the erythema in the first 24–48 h, associated with increased COX-2 expression at 24 h. Leukocyte chemoattractants 11-, 12- and 8-monohydroxy-eicosatetraenoic acid (HETE) are elevated from 4 to 72 h, in association with peak dermal neutrophil influx at 24 h, and increased dermal CD^{3+} lymphocytes and 12- and 15-LOX expression from 24 to 72 h. On the other hand, anti-inflammatory metabolite 15-HETE shows later expression, peaking at 72 h. Thus, sunburn is characterized by overlapping sequential profiles of increases in COX products followed by LOX products that may regulate subsequent events and ultimately its resolution (see Fig. 1). The enhanced expression of 15-HETE at 72 h is interesting since it forms the precursor to anti-inflammatory bioactive lipid: lipoxin A_4 (LXA_4).

LXA_4 is an eicosanoid derived from AA. The sequential action of lipoxygenase enzymes – either 15-lipoxygenase and 5-lipoxygenase (this occurs mainly in the mucosal tissues) or 5-lipoxygenase and 12-lipoxygenase (this occurs during leukocyte–platelet interaction) – controls its biosynthesis [15]. LXA_4 has an important role in resolution of inflammation and regulates the removal of leukocytes and debris from the site of inflammation. The production of epi-lipoxin A_4, an epimer of LXA_4 that also has pro-resolving properties, is triggered by aspirin, and statins also enhance epi-lipoxin production that may explain their benefits in patients with cardiovascular disease. As reported by

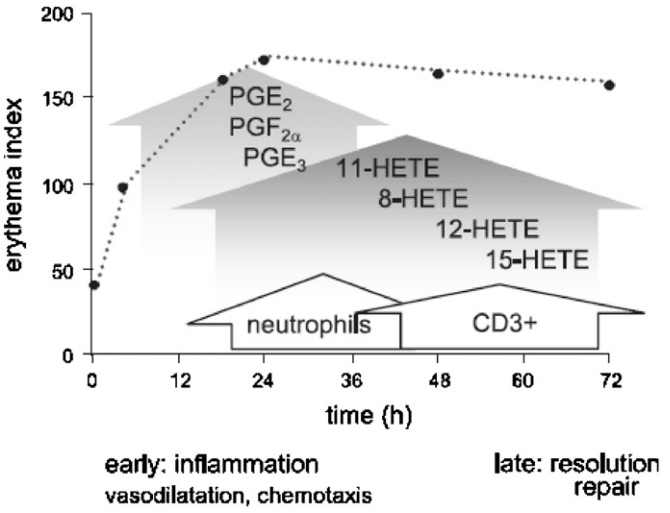

Fig. 1. Sequence of formation of various prostanoids following exposure of normal healthy subjects to UVB for 72 h. Data is taken from Ref. [14]. In this study, possible formation of pro-resolving bioactive lipids such as lipoxins was not measured. Increased formation of 12-HETE and 15-HETE at the end of 72 h when the inflammatory process induced by UVB is resolving suggests that, possibly, they are converted to form lipoxins that possess anti-inflammatory action. In a similar fashion, radiation also may have same type of action on eicosanoid metabolism.

Rhodes et al. [14], a switch between pro-inflammatory and pro-resolving lipid mediators is observed during inflammation. One signal for the switch appears to be the enhanced production of PGE_2 and PGD_2 of 15-lipoxygenase mRNA that stimulates LXA_4 production at the expense of the pro-inflammatory AA-derived LTB_4. In fact, certain microorganisms have been shown to trick a host's immune system into reducing its defenses by enhancing the conversion of AA into lipoxin precursor 15-HETE leading to excess production of LXs [15]. LXA_4 promotes the resolution of inflammation, at least in part, by acting on specific G-protein coupled receptors (GPCRs) expressed by leukocytes [15,16]. It is interesting to note that several PUFAs may also bind to GPCRs (especially GPR40, GPR41, GPR43, GPR84 and GPR120), to produce their anti-inflammatory actions [17–19], possibly, by augmenting the formation of LXs and/or similar compounds. LXA_4 prevents neutrophil infiltration and recruits and stimulates non-phlogistic monocytes, which engulf and destroy dying neutrophils. In addition, neutrophils produce more LXA_4 to facilitate resolution process. Macrophages also have the ability to produce LXA_4 that further aids to clear up debris. Resolution is further boosted by the indirect inhibition by LXA_4 of LTB_4 receptors. Hence, overexpression of 15-lipoxygenase, which increases LXA_4 production, protects against inflammatory diseases and abrogates inflammation that may be essential to protect and/or prevent damage to tissues by radiation. This is supported by the observation that reduced levels of LXA_4 and 15-lipoxygenase are associated with ulcerative colitis and Alzheimer's disease that are pro-inflammatory conditions [15,16,20–22].

It is interesting to note that treatment of mice with LTC_4, D_4, E_4 or B_4 prior to sublethal irradiation increased the number of endogenous hematopoietic stem cells, with LTC_4 producing the greatest response ($LTC_4 > LTB_4 > LTE_4 > LTD_4$) [23]. Subsequent studies revealed that LTC_4 enhanced the radiation survival. Optimal protection was noted 10 μg per mouse (400 μg/kg body wt) administered subcutaneously 5–10 min prior to irradiation. But, paradoxically, tissue distribution analyses did not support a direct role for the protective action seen with LTs against radiation since the highest levels of LTC_4 in the tissues did not correlate with the