

Prostanoids and Their Mediated Inflammatory Responses in Lung Cancer

Aghogho Ohwofasa¹, Aliyu Abubakar Aliyu^{1*} and Sadeeq Muhammad Sheshe¹

¹Department of Biosciences, COMSATS University Islamabad, Pakistan.

Mini-review Article

ABSTRACT

Prostanoids are biochemically important molecules with significant roles in pain and inflammatory responses. These responses are studied in several cancers including lung cancer because they are involved in the processes of cancer development. The aim of this article is to review the existing literature on the inflammatory responses in lung cancer mediated by prostanoids. Information regarding different classes of prostanoids, lung cancer and their incidence are discussed. Nonetheless, the review also covers recent information on roles of prostanoids in lung cancer development and its risk factor.

Keywords: Prostanoid; inflammation; lung cancer.

1. INTRODUCTION

The prostanoids are one of the families 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,

*Corresponding author: E-mail: aliyu4abubakar14@yahoo.com;

vasoconstriction or relaxation [1]. In cancer, prostanoids affect the induction of growth factors and enzymes, apoptosis, immunosuppression, angiogenesis, proliferation and invasion of tissues [2]. The 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].

Inflammatory responses are critical cellular processes associated with many physiological and pathological changes in the body [1]. Thus, many factors and agents are involved in inflammatory responses. In cancers, inflammatory responses are important hallmarks of the disease development and progression [2]. Important chemical compounds released by various cells mediate inflammatory responses specifically during cancer. Prostanoids are an example of such chemical compounds released by cells to mediate inflammatory responses as well as some other cellular roles [1, 3]. As such, the release of these compounds in tumour cells particularly lung cancer is an interesting phenomenon with respect to the disease pathogenesis.

In this review, we briefly discuss prostanoid and its biosynthesis, how prostanoid associate with the lung cancer, prostanoid inflammatory roles, risk factors and its diagnosis.

2. CLASSES OF PROSTANOIDS

Prostanoids are a subgroup of eicosanoid, classified into prostaglandin (PG) and Thromboxanes (Tx), containing cyclopentane and cyclohexane ring respectively [5]. Based on the modification of cyclopentane ring, prostaglandins 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

compared to normal tissues, pinpointing the potential role of this molecule in tumorigenesis and progression of cancer [7]. Thromboxane synthase has been found to be moderately expressed in bronchial epithelial cells from normal lung tissues and weakly expressed in vascular smooth muscle cells [8].

3. PROSTANOID BIOSYNTHESIS

Different studies demonstrated that the prostanoid biosynthesis profile of cancerous cells are different from those of normal tissues [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 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 most important source of prostanoid formation in inflammation and cancer, induced by cytokines, shear stress, and tumor promoters [3]. The prostanoid produced depends on the cell type and enzymes present in the cell that needs to cross the cell membrane to exert some biological action [11]. However, prostanoids are chemically unstable molecules (PGG, PGH, PGI and TXA) with an 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].

4. ROLES OF PROSTANOIDS IN INFLAMMATION

Inflammation occurs because of an immune system response to infection and injury. It is been implicated in cancer pathogenesis and stroke, as well as in arthritis, neurodegenerative and cardiovascular diseases [13]. The

biosynthesis of prostanoid 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 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 because 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 has anticipated that failure of acute inflammation to resolve may incline to auto-immunity, chronic dysplastic inflammation and excessive tissue damage [16].

5. LUNGS CANCER

This is referred to as an unusual and uncontrolled cell growth in the tissues of the lungs that result in a tumour [17]. It is sometimes, referred to as bronchogenic carcinoma [18]. Neighbouring cells could be affected when tumour cells metastasize [19]. Lung cancers are 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 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 a 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 include; loss of weight, chest pains, coughing of blood, swelling in the face and loss of appetite [21].

6. INCIDENCE OF LUNGS CANCER

In a survey carried out by the world health organization in 2012, lungs cancer accounted for about 1.8 million new cases and resulted in about 1.6 million deaths [22]. As at 2016, about 13% of all cancer diagnosed was attributed to lungs cancer, with 225,000 new cases expected to be diagnose [23]. In America, about 415,000 Americans have been diagnosed with this disease at one point or the other in their lives [24], while about 158,000 Americans are expected to die from lungs cancer in 2016. This would account for about 27% of all cancer deaths [23]. Based on gender, 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].

7. RISK FACTORS ASSOCIATED WITH LUNGS CANCER

Table 1 summarizes the factors that may increase/decrease the risk of lungs cancer. Several factors such as smoking, history of lungs diseases and exposures to heavy metals (mostly via occupational activities) increase the risk of lungs cancer. Dietary habits and physical activities both have shown diverse effects on the risk of lungs cancer.

8. INFLAMMATION IN CANCER

Inflammation is defined as the natural way in which the body responds to potentially harmful events [27]. It plays a protective role by recruiting cells and molecules present within the host immune system to the site of injury [28]. The recruited cells eliminate damaged/dead cells and tissues [28].

There are two types of Inflammation: acute and chronic inflammation [27]. The acute Inflammation is associated with four known symptoms such as swelling, calor (heat), rubor (redness) and dolor (pain). While the chronic form has no physical symptoms and it plays a key role in the formation of cancer, contributing to about 15 percent of all solid tumours [29].

Table 1. Factors that influence the risk of lungs cancer [26]

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 a 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

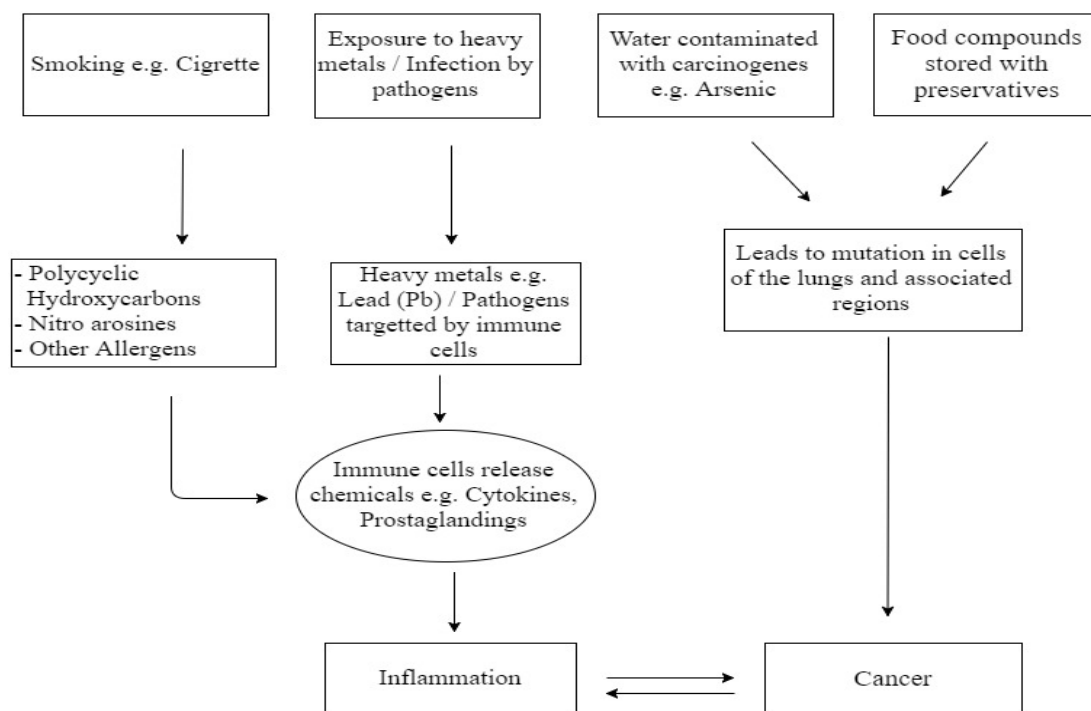


Fig. 1. lung cancer risk factors associated with inflammation at the molecular level

In a normal wound healing process, inflammation and all cellular reproduction needed are recruited to repair the damaged cells/tissues [30]. Subsequently, the activity of the cells tends to subside [30]. In a situation where this natural process is sustained for a prolonged or inappropriate time, it increases an individual's risk of cancer [31]. Chemicals such as reactive oxygen species (ROS) and Nitric oxide species (NOS) are normally produced by the immune system to acts as a defense mechanism against infections [32]. They play this role by damaging the DNA of the invading organism. Now if these species persist for a longer period after destroying the foreign DNA, they can begin to cause permanent damage to our own cells (mutations) [33].

Over time, these mutations accumulate in the epithelial cells and lead to dysregulation of their growth. This may lead to the production of cytokines and chemokines that attract immune cells to facilitate cancer development [34]. The cytokines and chemokines produced by the inflammatory cells also trigger it to produce metalloproteinases (MMPs). These are simply proteins with the ability to degrade components of the extracellular matrix [35]. Major ones involved in tumour angiogenesis include MMP-2, MMP-9 and MMP-14 [36]. They have been

implicated in all stages of cancer including metastasis down to proliferation and evasion of the immune system [37]. In a related research carried out by Atkinson and Senior [38], it was shown that the cells of the normal lungs do not produce MMP-9. However, 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. [39] 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 [33]. 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.

Please mention ref. 40

An important pro-inflammatory cytokine is the Tumour necrosis factor alpha (TNF- α) which is known as a key downstream mediator in inflammation [32]. It plays a very important role in early tumour events such as regulating a cascade of cytokines and proangiogenic activities [41]. Therefore, TNF- α through inflammation can act as a tumour promoter [42].

Pro-inflammatory interleukins such as IL-18, IL-12 and IL-8 have been observed to have increased serum levels in lungs cancer [43].

9. PROSTANOIDS IN LUNGS CARCINOGENESIS

To date, the best evidence showing the role of inflammation and inflammatory mediators to cancer development comes from the clinical and epidemiologic studies [44]. In some studies, it was shown that the daily use of non-steroidal anti-inflammatory drugs (NSAIDs) plays a beneficial role in reducing the incidence, mortality and metastasis of various solid tumours [44]. The molecular mechanism in which NSAIDs carry out such roles has not fully established, but they reduce the production of prostaglandins by inhibiting the activity of the cyclooxygenase (cox) enzymes [45].

This prostaglandin being one of the major prostanoids have since been implicated in various biological responses such as inflammation and tumorigenesis [46] with only prostaglandin E₂ (PGE₂) playing a predominant role in tumour progression and metastasis [47]. Cox-1 enzymes are constitutively expressed in most tissues and play a role in maintaining tissues homeostasis [27].

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], probably due to the lack of 15-PGDH expression in the tumour tissues.

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 of older research works done by Mutoh *et al.* [53]. This further confirmed 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.

10. DIAGNOSIS OF LUNGS CANCER

The Figure shown below highlights the clinical diagnosis of lung cancer.

11. THERAPIES AGAINST LUNG CANCER TARGETING THE INFLAMMATION

Fig. 3 briefly describes certain therapeutic approaches employed in the treatment of lung cancer that targets inflammatory mechanisms. Prostaglandins and other eicosanoids are major proponents of inflammations through the COX-enzymes pathway. Celecoxib an NSAID used in the treatment of non-small cell lung cancer (NSCLC) in combination with the anti-folate drug Pemetrexed [56]. Similarly, combined treatment with NSAIDs, successfully decreases lung cancer metastasis in a group of patients [57]. Other approaches include the use of Antibodies to target Tumor Associated macrophages targeting cytokine-mediated inflammatory mechanisms [58]. The macrophages induce inflammation in the tumor microenvironment via production of pro-inflammatory cytokines such as IL-4 [59]. Also, corticosteroids are used in targeting inflammatory mechanisms in cancer. Alternative techniques in lung cancer therapy continue to exploit other key cellular mechanisms associated with inflammation including angiogenesis [60].

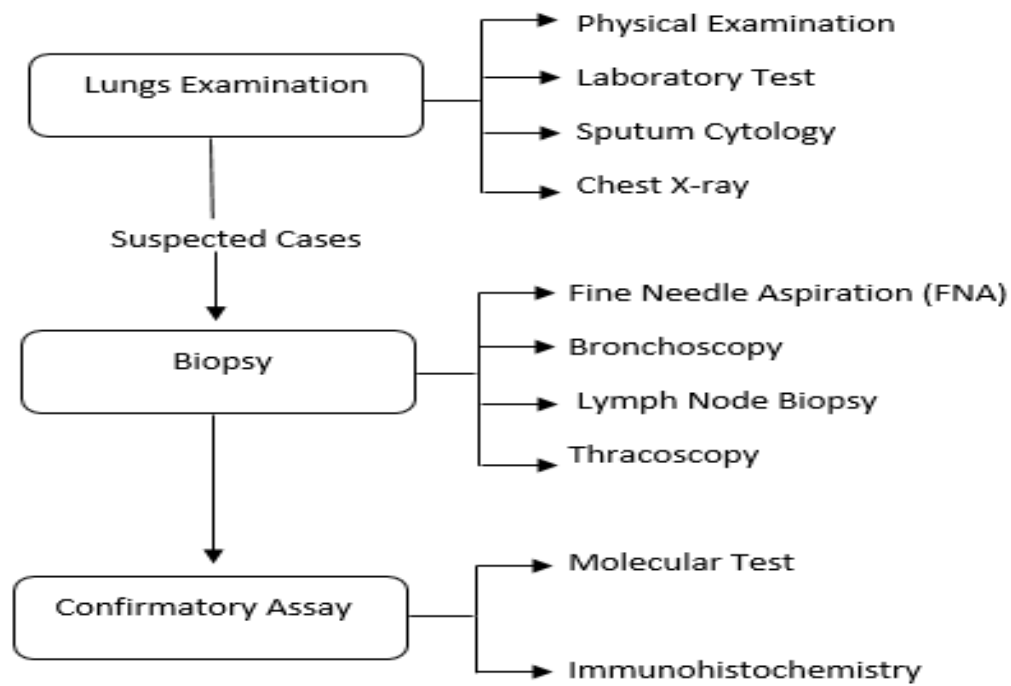


Fig. 2. Clinical diagnosis of lungs cancer adopted from [55]

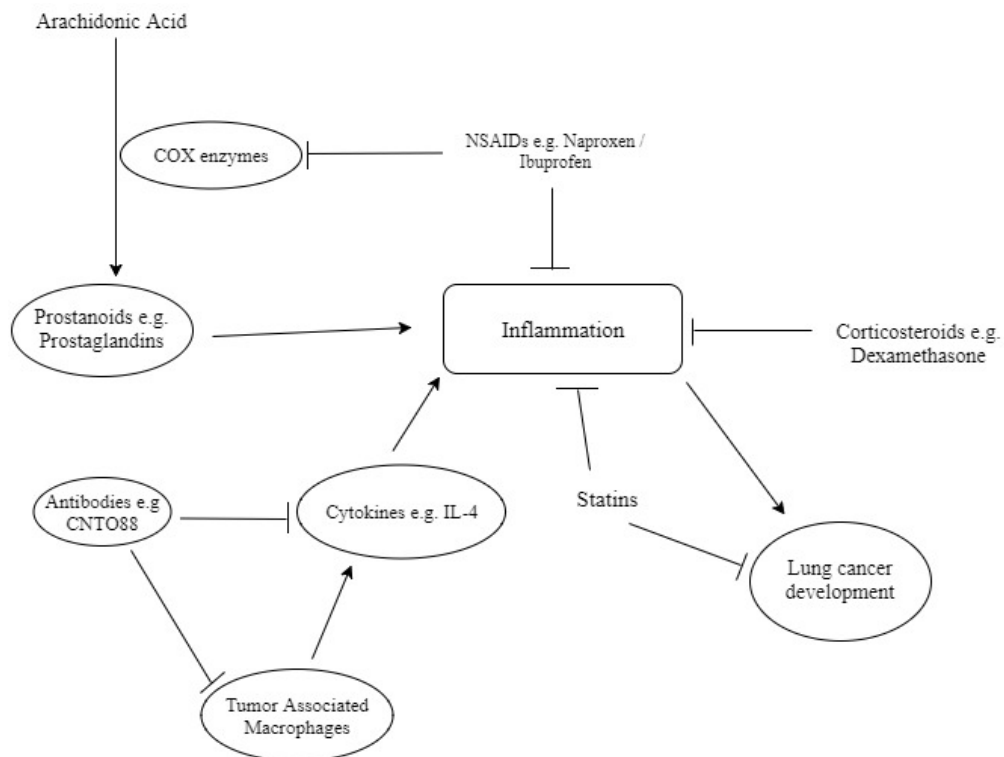


Fig. 3. Targeting the inflammatory process in lung cancer development

12. CONCLUSION

Inflammation is an important aspect of both physiological and pathological conditions. Prostanoids role in the 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.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Smyth, E.M.; Grosser, T.; Wang, M.; Yu, Y.; FitzGerald, G.A. Prostanoids in health and disease. *J. lipid Res.* 2009, 50(Supplement):S423-8.
2. Greenhough, A.; Smartt, H.J.; Moore, A.E.; Roberts, H.R.; Williams, A.C.; Paraskeva, C.; Kaidi, A. The COX-2/PGE 2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment. *Carcinogenesis* 2009, 30(3):377-386.
3. Yang, Y.; Tang, L.Q.; Wei, W. Prostanoids receptors signaling in different diseases/cancers progression. *J. Recept. Signal Transduct. Res.* 2013, 33(1):14-27.
4. Bos, C.L.; Richel, D.J.; Ritsema, T.; Peppelenbosch, M.P.; Versteeg, H.H. Prostanoids and prostanoid receptors in signal transduction. *Int. J. Biochem. Cell Biol.* 2004, 36(7):1187-1205.
5. Gustafsson A.A.; *Prostanoids and colorectal cancer*. Intellecta Infolog AB, Göteborg. 2010. <http://hdl.handle.net/2077/23137>
6. Brožek, J.L.; Bousquet, J.; Baena-Cagnani, C.E.; Bonini, S.; Canonica, G.W.; Casale, T.B.; van Wijk, R.G.; Ohta, K.; Zuberbier, T.; Schünemann H.J. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J. Allergy Clin. Immunol.* 2010, 126(3):466-476.
7. Cathcart, M.C.; Gately, K.; Cummins, R.; Drakeford, C.; Kay, E.W.; O'Byrne, K.J.; Pidgeon, G.P. Thromboxane synthase expression and correlation with VEGF and angiogenesis in non-small cell lung cancer. *Biochim. Biophys. Acta* 2014, 1842(5):747-755.
8. Nie, D.; Che, M.; Zacharek, A.; Qiao, Y.; Li, L.; Li, X.; Lamberti, M.; Tang, K.; Cai, Y.; Guo, Y.; Grignon, D. Differential expression of thromboxane synthase in prostate carcinoma: role in tumor cell motility. *Am. J. Pathol.* 2004, 164(2):429-439.
9. Cathcart, M.C.; Reynolds, J.V., O'Byrne K.J., Pidgeon, G.P. The role of prostacyclin synthase and thromboxane synthase signaling in the development and progression of cancer. *Biochim. Biophys. Acta – Rev. Cancer* 2010, 1805(2):153-166.
10. Capra, V.; Bäck, M.; Barbieri, S.S.; Camera, M.; Tremoli, E.; Rovati, G.E. Eicosanoids and their drugs in cardiovascular diseases: focus on atherosclerosis and stroke. *Med. Res. Rev.* 2013, 33(2):364-438.
11. Dey, I.; Lejeune, M.; Chadee, K. Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. *Br. J. Pharmacol.* 2006, 149(6):611-623.
12. Samad, T.A.; Saperstein, A.; Woolf, C.J. Prostanoids and pain: Unraveling mechanisms and revealing therapeutic targets. *Trends Mol. Med* 2002, 8(8):390-396.
13. Ricciotti, E.; FitzGerald, G. A. Prostaglandins and inflammation. *Arterioscler. Thromb. Vasc. Biol.* 2011, 31(5):986-1000.
14. Serhan, C.N. Lipoxins and aspirin triggered 15 –epi-lipoxins are endogenous components of anti-inflammation: emergence of the counter regulatory side. *Arch. Immunol. Ther. Exp.* 2001, 49:177-188.
15. Simmons, D.L.; Botting, R.M.; Hla, T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacol. Rev.* 2004, 56:387-437.
16. Nathan, C. Points of control in inflammation. *Nature* 2002, 420:846-885.
17. NCI. National Cancer Institute. Non-Small Cell lung Cancer Treatment-Patient Version (PDQ), 2015. Available at: <https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq> (Access date: 16th June, 2018).
18. Robert, L.K. Lung Carcinoma. *Tumors of*

- the lungs. Merck Manual Professional Edition, Online edition. Available at: <https://www.merckmanuals.com/professional/all/pulmonary-disorders/tumors-of-the-lungs/lung-carcinoma#sec05-ch062-ch062b-1405> (Access date: 16th June, 2018).
19. Falk, S.; Williams, C. *Lung Cancer—the facts*, Third ed.; Oxford University Press, New York, NY, USA, 2010; Chapter 1, pp. 3–4. ISBN 978-0-19-956933-5.
 20. Melissa, C.S. Lung Cancer. Available at: https://www.medicinenet.com/lung_cancer/article.htm#lung_cancer_facts (Access date: 16th June, 2018).
 21. Horn, L.; Lovly, C.M.; Johnson, D.H. Neoplasms of the lung. In *Harrison's Principles of Internal Medicine*, 19th ed.; Kasper, D.L.; Hauser, S.L.; Jameson, J.L.; Fauci, A.S.; Longo, D.L.; Loscalzo, J. McGraw-Hill: New York City, US, 2015; ISBN 978-0-07-180216-1.
 22. World Health Organization (WHO). International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Lung Cancer.
 23. Miller, K.D.; Siegel, R.L.; Lin, C.C.; Mariotto, A.B.; Kramer, J.L.; Rowland, J.H.; Stein, K.D.; Alteri, R.; Jemal, A. Cancer treatment and survivorship statistics, 2016. *CA Cancer J. Clin.* 2016, 66(4):271-289.
 24. USNIH (2013). U.S. National Institutes of Health. National Cancer Institute. SEER Cancer Statistics Review, 1975-2013.
 25. American Cancer Society. Cancer Facts & Figures, 2008. Available at: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf> (Access date: 16th June, 2018).
 26. World Cancer Research Fund/American Institute of Cancer Research (WCRF, 2018). Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. Continuous Update Project Report 2018. Available at: <http://www.aicr.org/continuous-update-project/reports/lung-cancer-2018.pdf> Access Date 16th June, 2018.
 27. Nordqvist, C. Everything you need to know about inflammation. *Medical News Today*, 2017. Retrieved from <https://www.medicalnewstoday.com/articles/248423.php> (Access date: 16th June 2018).
 28. Kumar, V.; Abbas, A.K.; Fausto, N.; Aster, J.C. *Inflammation and Repair*, 9th ed. Philadelphia, PA: Elsevier/Saunders, pp. 29-74.
 29. Ahmad, A.; Banerjee, S.; Wang, Z.; Kong, D.; Majumdar, A.P.; Sarkar, F.H. Aging and inflammation: etiological culprits of cancer. *Curr Aging Sci.* 2009, 2(3):174-186.
 30. Gonzalez, A.C. de O.; Costa, T.F.; Andrade, Z de A., Medrado A.R.A.P. Wound healing - A literature review. *An. Bras. Dermatol.* 2016, 91(5):614-620.
 31. Shanthini, M.C.; Frances, R.B. Inflammation and cancer: advances and new agents. *Nature Rev. Clin. Oncol.* 2015, 12:584-596.
 32. Coussens, L.M.; Werb, Z. Inflammation and cancer. *Nature* 2002, 420(6917):860-867.
 33. Shacter, E.; Weitzman, S.A. Chronic inflammation and cancer. *Oncology* 2002, 16(2):217-229.
 34. Coelho, A.; Calçada, C.; Catarino, R.; Pinto, D.; Fonseca, G.; Medeiros, R. CXCL12-3' A polymorphism and lung cancer metastases protection: new perspectives in immunotherapy? *Cancer Immunol. Immunother.* 2006, 55(6):639-643.
 35. Liu, D.; Guo, H.; Li, Y.; Xu, X.; Yang, K.; Bai, Y. Association between polymorphisms in the promoter regions of matrix metalloproteinases (MMPs) and risk of cancer metastasis: a metaanalysis. *PLoS One* 2012, 7(2):e31251.
 36. Kessenbrock, K.; Plaks, V.; Werb, Z. Matrix metalloproteinases: regulators of the tumor microenvironment. *Cell* 2010, 141(1):52-67.
 37. González-Arriaga, P.; Pascual, T.; García-Alvarez, A.; Fernández-Somoano, A.; López-Cima, M.F.; Tardón, A. Genetic polymorphisms in MMP 2, 9 and 3 genes modify lung cancer risk and survival. *BMC Cancer* 2012, 12:121.
 38. Atkinson, J.J.; Senior, R.M. Matrix metalloproteinase-9 in lung remodeling. *Am. J. Respir. Cell Mol. Biol.* 2003, 28(1):12–24.
 39. Gomes, M.; Teixeira, A.L.; Coelho, A.; Araújo, A.; Medeiros, R. The role of inflammation in lung cancer. *Adv. Exp. Med. Biol.*, 2014, 816:1-23.
 40. Hanahan, D., Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell* 2011, 144(5):646-674.

41. Balkwill, F. Tumor necrosis factor or tumor promoting factor? *Cytokine Growth Factor Rev.* 2002, 13(2):135-141.
42. Lin, W.W.; Karin, M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J. Clin. Invest.* 2007, 117(5):1175-1183.
43. Azevedo, A.; Cunha, V.; Teixeira, A.L.; Medeiros, R. IL-6/IL-6R as a potential key signaling pathway in prostate cancer development. *World J. Clin. Oncol.* 2011, 2(12):384-396.
44. Crusz, S.M.; Balkwill, F.R. Inflammation and cancer: advances and new agents. *Nat. Rev. Clin. Oncol.* 2015, 12:584-596.
45. Dingzhi, W.; Raymond, N.D. The Role of Prostaglandin E2 in Tumor-Associated Immunosuppression. *Trends Mol. Med.* 2016, 22(1):1-3.
46. Hiromichi, F. The Roles of EP4 Prostanoid Receptors in Cancer Malignancy Signaling. *Biol. Pharm. Bull.* 2016, 39:149-155.
47. Xia, D.; Wang, D.; Kim, S.H.; DuBois, R.N. Prostaglandin E2 promotes intestinal tumor growth via DNA methylation. *Nat. Med.* 2012, 18:224-226.
48. Wallace, J.L. Prostaglandin biology in inflammatory bowel disease. *Gastroenterol. Clin. N. Am.* 2011, 30(4):971-980.
49. Scher, J.U.; Pillinger, M.H. The anti-inflammatory effects of prostaglandins. *J. Investig. Med.* 2009, 57(6):703-708.
50. Wang, D.; Dubois, R.N. Cyclooxygenase-2: a potential target in breast cancer. *Semin. Oncol.* 2004, 31:64-73.
51. Thiel, A.; Ganesan, A.; Mrena, J.; Junnila, S.; Nykänen, A.; Hemmes, A.; Tai, H.H.; Monni, O.; Kokkola, A.; Haglund, C.; Petrova, T.V. 15-hydroxyprostaglandin dehydrogenase is down-regulated in gastric cancer. *Clin. Cancer Res.* 2009, 15:4572-4580.
52. Nakanishi, M.; Montrose, D.C.; Clark, P.; Nambiar, P.R.; Belinsky, G.S.; Claffey, K.P.; Xu, D.; Rosenberg, D.W. Genetic deletion of mPGES-1 suppresses intestinal tumorigenesis. *Cancer Res.* 2008, 68:3251-3259.
53. Mutoh, M.; Watanabe, K.; Kitamura, T.; Shoji, Y.; Takahashi, M.; Kawamori, T.; Tani, K.; Kobayashi, M.; Maruyama, T.; Kobayashi, K.; Ohuchida, S. Involvement of prostaglandin E receptor subtype EP4 in colon carcinogenesis. *Cancer Res.* 2002, 62:28-32.
54. Zelenay, S.; Van Der Veen, A.G.; Böttcher, J.P.; Snelgrove, K.J.; Rogers, N. Cyclooxygenase-dependent tumor growth through evasion of immunity. *Cell* 2015, 162:1257-1270.
55. "Non Small Cell Lung Cancer Treatment (PDQ)- Patient Version. Originally Published by the National Cancer Institute. Available at: <https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq> Access date: (Access date: 16th June 2018).
56. Kawazoe, H.; Yano, A.; Ishida, Y.; Takechi, K.; Katayama, H.; Ito, R.; Yakushijin, Y.; Moriguchi, T.; Tanaka, M.; Tanaka, A.; Araki, H. Non-steroidal anti-inflammatory drugs induce severe hematologic toxicities in lung cancer patients receiving pemetrexed plus carboplatin: A retrospective cohort study. *PloS one.* 2017 Feb 3; 12(2):e0171066.
57. Zhao, X.; Zhi, X.; Haoseng, Li. "NSAIDs Use and Reduced Metastasis in Cancer Patients: results from a meta-analysis. *Scientific reports* 7. 2017, no. 1: 1875.
58. Mantovani A.; Marchesi, F.; Malesci, A.; Laghi, L.; Allavena, P. Tumour-associated macrophages as treatment targets in oncology. *Nature reviews Clinical oncology.* 2017 Jul; 14(7):399.
59. Wang, D.; DuBois, R. Immunosuppression associated with chronic inflammation in the tumor microenvironment. *Carcinogenesis.* 2015 Sep 8; 36(10):1085-93.
60. Kalia, M. Biomarkers for personalized oncology: recent advances and future challenges. *Metabolism.* 2015 Mar 1; 64(3):S16-21.