**Review and Research on Cancer Treatment**
Volume 4, Issue 1 (2018)

# The inflammatory components in lung cancer

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**Abstract:** The immune system is one of the most complicated and least known part of the human body. According to Virchow's observations and the current data, its response can cause both promotion and suppression of formation and development of the neoplasm. It is estimated that as many as 25% of all cancers are caused by chronic inflammation. Better understanding of the delicate balance between these activities is essential for development of proper preventive and treatment methods as well as new biological markers. In our paper we focus on biochemical and molecular mechanisms of tumorigenic activity of chronic inflammation in lung cancer - the most frequent malignant neoplasm characterized by high mortality. Moreover, we describe mechanisms in which the immune system fights against tumours cells. The last part is concerned with new strategies in lung cancer diagnosis and treatment: biomarkers and immunotherapy.
Keywords: Lung cancer, NSCLC, inflammation, biomarkers, immunotherapy

## 1. Introduction

### 1.1. The immune system and its role in cancerogenesis

In 1863 Rudolf Virchow observed that:

- Cells of the immune system occur in tumours;
- Cancerogenesis tends to appear at sites of the long-lasting inflammation [1, 2].

When we take into consideration all sources of inflammatory conditions (such as viral infections, exposure to allergens, autoimmune disorders and even obesity), it reveals that they are responsible for approximately 15 to 25% of tumours [1, 3]. As Figure 1 shows, the response of the immune system can result in both: anti- and pro-tumorigenic effect. The first case is typical for efficient immune effector system [4], the second for chronic inflammation which predispose cells for oncogenic transformation [5]. The range of mechanisms involved in both responses is outlined in further chapters.

The influence of the immune system on cancerogenesis has been described for many organs, especially: intestines, liver, stomach and lungs. The examples of tumours with corresponding inflammatory state are summarized in Table 1.

Table 1. The inflammatory states and their correlating tumours.

| Source of inflammation | Tumour | References |
|---|---|---|
| Chronic viral hepatitis | Liver cancer | [6, 7, 8] |
| Helicobacter pylori | Gastric cancer | [9, 10] |
| Tumour-associated macrophages (TAMs) activation | Oral squamous cell carcinoma (OSCC) | [11, 12] |
| Inflammatory Bowel Disease | Colorectal cancer | [13,14] |
| Crohn's disease[1] | Colorectal cancer | [15, 16, 17] |
| Ulcerative colitis | Colorectal cancer | [18, 19, 20] |
| Hashimoto's thyroiditis | Papillary thyroid cancer (PTC) | [21, 22] |
| Asbestos | Mesothelioma, lung cancer | [23, 24, 25] |
| Tobacco smoking | Lung cancer | [26, 27, 28] |

[1] In memorial of Polish surgeon Antoni Leśniowski, who was first to describe *ileitis terminalis,* also called **Leśniowski-Crohn's disease** (Lichtarowicz, Mayberry, 1988).

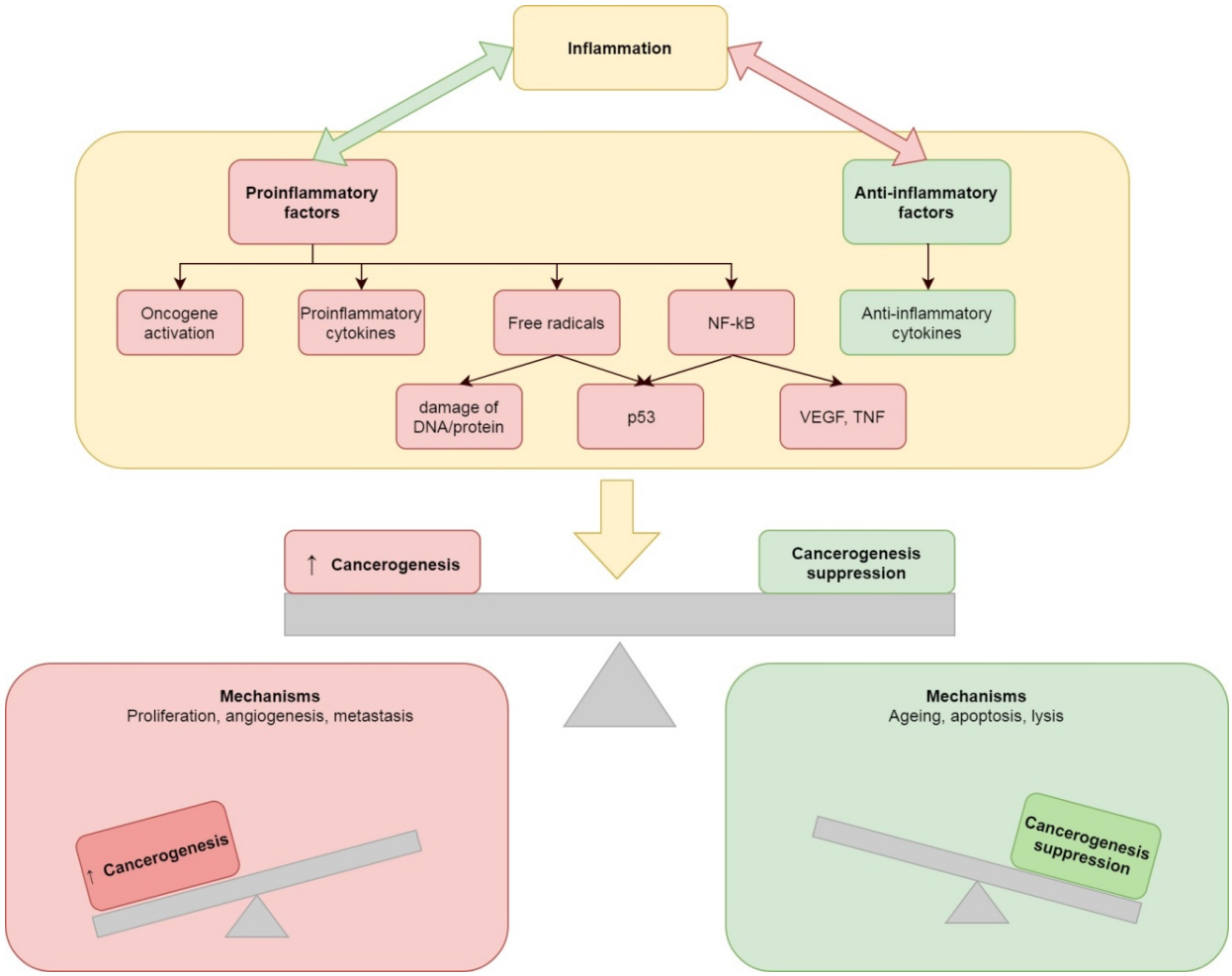


Fig. 1. The balance between both pro-tumorigenic and anti-tumorigenic effect of immune response. Based on the diagram from [2].

### 1.2. Lung cancer

Lung cancer is the most common malignant neoplasm [29] and the leading cause of death of tumour [30]. Current research show that ASIR (standardized incidence rate) is equal 23.1 and ASMR (standardized mortality rate) - 19.7 (per 100 000) [29]. Both environmental and genetic factors are associated with lung cancer [31]. Moreover, environmental factors (such as smoking and exposure to asbestos), which results in inflammation, play an important role in the etiopathogenesis of lung cancer [2, 32].

Lung cancer can be classified according to histological [33] and clinical [34] parameters. Focusing on the clinical classification, we can distinguish:

- Small-cell lung cancer (SCLC);
- Non-small-cellular lung cancer (NSCLC) which is also divided into:
  - ✓ Squamous cell lung carcinoma (SCC),
  - ✓ Adenocarcinoma (AC),
  - ✓ Large-cell lung carcinoma (LCC).

## 2. The fight between cancer and the immune system

The anti-tumorigenic response is possible thanks to tumour-associated antigens (TAAs). Dendritic cells (DCs) present these antigens by MHC class II. Other antigen presenting cells (APCs) perform this function to a lesser extent [35]. DCs/APCs migrate to lymph nodes. It results in interaction between TAA and naïve T-cells. Due to this interaction the first signal is conducted by the antigen receptor – T-cell receptor (TCR). The second signal, needed to T-cells activation, is called co-stimulation [36]. These signals activate effector T-cells (both CD4+ and CD8+, called helper and cytotoxic T-cells (CTLs), respectively). Activated CD4+ T-cells secrete cytokines, which take part in e.g. CTLs' and B-cell activation, phagocytosis

promotion and stimulation of natural killer cells (NKs).

However, the response of the immune system is often insufficient [37]. Tumour fights with patient's immunological system through:

- the generation of antigen-loss variants
- the immunological tolerance
- the lesser expression of MHC on tumour cells' surface
- the secretion of immunoinhibitors

The **origination of antigen-loss variants** depends on selection of tumour cell subpopulations which do not express antigens causing anti-tumorigenic immune response. It enables protection against immune targeting [38]. The **tolerance mechanisms** against some antigens result in the lack of response to them with relevant immune response against others antigens [39]. Moreover, host cells fighting against tumour are recognized as autoreactive and eliminated. The defence strategy bases on **decreased expression level of MHC on tumour cell surface** limits the presenting of TAAs. More importantly, due to this mechanism tumour cells are the target for NK-cells [40]. Finally, malignant cells can secrete **immunoinhibitors.** One of them is transforming growth factor beta (TGF-β) [35]. Physiologically, TGF-β regulates many life processes, such as: cell growth, differentiation, inflammation and angiogenesis. However, the overexpression of this cytokine is correlated with tumor progression, metastasis and poor prognostic outcome [41].

## 3. Inflammatory biomarkers in lung cancer

In fact, all of inflammatory genes, theirs products, circulating cytokines and microRNAs can be considered as biomarkers in lung cancer [2]. For the purpose of our article, we will only focus on microRNAs affecting inflammatory genes and circulating cytokines.

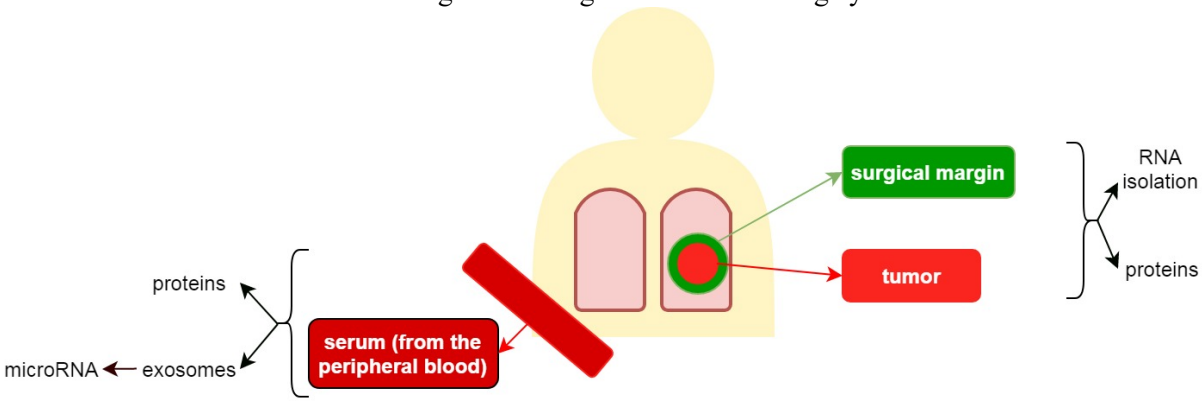


Fig. 2. The possibilities of biological material selection for assessment of expression level of different biomarkers (microRNA, genes, proteins).

Both of them tend to be suitable biomarkers for early cancer detection because of the relative non-invasiveness and easiness in collection of biological material [42]. They can be assessed in the serum samples, while the inflammatory genes expression should be evaluated in tumour tissue obtained during pulmonectomy/lobectomy [43] (see Figure 2). The examples of circulating proteins and microRNAs which can be considered as inflammatory biomarkers in lung cancer are summarized in Table 2.

Table 2. The examples of circulating proteins and microRNAs which can be considered as inflammatory biomarkers in lung cancer (with relevant references).

| Biomarker | References |
|---|---|
| circulating proteins | |
| C-reactive protein (**CRP**) | [44, 45] |
| Interleukin 6 (**IL-6**) | [46, 47] |
| Interleukin 8 (**IL-8**) | [48, 49] |
| microRNAs | |
| microRNA-21 | [50, 51] |
| microRNA-17-92 cluster | [52, 53] |

**MicroRNAs** are the class of short (20-25 nucleotides), evolutionarily conserved, non-coding RNA [54]. They down-regulate genes expression by both: translational repression and

mRNA degradation [55]. More importantly, single microRNAs can target many genes [56]. We will focus on *miRNA-21* and *microRNA-17-92* cluster. ***miRNA-21*** regulates the expression of IL-12 [57]. This interleukin performs many roles e.g.: it is engaged in origination of Th1 cells [58] and is the suppressor of angiogenesis [59]. The upregulation of *microRNA-21* observed in lung cancer [50] results in the downregulation of its targets. Thus, important functions of IL-12 are impaired. While, *microRNA-17-92* cluster is the set of seven microRNAs: *microRNA-17-3p, microRNA-17-5p, microRNA-18a, microRNA-19a, microRNA-20a, microRNA-19b-1* and *microRNA-92a* [60]. Its overexpression is often observed in lung cancer [52]**.** This MicroRNA class results in e.g. cell proliferation under normoxia, inhibition of hypoxia-induced apoptosis and regulation of angiogenesis [61].

The second group of potential biomarkers are circulating proteins, especially cytokines. These small proteins are secreted by cells and influence these or other cells [37]. They play key role in communication between cells [62]. There are distinguished pro- (e.g. IL-1β, IL-8, IL-12) and anti-inflammatory (IL-4, IL-5, IL-10) cytokines [63].

**IL-8** is involved in wide range of processes, such as recruitment/activation of neutrophil, angiogenesis and metastasis in lung cancer (especially NSCLC). Oncogenic activity of IL-8 can be result of EGFR transactivation [64]. **IL-10** is anti-inflammatory cytokine. It is responsible for limiting host immune response to pathogens and homeostasis maintain [65]. Its role in the tumorigenesis is controversial: its expression levels were significantly increased in the lungs (mice model of lung cancer), higher level of IL-10 correlates with a poor prognosis in lung cancer patients [66]. Hsu et al. convince that IL-10 and EGFR regulate each other through positive feedback, which leads to lung cancer formation.

The C-reactive protein (**CRP**) is pentameric protein, which occurs in blood in response to inflammation. The performed meta-analysis of the role of its in lung cancer shows [44]:

- RR of lung cancer for one unit change in natural logarithm CRP was 1.28 (95% CI 1.17–1.41)
- CRP was significantly correlated with increased risk of lung cancer among men: RR=1.18 (95% CI 1.09–1.28)
- Any statistically significant difference among women wasn't observed.

## 4. The immunotherapy of lung cancer

The immunotherapy in treatment of neoplasm has been used for the first time in 1890 by doctor William Coley. He noticed that facial sarcoma could regress after bacterial infection [67]. Since that moment research in tumours immunotherapy have developed significantly [35]. Two types of immunotherapy are distinguished: active and passive (see Table 3).

Table 3. The definitions of active and passive immunotherapy with examples. Based on [35].

| Type | Definition | Examples |
|---|---|---|
| Active | Stimulation of immunological system to fight against neoplasm | Vaccines (containing tumours antigens and adjuvants)<br>Nonspecific immunomodulators |
| Passive | The application of immunologically active factors synthesized/formed outside patient's organism | Adoptive T-cells<br>Monoclonal antibodies |

Active immunotherapy depends on stimulation of immunological system to fight against tumour. It comprised of vaccination and administration of nonspecific immuno-modulators. The possibility of vaccinations usage is notably exploited especially in combination therapy of NSCLC. Many clinical trials have been performed based on that topic (e.g. MAGE-A3, PRAME, Lucanix, CimaVax) [68]. In this paragraph, we focus on vaccines targeting MUC-1 (L-BLP25 and TG4010). It is transmembrane protein, which increased expression is observed in NSCLC (AC: 86%, others: 74%) [35, 69]. Genetic abnormalities of *MUC-1* cause:

- resistance to chemotherapy,
- protection against apoptosis,
- immunosuppression [70].

Since overexpression of *MUC-1* and decreased level of patients' own antibodies against *MUC-1* result in poor prognosis, this direction of research seems to be reasonable [71].

As shown in Table 3, passive immunotherapy can be defined as application of immunologically active factors synthesized or formed outside patient's body. Adoptive cell transfer (ACT) is considered as its example. Its following steps are shown on Figure 3.

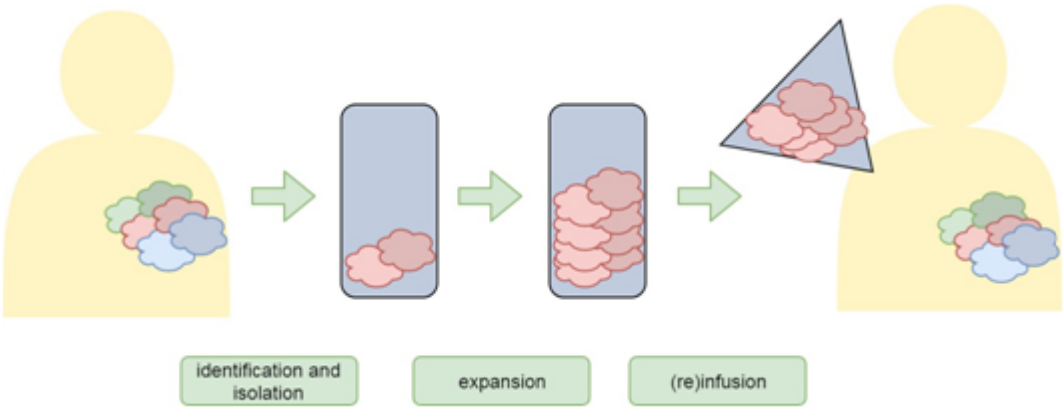


Fig. 3. Following steps of adoptive cell transfer. The last step is infusion of patient's own T-cells, which are characterized by anti-tumour properties.

Thanks to this procedure infused T-cells have relatively high avidity, which can be also increased by genetic modification. Clinical trials of ACT in lung cancer focus on: lymphokine-activated killer (LAK), cytokine-induced killer (CIK) and natural killer (NKT) cells [72].

## 5. Summary

Better understanding of the delicate balance between opposite activities is essential to the preparation of proper prophylactic methods, finding new biological markers and the development of new treatment methods. Circulating microRNAs isolated from serum exosomes or serum samples are promising biomarkers for detection and predication of the clinical curse of lung cancer. Moreover, the immunotherapy can be considered as the possible treatment.

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