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THE ROLE OF PROTO-ONCOGENES AND STIMULATION OF GROWTH FACTOR RECEPTORS IN CANCEROGENESIS OF NON-SMALL CELL LUNG CANCER

SUMMARY

Non-small cell lung cancer (NSCLC) is of great interest in human pathology because its apparent aggressiveness cannot be stopped by applied treatment procedures. The lack of highly specific screening tests prevents an early diagnosis of the disease. Insidious beginning and diverse and unclear clinical picture are responsible for the fact that most cases are diagnosed at advanced stages. An increasing number of patients and a short length of survival are additional factors that make this disease an imperative in the clinical practice, while vague and mutually dependent etiological factors represent a challenge in laboratory studies of the pathogenesis.

Better understanding of cancerogenesis of lung cancer will give answers to the questions like: "Which molecules are associated with response or resistance to standard treatment?" and "Which of the newly synthesized drugs with ongoing clinical trials has the best clinical response in patients?" Recent studies have shown that molecular markers associated with resistance to cisplatin-based adjuvant treatment include expression of the genes from the group ERCC1 (excision repair cross- complementation group 1) and mutation of RAS proto-oncogenes. Such research suggests that molecular investigations can guide the choice of treatment for both primary and adjuvant chemotherapy. The best example for this is patients' response to chemotherapy when inhibitors of the EGFR tyrosine kinase are applied.

The future of lung cancer treatment lies in development of unconventional drugs which would be based on the biological characteristics of the tumor.

Key words: **non-small cell lung cancer, protooncogenes, growth factor receptors**

INTRODUCTION

Cancerogenesis is a multiphase process in which a normal cell first turns into a malignant cell and then into a malignant tumor. It is a well-known fact that it sometimes takes a few decades from the moment of exposure to a carcinogen to the actual appearance of the symptoms of a malignant disease. This tells us that during that time numerous pathological processes take place, which finally leads to the appearance of malignancy. Cancerogenesis begins with the host's exposure to a carcinogen, i.e. an agent capable of inducing a cancer. Tumors are caused by accumulation of genetic mutations that disturb normal control of the cell growth and terminal cell differentiation. It is the accumulation of mutations that is important for malignant transformation, and not their order. Malignant transformation is a result of years, even decades of accumulation of genetic changes in the epithelial

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stem cells on the mucous membrane of the lungs. This process is usually accompanied either by increased (uncontrolled) gene activity which physiologically stimulates the cell processes of proliferation or growth, or by genes that control excessive (uncontrolled) proliferation or cell growth become inactivated. Carcinogenic agents cause changes in genes either by directly damaging a DNA molecule or by affecting normal cell repair mechanisms.

Functionally and didactically, the genes of cancerogenesis can be divided into: proto-oncogenes (RAS, MYC, ERB-B), tumor suppressor genes (Rb, p53), cell division control genes and genes that determine molecules whose role is to repair damaged DNA molecules.

Non-small cell lung cancer (NSCLC) is of great interest in human pathology because its apparent aggressiveness cannot be stopped by applied treatment procedures. The lack of highly specific screening tests prevents an early diagnosis of the disease. Insidious beginning and diverse and unclear clinical picture are responsible for the fact that most cases are diagnosed at advanced stages. An increasing number of patients (1) and a short length of survival (2) are additional factors that make this disease an imperative in the clinical practice, while vague and mutually dependent etiological factors represent a challenge in laboratory studies of the pathogenesis.

At present, combined treatment modalities are mostly used because at the moment of diagnosis it is most often the case of a clinically obvious primary tumor, macroscopic metastases in regional lymph glands and microscopic, subclinical regions of haematogenous dissemination. However, these combined treatment modalities do not give satisfactory results in the patients' survival times.

Biochemical changes of the malignant phenotype might be the objective of new treatment strategies that would be more successful than the currently used conventional cytotoxic treatments. The results of investigations carried out so far can also be applied in the field of diagnosis and prognosis, especially in chronic smokers (3). Clinical aggressiveness of tumors can be more precisely predicted by identifying genes and their products that are functionally related to the phenotype of the cells that invade other tissues (4).

PROTO-ONCOGENES IN CANCEROGENESIS OF NON-SMALL CELL LUNG CANCER

Proto-oncogenes are assumed to be functioning in mitogenic processes in the following way: growth factors initiate transmission of signals for growth through a cell by binding for its receptor. The signal is then transmitted by tyrosine kinases at the inner side of the cell membrane produced by SRC, ABL, FES genes. RAS proteins, similar to G proteins that are at the cytoplasmic side of the membrane, function as GTP phosphatases and transmit those signals to the serine-threonine kinase in the cytoplasm, produced by MYC and MOS genes. Finally, the signal ends in the nucleus where it induces nuclear proto-oncogenes – FOS, JUN, MYB, whose proteins bind directly or in a complex with other proteins to specific regulatory sequences of the target genes thus changing the transcription and finally bringing to DNA synthesis.

RAS genes belong to the group of ubiquitous, eukaryotic genes that play an important role in the cell proliferation and differentiation. The group of RAS genes consists of H-,K- and N-RAS genes that code almost identical 21 kD proteins designated as p21. These are proteins of the superfamily of monomeric GTP binding proteins including those from the three other groups of superfamilies of RHO, RAB and ARG genes. All these proteins are bound to the inner side of the plasma membrane near the growth factor receptors, transducing mitogenic signal from the receptors to the cytoplasm.

Biochemically, the RAS super-family is characterized with high affinity for guanine nucleotides and ability to induce hydrolysis from GTP to GDP and phosphates. Hydrolysation of GTP as an active form to biochemically inactive GDP represents a molecular switch of the cell growth and differentiation. Therefore, stimulation of the growth factor receptors induces activation of the RAS genes which results in an increase of the cell concentration of RAS-GTP. If the RAS genes are in any way mutated, their changed proteins are constantly active regardless of the fact whether there is stimulation by the growth factors or not. This way, the malignant cell is constantly prolifering, which is one of the major characteristics of the malignant phenotype.

One of the first papers that suggested a significant correlation between K-RAS mutations and lung adenocarcinoma was written by Slebos ten years ago (5). Almost all mutations take place in the K-RAS gene, but H-RAS and N-RAS mutations are also detected. Almost all K-RAS mutations occur in codon 12, and the predominant mutation is G→ T transversion. When the mutation is present, i.e. in K-RAS positive patients, it presents a negative prognostic factor because these patients have worse survival than K-RAS negative patients with lung adenocarcinoma. This difference can be partly due to the fact that K-RAS positive tumors are less sensitive to therapeutic procedures (6-9,10-13).

In around 60% of the oncological patients treated with radiotherapy and/or surgery, regardless of the histological type or the stage of the disease, the growth of tumor was not successfully stopped (14). Therefore, with the aim to improve radiotherapeutic treatment modalities, it is very important to reveal the reasons for failure of this therapy. One way to improve the effects of radiotherapy is to predict tumor and normal tissue responses in each of the patients, which means that the therapy will be adjusted to suit each individual patient.

The predominant type of abnormality of the RAS genes in human malignancies is the gene amplification in codons 12, 13 and 61 (3, 4). This type of mutations is not found only in lung cancer, but also in colorectal cancer or adenocarcinoma of the pancreas. The incidence of the RAS mutations detected in the samples of non-small cell lung cancer is relatively high and varies among histological types: 12-41% in epidermal lung cancer, 30-56% in adenocarcinoma, while in large cell cancer it is lower than 27% (according to some authors even lower) (15). RAS mutations in non-small cell lung cancer are associated with shorter survival times of the patients (5,8,10).

It has been determined that, at an early stage of lung adenocarcinoma carcinogenesis, one of first mutated oncogenes, K-RAS, not only has the role in transformation of a cell into malignant, but it also enables early noninvasive metastases along the alveolar septa by means of mechanism of accelerated movement (16).

Synthesized inhibitors - farnesyl/transferase and geranyl/transferase, as mediators of the function of the RAS proto-oncogenes, are developed in order to inhibit the growth of tumor cells with RAS mutations. However, an early phase II study of the inhibitors of farnesyl/transferase R 115777 showed that there is no real response in patients with NSCLC (17).

The cells of non-small cell lung cancer have aberrant expression of the ERB-B family of dominant proto-oncogenes. This family consists of ERB-B1 and ERB-B2 genes (also known as HER-2/neu). Both these proto-oncogenes code for the tyrosine-kinase that is joined to the membrane and has a function of a receptor for the growth factors. The ERB-B1 gene is amplified in more than 20% of the epidermal lung cancer, and there is an excessive expression of the ERB-B1 protein in all histological types if non-small lung cancer (90% in epidermal cancer, 20-75% in adenocarcinoma and rarely in large cell cancer) (18). There is also an amplification of the ERB-B2 proto-oncogenes and excessive expression of the coded proteins in the lung cancer cells, but it is rarer compared to expression of ERB-B1. However, the HER-2/neu gene amplification and hyper-expression of proteins are not the basic mechanisms of cancerogenesis of NSCLC (19). Furthermore, there is no agreement on its validity for prognosis of the patients' length of survival (20,21). Trastuzumab (Herceptin® produced by F. Hoffmann-La Roche) is a recombinant monoclonal antibody that recognizes HER2 and blocks its activity alone or in combination with chemotherapy (22).

As relevant for lung cancer, the following oncogenes are studied C-, N- and L-MYC. They are three-exonic genes: a C-MYC gene, approximately 5 kb long, located on the short arm of chromosome 8 (8q24), N-MYC, 6.5 kb long and located on the long arm of chromosome 2 (2p25) and L-MYC, also around 6.5 kb long and located on the long arm of chromosome 1 (1p32). The protein of the C-MYC gene has a role in DNA replication, gene expression at the level of transcription and RNA processing. N-MYC and L-MYC proteins are related to certain cell types and changed differentiation.

DNA amplification of the MYC gene family is found both in the cell culture and in the material obtained by tumor resection. It is more often found in the cell culture than in tumors (31% of the cell culture and 18% of the tumors) and it is more frequent in tumors of the patients that have already been treated compared to the tumors of the patients that have not been previously treated (23). DNA amplification of genes of the MYC family does not seem to be a primary event in cancerogenesis of lung cancer. Amplification of these genes has a significant contribution to the growth of already transformed cells, which this way become a dominant population in the tumor. DNA amplification, especially of the C-MYC genes, is associated with shorter survival times of the patients with non-small cell lung cancer. There is a significant correlation between metastases and the presence of the MYC proteins in the material obtained by resection of non-small cell lung cancer.

When MYC is bound to the protein MAX, it functions as a factor of transcription and it is necessary for the normal cell growth, differentiation and programmed cell death. Amplification of the MYC family is more frequent in patients with small cell cancer compared to those with non-small cell lung cancer (24,25).

GROWTH FACTORS IN CANCEROGENESIS OF NON-SMALL CELL LUNG CANCER

Growth factors are specific peptide molecules that take part in the cell proliferation. They provide the basis for communication among cells in a multicellular organism. Their function begins with binding to functional receptors, after which the signal is transmitted into the interior of a cell. New

findings in the field of function and structure of the growth factors have brought up the question of how appropriate the term is. The *peptide signal molecules* might be a more appropriate term than the growth factors. Although the growth factors usually stimulate the cell division, they can also stimulate their maturation and control the cell survival. Accordingly, the growth factors and their function should be considered in the biological environment in which they function.

The growth factors have autocrine and paracrine effects. The autocrine mechanism involves secretion of the growth factor from the cell, its binding to receptors of that cell and triggering the physiological response in it. The paracrine mechanism involves secretion of the growth factors into the surroundings of the cell while the secreted peptide regulates the function of the surrounding cells. Although the autocrine mechanism was discovered on a model of transformed cells, it is known that it, together with the paracrine mechanism, also regulates the function of normal tissues, especially the immune system. With this kind of function, the growth factors ensure the essential mechanism by means of which the cells communicate among themselves in their local environment. Besides having stimulating effects on division, the growth factors are known to have or change the local effects of classical hormones (e.g. ACTH, estradiol, thyroxine).

The epidermal growth factor (EGF) and the transforming growth factor (A- TGFA) are found in the cell cultures of non-small lung cancer, as well as in the tumor itself. They are both related to the receptor of the epidermal growth factor (EGFR), which is present in some non-small cell bronchial cancers, thus performing autocrine stimulation. An excessive expression of the epidermal growth factor receptors is found in 70% of NSCLC and it is a prognostic factor of bad survival rates in patients (26). The relation between EGFFR and its ligands, especially the transforming growth factor – ά, and lung cancer cells suggests an autocrine stimulation of the growth factor receptors (27). Gefitinib (ZD1839, Iressa) is a specific inhibitor of the EGFR-tyrosine kinase and has an antitumor effect both in affected patients and in xenograft models of human NSCLC. The patients who had a clinical response to gefitinib had deletion type mutations and point mutations in the kinase part of the receptors EGF (28). These somatic mutations caused a prolonged activity of the receptor, after its stimulation by EGF, and made it sensitive to gefitinib (29,30). The mutations were more frequent in nonsmokers, adenocarcinoma, women and Asian population.

These mutation never occur together with K-RAS mutations nor with TR53 mutations (6, 31-33). This is especially important because it gives a possibility of therapeutic treatment of this segment of the signal transmission.

The platet/derivated growth factor (PDGF) and the insulin-like growth factor-I (IGF I) are found in certain bronchial cancers. These two growth factors are assumed to have an autocrine role and to participate in formation of tumor strome.

The expression of the growth factors and their receptors in some non-small cell lung cancers is associated with an aggressive clinical course and increased resistance to chemotherapy (34-36).

CONCLUSION

Lung cancer is one of the most lethal cancers. Relapses are common after primary and adjuvant treatment, and development of lethal metastases is fast. The current classification of lung cancers does not take into account the biological characteristics of the tumor, which is why it has limiting values in estimates of time to relapse and survival. Therefore, great efforts are made to investigate molecular changes in tumors in order to predict the response to current treatment models and determine direction of development of new ones.

Better understanding of cancerogenesis of lung cancer will give answers to the questions like: "Which molecules are associated with response or resistance to standard treatment?" and "Which of the newly synthesized drugs with ongoing clinical trials has the best clinical response in patients?" Recent studies have shown that molecular markers associated with resistance to cisplatin-based adjuvant treatment include expression of the genes from the group ERCC1 (excision repair cross-complementation group 1) and mutation of RAS proto-oncogenes. Such research suggests that molecular investigations can guide the choice of treatment for both primary and adjuvant chemotherapy. The best example for this is patients' response to chemotherapy when inhibitors of the EGFR tyrosine kinase are applied. These results encourage profiling of new targets for development of unconventional drugs which would be based on the biological characteristics of the tumor and could be applied to each patient individually. The future of lung cancer treatment lies in personalized therapy.

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ULOGA PROTOONKOGENA I STIMULACIJE RECEPTORA FAKTORA RASTA U KANCEROGENEZI NEMIKROCELULARNOG KARCINOMA PLUĆA

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SAŽETAK

Nemikrocelularni karcinom pluća (eng. non-small cell lung cancer- NSCLC) je aktuelan u humanoj patologiji jer se izrazita agresivnost ne može zaustaviti primenjenim terapijskim postupcima. Nedostatak visoko specifičnih skrining testova onemogućava rano otkrivanje bolesti. Podmukli početak, razuđena, ali nedovoljno jasna klinička slika, razlozi su otkrivanja bolesti kod najvećeg broja bolesnika u poodmaklim stadijumima. Zabrinjavajući porast broja obolelih i kratko vreme preživljavanja pacijenata su dodatni faktori kojima se ova bolest nameće kao jedan od imperativa u kliničkoj praksi, a nejasni i međuzavisni etiološki faktori izazov u laboratorijskim istraživanjima patogeneze.

Bolje razumevanje kancerogeneze karcinoma pluća daće odgovore na sledeća pitanja: koji su molekuli povezani sa odgovorom ili rezistencijom na standardnu terapiju i koji od novo-sintetisanih lekova, a čija su klinička ispitivanja u toku, ima najbolji klinički odgovor među obolelima. Dosadašnja ispitivanja su ukazala da molekularni markeri povezani sa rezistencijom na adjuvantnu terapiju, zasnovanu na cisplatini, su ekspresija gena grupe ERCC1 (eng. excision repair cross- complementation group 1) i mutacija RAS protoonkogena. Ovakva istraživanja ukazuju da molekularna istraživanja mogu voditi izboru lečenja i za primarnu i za adjuvantnu hemioterapiju. Najbolji primer za to je povoljan odgovor bolesnika na hemioterapiju, kod kojih su primenjeni inhibitori tirozin kinaze epidermalnog faktora rasta.

Budućnost lečenja karcinoma pluća je u personalizovano određenoj terapiji prema biološkim karakteristikama tumora.

Ključne reči: **nemikrocelularni karcinom pluća, protoonkogeni, receptori faktora rasta**