

Prostanoids and their mediated inflammatory responses in lung cancer

ABSTRACT

Prostanoids are biochemically important molecules with important roles in pain and inflammatory responses. These responses are part of the significant processes in cancer development and were notably studied in many types of cancers including lung cancer. This review is aimed at reviewing existing literature on the inflammatory responses in lung cancer mediated by prostanoids. Extensive literature review was conducted and information regarding different classes of prostanoids were discussed. The review also covered recent information on roles of prostanoids in development of lung cancer.

Keywords: Prostanoid, Inflammation, lung cancer

INTRODUCTION

The prostanoids are a family of lipid mediators generated by the action of cyclooxygenase (COX) on a 20-carbon unsaturated fatty acid (Arachidonic acid). They are metabolites generally accepted to play a crucial role in inflammation, platelet aggregation, vasoconstriction or relaxation [1]. In cancer, prostanoids are also known to affect induction of growth factors and enzymes, apoptosis, immunosuppression, angiogenesis, proliferation and invasion of tissues [2].

Prostanoids are transported into the extracellular microenvironment by specific multidrug resistance-associated proteins (MRPs) after synthesis and bind to G-protein coupled receptors that contain seven transmembrane spanning domains [3].

Inhibition of their production has been used for over a century to combat a large variety of pathophysiological processes, with great clinical success [4].

CLASSES OF PROSTANOIDS

Prostanoids are a subgroup of eicosanoid, classified into prostaglandin (PG) and Thromboxanes (Tx), containing cyclopentane and cyclohexane ring respectively [5]. According to the modification of cyclopentane ring, prostaglandin are grouped into types A-I, in which type A, B, and C are believed not to occur naturally, but are produced during extraction procedures [4]. Thus, they can be subdivided into prostaglandin D (PGD), E (PGE), F (PGF), and I (PGI) naturally [1]. Prostaglandins maintain local body homeostasis and are ubiquitously produced, each cell type generates one or two dominant products acting as autocrine and paracrine lipid mediators [6].

Likewise, thromboxanes are subdivided into TxA and TxB. In tumor tissues, increase in thromboxane expression has been observed relatively to normal tissues, pinpointing the potential role for this molecule in tumorigenesis and progression of cancer [7]. Thromboxane synthase has found to be moderately expressed in normal lung tissues of bronchial epithelial cells and weakly expressed in vascular smooth muscle cells [8].

PROSTANOID BIOSYNTHESIS

Different studies demonstrated that the prostanoid biosynthesis profile of cancerous cells is different from that of normal tissue [9].

Prostanoids are formed by the action of prostaglandin G/H synthase or cyclooxygenase (COX), through the conversion of Arachidonic acid (AA). Arachidonic acid is abundant in humans released from cell membrane phospholipids through the action of phospholipase A2 and is converted in three different pathways to either prostanoids, hydroperoxyeicosatetraenoic (HpETEs) or epoxyeicosatrienoic acids (EETs) [5].

COX enzyme exists as two distinct isoforms, COX-1 or COX-2 [10]. Not exclusively COX-1 is the dominant source of prostanoids for housekeeping functions, such as gastric epithelial cytoprotection and hemostasis, expressed constitutively in most cells. COX-2, is the more important source of prostanoid formation in inflammation and cancer, induced by cytokines, shear stress, and tumor promoters [3]. The prostanoid produced depends on cell type and enzymes present in the cell and

need to cross the cell membrane to exert some biological action [11]. However, prostanoids are chemically unstable molecules (PGG, PGH, PGI and TXA) with approximate half-life of 30 seconds to a few minutes and even though other PGs are more stable they are metabolized quickly [3]. Synthesis of prostanoid is essential for the generation of inflammatory pain and depends not only on prostanoid production at the site of inflammation, but also on the actions of prostanoids synthesized within the central nervous system (CNS) [12].

ROLES OF PROSTANOIDS IN INFLAMMATION

Inflammation resulted as an immune system response to infection and injury, it's been implicated in cancer pathogenesis and stroke, as well as in arthritis, neurodegenerative and cardiovascular disease [13].

The biosynthesis of prostanoid is significantly increased in inflamed tissue [1]. Similarly, Samad *et al.* [12], also reported that increase in prostanoid synthesis and pain hypersensitivity are associated with tissue injury and inflammation.

Nonsteroidal anti-inflammatory drugs (NSAIDs), COX-1/COX-2 inhibitors and Aspirin are known to be used as an anti-inflammatory agents, highlighting the proinflammatory role of the prostanoids [1,14]

COX-2 is the major source of proinflammatory prostanoids whilst COX-1 accounts for 10-15% of the prostanoid formation induced by lipopolysaccharide in humans [15]. Impaired inflammation responses although diverged in time course and intensity has been shown in both COX-1 and COX-2 deficient mice [1]. The initial phase of acute inflammation in humans was as a result of COX-2 derived product, with COX-2 upregulation occurring within several hours.

Despite the clinical efficacy of NSAIDs, prostaglandins may function in both the promotion and resolution of inflammation [13].

Continuous dysfunction of the inflammatory response, leads to scarring and loss of organ function, hence it's anticipated that failure of acute inflammation to resolve may incline to auto-immunity, chronic dysplastic inflammation and excessive tissue damage [16].

LUNGS CANCER

This is referred to as an unusual and uncontrolled cell growth in the tissues of the lungs that results into a tumour [17]. It is sometimes referred to as bronchogenic carcinoma [18].

Neighbouring cells could be affected when tumour cells metastasize [19].

Lungs cancer is classified into two major groups based on how they grow and spread differently. They are; Small Cell lungs Cancer (SCLC) and Non-small lungs cancers (NSCLC). The latter is said to be the most common as it accounts for about 80% of all lungs cancers [17].

The NSCLC can further be divided into several types depending on the type of cells found in the tumour. The major type includes; Adenocarcinomas, Bronchioloalveolar Carcinoma, Large cell carcinomas and Squamous cell Carcinomas [20].

The most common symptoms associated with all lungs cancer includes; Loss of weight, Chest pains, coughing of blood, swelling in the face and loss of appetite [21].

INCIDENCE OF LUNGS CANCER

In a survey carried out by the world health organization in 2012, it was stated that lungs cancer accounted for about 1.8 million new cases and resulted to about 1.6 million deaths [22].

As at 2016, about 13% of all cancer diagnosis were attributed to lungs cancer, with 225,000 new cases expected to be diagnosed [23].

In America, about 415,000 American's have been diagnosed with this disease at one point or the other in their lives [24], while about 158,000 American's are expected to die from lungs cancer in 2016. This would account for about 27% of all cancer deaths [23].

Talking about gender, it is believed that more men are diagnosed with this disease more often than women (With about 60.7 and 47.7 per 100,000 respectively) [24].

Of this figure, about 83% of those with this disease were 60 years of age and above [24].

In terms of other cancer types, lungs cancer is the second most common cancer (Second after Prostate cancer) diagnosed in men while in women, it is second only after breast cancer [25].

RISK FACTORS ASSOCIATED WITH LUNGS CANCER

Table 1 summarizes the factors which may increase/decrease the risk of lungs cancer. It can be seen that smoking, history of lungs diseases and exposures to heavy metals (mostly via occupational activities) have since been known to increase the risk of lungs cancer. Dietary habits and physical activities both have shown diverse effects on the risk of lungs cancer.

Table 1: Factors Which Increases/Decreases the Risk of Lungs Cancer.

Cause	Effect	Strength of evidence
Smoking	Increased risk of lung cancer	Established cause of lung Cancer
History of lungs disease e.g. emphysema	Increased risk of lung cancer	Established cause of lung Cancer
Exposure of heavy metals, Asbestos and Radon	Increased risk of lung cancer	Established cause of lung Cancer
Drinking water contaminated with Arsenic	Increased risk of lung cancer	Strong Evidence
Intake of high dose of beta carotene in current and former smokers	Increased risk of lung cancer	Strong Evidence
Consuming foods such as red meat, processed meat and alcoholic drinks	Increased risk of lung cancer	Strong Evidence
Physical activity	Decreased risk of lungs cancer	Some Evidence
Consuming foods containing Isoflavones	Decreased risk of lungs cancer	Some Evidence
Consuming foods containing Vitamin C	Decreased risk of lungs cancer	Some Evidence
Consuming vegetable and fruits	Decreased risk of lungs cancer	Some Evidence

DIAGNOSIS OF LUNGS CANCER

The clinical diagnosis of lung cancer is represented in a flow chart

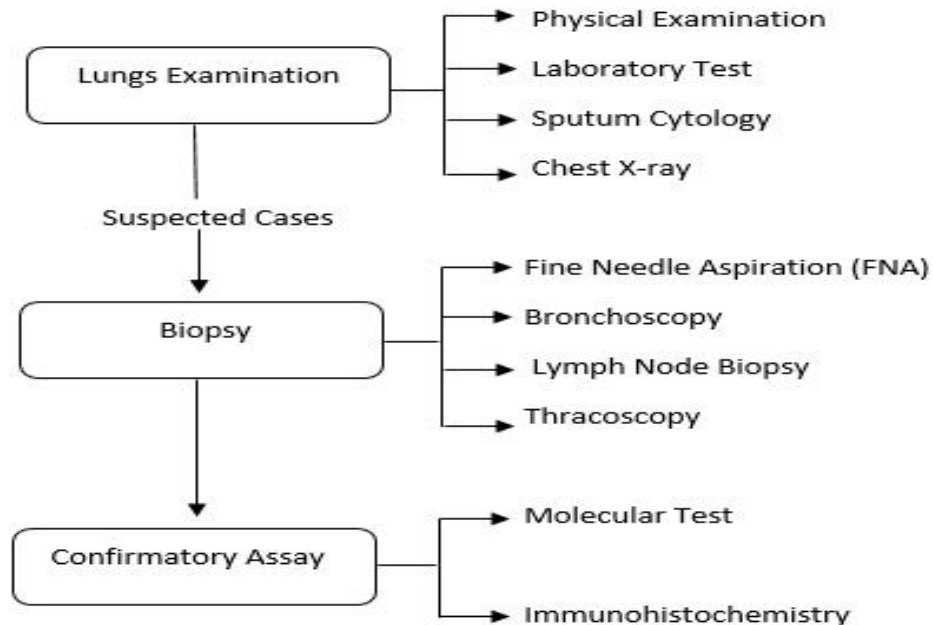


Figure 1: Showing the Clinical Diagnosis of lungs Cancer.

INFLAMMATION IN CANCER

Inflammation is simply defined as the natural way in which the body respond to potentially harmful events [26]. It plays a protective role by recruiting cells and molecules present within the host immune system to the site of injury [27]. The recruited cells are now charged with the responsibility of removing damaged/dead cells and tissues [27].

It can generally be classified into two main type's i.e Acute and Chronic inflammation [26]. The Acute Inflammation is associated with four known symptoms such as Tumour, Calor (heat), Rubor (redness) and Dolor (pain). While the Chronic form has no physical symptoms and has been identified to play a key role in the formation of cancer, contributing to about 15 percent of all solid tumours [28].

In a normal wound healing process, inflammation and all cellular reproduction needed are recruited to repair the damaged cells/tissues [29]. After the damaged cell has been repaired, their activity tends to subside [29]. In a situation where this natural process is sustained for a prolonged or inappropriate time, it increases an individual's risk to cancer [30]. Chemicals such as reactive oxygen species (ROS) and Nitric oxide species (NOS) are normally produced by the immune system to acts as a defence mechanism against infections [31]. They play this role by damaging the DNA of the invading organism. Now if these species persist for a longer period of time after destroying the foreign DNA, they can begin to cause permanent damage to our own cells (mutations) [32].

Overtime, these mutations accumulate in the epithelial cells and leads to dysregulation of their growth. This may lead to the production of cytokines and chemokines which attract immune cells to facilitate cancer development [33]. The cytokines and chemokines produced by the inflammatory cells also triggers it to produce metalloproteinases (MMPs). These are simply proteins with the ability of degrading components of the extracellular matrix [34]. Major ones involved in tumour angiogenesis includes MMP-2, MMP-9 and MMP-14 [35]. They have been implicated in all stages of cancer including metastasis down to proliferation and evasion of the immune system [36]. In a related research carried out by Atkinson and Senior [37], it was shown that the cells of the normal lungs does not produce MMP-9. But under different forms of stimulation, fibroblasts, smooth muscles cells and endothelial cells all produce MMP-9.

All of these clearly show how a microenvironment of chronic inflammation may lead to tumour initiation and subsequently to cancer. Furthermore, Gomes *et al.* [38] confirmed the microenvironment surrounding the lung cancer tumour consist of cytokine, hormones, growth factors, fibroblasts, inflammatory and tumour cells among others.

Due to the above mechanism described, inflammation has since been established as a major player in the development of cancer [31]. In a work carried out by Hanahan and Weinberg [39], it was stated that many of the mediators released during chronic inflammation promote uncontrolled cell division, increased mutagenesis and induces angiogenesis. All of these combine together to trigger the initiation of a malignant phenotype and therefore tumour progression may be promoted.

An important pro-inflammatory cytokine is the Tumour necrosis factor alpha (TNF- α) which is known as a key downstream mediator in inflammation [31]. It plays a very important role in early tumour events such as regulating a cascade of cytokines and pro-angiogenic activities [40]. Therefore TNF- α through inflammation can act as a tumour promoter [41].

Pro-inflammatory interleukins such as IL-18, IL-12 and IL-8 have been observed to have increased serum levels in lungs cancer [42].

PROSTANOIDS IN LUNGS CARCINOGENESIS

Till date, the best evidence showing the role of inflammation and inflammatory mediators to cancer development comes from the clinical and epidemiologic studies [43]. In their study, it was shown that the daily use of non-steroidal anti-inflammatory drugs (NSAIDS) plays a beneficial role by reducing the incidence, mortality and metastasis of various solid tumours [43].

The molecular mechanism in which NSAIDS carry out such roles has not yet been fully established, but they are thought to reduce the production of prostaglandins by inhibiting the activity of the cyclooxygenase (cox) enzymes [44].

This prostaglandin being one of the major prostanoids have since been implicated in various biological responses such as inflammation and tumorigenesis [45] with only prostaglandin E2 (PGE2) playing a predominant role in tumour progression and metastasis [46].

Cox-1 enzymes have been found to be constitutively expressed in most tissues and plays a role in maintaining tissues homeostasis. As oppose to cox 1, cox 2 is mostly absent in most genes but it is highly inducible at sites of inflammation and cancers [47].

At the initial phase of an inflammatory response, PGE2 together with related prostanoids e.g. Prostacyclin (PGI2) acts as vasodilators. They do so by facilitating the tissue influx of neutrophils and macrophages to the site of infection or tissue injury.

PGE2 also increases the pain response by stimulating the sensory nerves [48].

However, it must be stated here that contrary to existing knowledge, PGE2 has also shown evidence of being a major player in the anti-inflammatory process [49].

In various human malignancies such as lungs and colon cancer, PGE2 was found to be the most

abundant [50]. In contrast, Hydroxyprostaglandin dehydrogenase 15 NAD (15-PGDH) mainly responsible for metabolizing intracellular PGE2 is highly expressed in normal tissues but lacking in these cancerous cells [51]. It could be the lack of 15-PGDH expression in these tumours that results in high levels of PGE2.

In other forms of cancer such as colorectal cancer (CRC), it was shown that Cox2-derived PGE2 did promote tumour growth. By inhibiting the endogenous PGE2 by genetic deletion of prostaglandin E synthase, it was found that intestinal tumorigenesis was suppressed [52]. This was in support with older research works done by Mutoh *et al.* [53]. This further confirm the central role of PGE2 in colorectal tumorigenesis.

With the recent direct evidence provided by Zelenay *et al.* [54] which showed how PGE2 promotes tumour growth by evading immune attack, it could be possible that the same mechanism may be found in lungs carcinogenesis.

CONCLUSION

Inflammation is an important aspect in both physiological and pathological conditions. Prostanoids role in promotion of inflammation could establish their influence and roles in lung cancer development. It could therefore be concluded that with major roles in inflammatory processes, carcinogenesis of lung cancer could be affected by inflammatory responses mediated by prostanoids.

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