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Inflammation and Cancer

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Preface

It was Aulus Cornelius Celsus, a physician in first-century Rome, who first defined *inflammation* as *calor* (heat), *dolor* (pain), *rubor* (redness), and *tumor* (swelling). However, it was Rudolf Virchow who in the mid-1800s linked inflammation with atherosclerosis, rheumatoid arthritis, multiple sclerosis, asthma, Alzheimer's disease, cancer, and other chronic diseases. The suffix "*-itis*" was introduced to indicate inflammation in words such as *bronchitis* (inflammation of the bronchus) and *colitis* (inflammation of the colon). Extensive research has revealed that inflammation precedes most cancers; for example, cancers of the liver, lung, colon, cervix, pancreas, stomach, and prostate are preceded by hepatitis, bronchitis, colitis, cervicitis, pancreatitis, gastritis, and prostatitis, respectively.

Within the past three decades, researchers have determined the molecular basis of most kinds of inflammation. Furthermore, various cell-signaling pathways that lead to inflammation have also been relatively well defined, leading to the development of various therapeutics that can modulate these pathways and thus alter the course of disease.

The current monograph deals with the role of inflammation in cancer, and some of the leaders in the field have contributed to this volume. We would like to thank these experts for their contributions and the publisher for giving us the opportunity to edit this volume.

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Chapter 1
The Role of Inflammation in Lung Cancer

Mónica Gomes, Ana Luísa Teixeira, Ana Coelho, António Araújo and Rui Medeiros

Abstract Lung cancer remains a serious public health problem and is the first cause of cancer death worldwide, and the overall 5-year survival rate for all stages is 14–17 % for Non-small-cell lung cancer and 6 % for small-cell lung cancer. Clinical and epidemiologic studies have suggested a strong association among chronic infection, inflammation, and cancer. Immune system plays a critical role in maintaining tissue homeostasis, cell turnover, tissue remodeling, and preventing

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infection and cell transformation. The inflammatory component in the development of the neoplasm includes a diverse leukocyte population; these components are considered inflammatory tumor key factors promoting tumor progression due to its ability to release a variety of cytokines, chemokines, and cytotoxic mediators such as reactive oxygen species (ROS), metalloproteinases, interleukins, and interferons. Cancer-related inflammation affects many aspects of malignancy, including the proliferation and survival of malignant cells, angiogenesis, tumor metastasis, and tumor response to chemotherapeutic drugs and hormones. Moreover, epidemiologic studies and meta-analysis have shown that prolonged use of non-steroid anti-inflammatory (NSAID) drugs reduces the risk of several solid tumor including lung cancer. Strong lines of evidence suggest that the chemopreventive properties of chronic NSAID administration are based on their COX-inhibitory activity. However, the prevention is a much better and more economical way to fight against cancer than treating an already advanced and often incurable disease.

1.1 Introduction: Incidence, Survival, Major Gene Products and Current Therapies for Lung Cancer

In 2008, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in this year in worldwide, with 56 % of cases and 64 % of the deaths in the economically developing world (Jemal et al. 2011). Lung cancer was found to be the most commonly diagnosed cancer as well as the primary cause of cancer-related mortality for males worldwide and the second leading cause of cancer-related deaths for women (Jemal et al. 2011; Siegel et al. 2012). For the year 2012, it is estimated that lung cancer will account for 26 % of all female cancer deaths and 29 % of all male cancer deaths (Siegel et al. 2012). Breast cancer in females and lung cancer in males are the most frequently diagnosed cancers and the leading cause of cancer death for each sex in both economically developed and developing countries, except lung cancer is preceded by prostate cancer as the most frequent cancer among males in economically developed countries (Jemal et al. 2011).

Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males in 2008, globally. Among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death (Jemal et al. 2011; Ferlay et al. 2010). Lung cancer accounts for 13 % (1.6 million) of the total cases and 18 % (1.4 million) of the deaths in 2008 (Ferlay et al. 2010; Jemal et al. 2011).

The observed variations in lung cancer rates and trends across countries or between males and females within each country largely reflect differences in the stage and degree of the tobacco epidemic (Jemal et al. 2011).

Lung cancer can be divided into two major groups: small-cell lung cancer (SCLC) and non-small-cell cancer (NSCLC) (Hoffman et al. 2000; Molina et al. 2008), NSCLC accounts for approximately 85 % of all cases of lung cancer

(Molina et al. 2008; Araujo et al. 2007). These lung cancer cells can again be categorized based on their histological characteristics as squamous cell carcinoma, large cell carcinoma, and adenocarcinoma (Tang et al. 2013). NSCLC spreads slower than SCLC, so many patients who are diagnosed at an earlier stage are potentially curable, though NSCLC may often relapse at other metastatic site. Furthermore, NSCLC is generally less responsive to chemotherapy than SCLC, so that even with surgical resection at early diagnosis, approximately 50 % of NSCLC patients face recurring cancers (Tang et al. 2013).The 1-year survival rate for lung cancer was 43 % in 2003–2006. However, despite extensive preclinical and clinical research, the overall 5-year survival rate for all stages is still as low as 14–17 % for NSCLC (Araujo et al. 2007; Peebles et al. 2007) and even lower in SCLC (6 %) (Wu et al. 2012).

In recent years, knowledge concerning the molecular mechanisms underlying cellular transformation and development of cancer has been greatly expanded (Araujo et al. 2007). Alteration of the major cell signaling and regulatory pathways either by overexpression or gene sequence variation is a frequent event in lung cancer. These changes include alterations in receptor tyrosine kinases (TKs), such as epidermal growth factor receptor (EGFR), and alterations in angiogenesis pathways, apoptosis, proteasome regulation, and cell cycle control, among others (Molina et al. 2008).

The EGFR is a tyrosine kinase that contributes to the regulation of cellular homeostasis. It is a 170-KDa membrane protein that stimulates downstream cell proliferation, survival, and tumorigenesis (Wheeler et al. 2010; Cohen 1965). EGFR has been implicated in the growth of several human epithelial malignancies, including lung cancer. It is overexpressed in several cancers, including approximately 40–80 % of NSCLC, which made EGFR a popular target for new drug treatment exploration (Tang et al. 2013).

The ALK tyrosine kinase receptor has gained much attention recently as a newly emerging relevant biomarker and therapeutic target in NSCLC (Wu et al. 2012). The activation of ALK is primarily through the formation of fusion genes. EML4-ALK translocation is the most common ALK gene rearrangement. This rearrangement in NSCLC patients is mainly found in younger non-smoking patients with adenocarcinoma (Wu et al. 2012; Kwak et al. 2010). EML4-ALK rearrangements are mutually exclusive with EGFR or KRAS mutations (Wu et al. 2012; Li et al. 2013). It has been reported that approximately 2–11 % of tumors carrying positive EML4-ALK (Li et al. 2013).

KRAS mutations are a negative predictor of response to EGFR TKs, mainly accounting for primary resistence (Linardou et al. 2008; de Mello et al. 2011). Most KRAS mutations in lung adenocarcinoma are associated with smoking. KRAS positive mutations are limited to NSCLC and are mutually exclusive to mutations in EGFR and ALK (Linardou et al. 2008; Wu et al. 2012).

Lung cancer is a very aggressive cancer and its treatment still remains a challenge for health professionals. Conventional treatments are based on surgery, radiation therapy, and chemotherapy. The selection of therapeutic regimen is based on the cancer type (small-cell or non-small-cell), stage of disease, patient's functional

ability, and genetic characterization (Wu et al. 2012; Tang et al. 2013; Hoffman et al. 2000).

The majority of stage I through stage IIIA lung cancer patients generally choose surgery as their primary option. Another popular option is preoperative chemotherapy, which has been shown to improve survival rate in patients with NSCLC. Patients who require complete resection and no preoperative chemotherapy usually invest in adjuvant chemotherapy. For patients with unresectable NSCLC, RT and chemotherapy are excellent options for treatment (Tang et al. 2013). Further, certain agents have been combined with the chemotherapy to enhance its effects. The anti-vascular endothelial growth factor agent, bevacizumab, for example, when combined with chemotherapy, has resulted in increased survival rate when compared to chemotherapy treatment alone (Tang et al. 2013).

For first-line chemotherapy, a platinum-based two-drug combination is suggested for patients (Azzoli et al. 2009; Molina et al. 2008). Studies show that the cisplatin, when used in combination chemotherapy, is associated with improved response rates, no change in survival rate, and increased toxicity when compared with the carboplatin (Tang et al. 2013). Also, another drug bevacizumab has demonstrated great potential when used in combination with carboplatin or paclitaxel in NSCLC patients (Tang et al. 2013; Molina et al. 2008).

The second-line chemotherapy treatment options, after primary treatment fails to yield effective results, do differ from the first-line drugs. Approximately 30 % of NSCLC patients who undergo first-line cancer treatment are candidates for second- or third-line therapeutics. The first agent that was approved for second-line therapeutics was docetaxel (Fossella et al. 2000). Other drugs that were also soon approved include pemetrexed, erlotinib, and gefitinib (Tang et al. 2013). Undergoing research is currently evaluating other possible strategies for second-line therapeutics.

1.2 Inflammatory Signaling Pathways Associated with Lung Cancer

Cancer is a hyperproliferative disorder that involves morphological cellular transformation, dysregulation of apoptosis, uncontrolled cellular proliferation, invasion, angiogenesis, and metastasis (Lin and Karin 2007; Hanahan and Weinberg 2011).

Clinical and epidemiologic studies have suggested strong association between chronic infection, inflammation, and cancer (Coussens and Werb 2002; Lin and Karin 2007; Ribeiro et al. 2007). Up to 20 % of cancers are linked to chronic infections, 30 % can be attributed to tobacco smoking and inhaled pollutants (such as silica and asbestos), and 35 % to dietary factors (20 % of cancer burden is linked to obesity) (Aggarwal et al. 2009).

Approximately 150 ago, Virchow postulated that inflammation is a predisposing factor of tumorigenesis (Lu et al. 2006; Balkwill and Mantovani 2001; Schottenfeld and Beebe-Dimmer 2006). This hypothesis was based on his observation that