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Long non-coding RNA as potential biomarkers in non-small-cell lung cancer: What do we know so far?

Maria Aleksandra Osielska*, Paweł Piotr Jagodziński

Department of Biochemistry and Molecular Biology, Poznań University of Medical Sciences, Poznań, Poland

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ABSTRACT

Non-small-cell lung cancer (NSCLC) remains one of the most frequent types of lung cancer characterized by its local advancement at diagnosis. Therefore, identification of new prognostic biomarkers has become one of the most important issue in NSCLC therapy. It is now well understood that genetic and epigenetic alterations are responsible for NSCLC development. Moreover, it has been recently revealed that the non-protein coding regions of the genome may serve as a template for transcription of various type of RNAs, collectively referred to as non-coding RNAs. Non-coding RNAs, including long non-coding RNAs (lncRNAs) are involved in multiple cellular processes and it has been suggested that aberrant expression of lncRNAs may lead to tumour development, including NSCLC. Furthermore, some of the established risk factors for NSCLC may have an impact on expression level of several types of lncRNAs, and thus, affect the lung carcinogenesis through lncRNAs regulation. In this review, we would like to summarise the to-date knowledge about lncRNAs as potential biomarkers in NSCLC and the role of various environmental factors, such as smoking and air pollution, in development and progression of this tumour and their effect on lncRNAs expression.

1. Introduction

Carcinogenesis is triggered by genetic and epigenetic alterations that lead to abnormal gene expression and uncontrolled cell division. Genetic changes that contribute to tumour development encompass alterations in DNA sequence of key regulatory genes, whereas epigenetics mechanisms involved in this process are mainly associated with DNA methylation, chromatin remodelling and RNA interference [1]. Furthermore, according to the Encyclopedia of DNA Elements (ENCODE), only 2% of the genome is translated into proteins, whereas the rest is transcribed into RNA. Thanks to recent advances in molecular biology methods, those RNA molecules have been identified as non-coding RNAs (ncRNAs) [2–4]. Despite an immense number of publications, still relatively little has been known about the general structure, function and transcriptional control of ncRNAs, while the knowledge about their potential functions is even poorer. Although some studies considered ncRNAs to be simply a transcriptional "noise" [5], some evidence suggests that they are biologically relevant, serving as the regulators of gene expression and cellular development [6,7]. Moreover, some studies linked ncRNAs with development and progression of various malignant tumours including NSCLC [8].

There are various classes of ncRNAs grouped according to their size, i.e. molecules shorter than 200 nucleotides (nt), e.g. microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), tRNA-derived small RNAs (tsRNAs), ncRNAs greater than 200 nt called long ncRNAs (lncRNAs), including large intergenic ncRNAs (lincRNAs) and very long ncRNAs (vlncRNAs) with length of hundreds of kilobases [9–11] (Fig. 1). Xu et al. analysed the available resources and indicated the presence of over 205,000 lncRNAs molecules in over 50 tissues and cell lines. The atlas of lncRNAs (LNCat) was created on the basis of these data [12]. The database combines information from many sources and aims at facilitating the understanding of the role of lncRNAs in human diseases. Recent studies showed altered expression of lncRNAs in NSCLC suggesting that these particles may be associated with this tumour [8]. Since NSCLC is diagnosed at an advanced stage, it has been believed that lncRNAs may become a new prognostic marker in NSCLC therapy [13]. This review aims at summarising the current knowledge about lncRNAs and estimating its potential role as biomarker in NSCLC. Furthermore, recent studies suggest that some of the established risk factors for NSCLC can affect expression of lncRNAs. Hence, we also investigated whether various environmental factors, such as smoking and air pollution, affect development and progression of NSCLC through their effect on expression of lncRNAs.

* Corresponding author at: Department of Biochemistry and Molecular Biology, Poznań, University of Medical Sciences, 6 Święcickiego Street, 60-781 Poznań, Poland.
E-mail address: maria.olewnik@gmail.com (M.A. Osielska).

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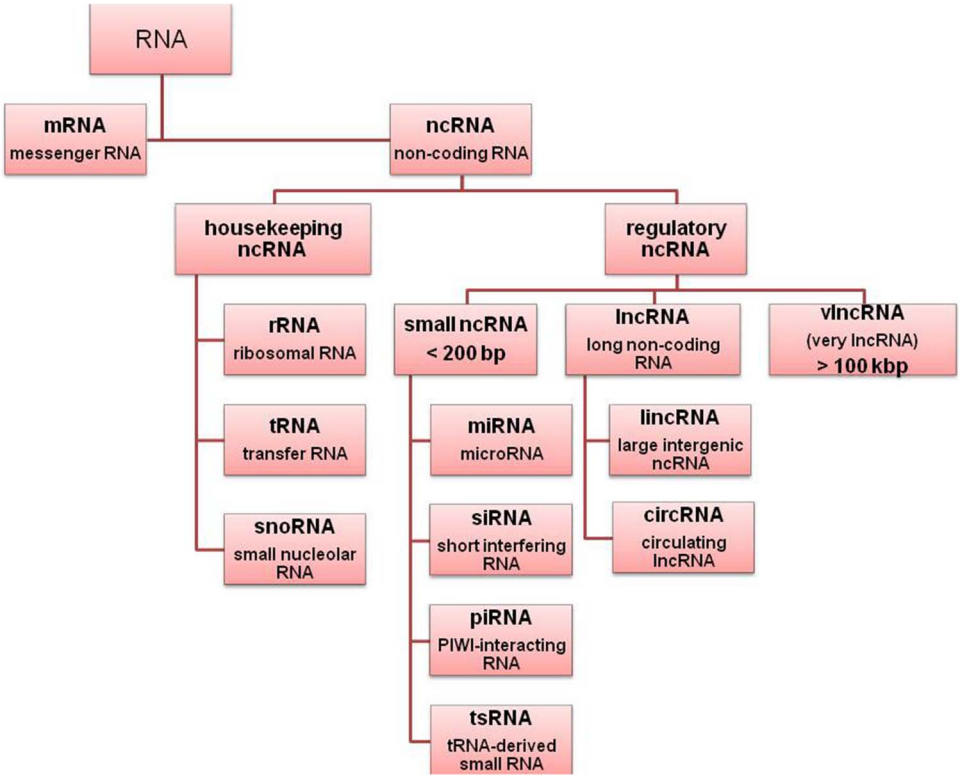

Fig. 1. Classification of RNA molecules.

2. Non-small cell lung cancer

Lung cancer is one of the most common malignant cancers in the world. In 2012 lung cancer was the most commonly diagnosed cancer (1.82 million cases) and the most common cause of cancer death (1.6 million deaths). Statistically, lung cancer is ranked 1st as regards cancer-related deaths among men with the highest rates recorded in Central and Eastern European countries, while among women this type of cancer is generally ranked lower [14].

There are two major histological types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for over 85% of all lung cancer cases and is one of the most common and aggressive types of lung cancer [15]. Three subtypes of NSCLC have been distinguished: adenocarcinoma (AC), squamous cell carcinoma (SCC) and large cell carcinoma (LCC) (Fig. 2) [16]. In NSCLC about 75–80% of instances qualify for surgical resection, while chemotherapy provides only limited benefit and short survival times [17]. In spite of progress in chemotherapy, the majority of patients is at advanced stages when diagnosed and the prognosis of NSCLC remains poor [18].

The best known risk factor for lung cancer is long-term exposure to carcinogens, especially those deriving from smoking. Other factors for lung cancer include: exposure to second-hand smoking, exposure to harmful industrial substances and chemicals, air pollution (car exhaust fumes, smog and especially $PM_{2.5}$ molecules) or exposure to other toxic substances inhaled into lungs [19]. The treatment and prognosis of the patient depends primarily on the clinical stage of the disease, the type of histological cancer, and the patient's overall health status [17].

Our better understanding of the molecular origin and progression of NSCLC may lead to an improvement in the prevention, diagnosis and treatment of this disease.

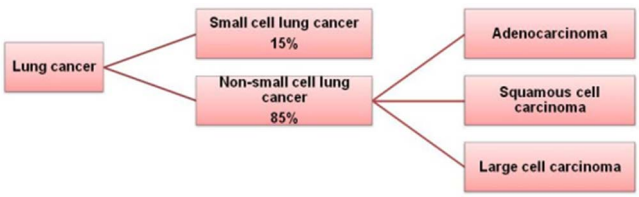

Fig. 2. Histological classification of lung cancer.

3. Biomarkers, diagnostic markers

One of the most important challenges in lung cancer therapy that still remains to be investigated is to find adequate tumour biomarkers for early diagnosis and metastasis. The World Health Organization (WHO) comprehensively defines biomarkers as “almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction.” (WHO International Programme on Chemical Safety. Biomarkers and Risk Assessment: Concepts and Principles. 1993. Retrieved from http://www.inchem.org/documents/ehc/ehc/ehc155.htm). Specific types of biomarkers, called tumour markers, the elevated level of which may be found in blood, urine, body tissues, etc. are produced by cancer or by other cells of the body in response to cancer or certain benign (non-cancerous) conditions and indicate the presence of one or more types of cancer. Usually these are proteins, but gene expression patterns and DNA changes have been increasingly often used as tumour markers. Molecular examination of lung cancer has mainly consisted in checking deregulation of protein-coding genes, miRNA and identification of oncogenes and suppressor genes for potential diagnostic and therapeutic purposes.

Finding biomarkers at early stage of the disease is a challenge because there are considerable uncertainties about accuracy of the majority of tests. First of all, correct marker level does not exclude cancer (it depends on the individual baseline level), while moderate increase in markers (especially those deriving from tissues) is also specific to non-