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PERSONALISED THERAPY OF BREAST CANCER – SIGNALLING PATHWAYS AND TARGETED THERAPY OF BREAST CANCER

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Summary

Personalised therapy of breast cancer is the optimal therapeutic approach to the patient, taking into consideration his personal characteristics, as well as clinical characteristics of the malignant deasease, involving pathohistological and molecular abnormalities of certain tumour. With the devolopment of molecular oncology methods, genetic profiling of each individual tumor is possible. Beside the major subtypes of breast carcinoma based on steroide receptors, Ki-67 proliferative index, and HER-2 receptors, numerous genetic subtypes of breast cancer have been found due to enormous genetic heterogeneity and instability of tumor cells. Some of genetic changes are considered as “driving” genes, resulting in dysregulations of crucial signalling transduction pathways involving in cell proliferation, angiogenesis, apoptosis, invasion or metastasis. Certain components of signalling transduction pathways can be targeted molecules of the so-called targeted biological therapy. Proper understanding of complexities of these dysregulated multiple intracellular signalling cascades in tumor cells is essential for the development of novel potential molecular therapeutic targets.

Keywords: breast cancer; signalling pathways; personalysed therapy.

The normal cells, as well as the tumor cells have capability to respond to the numerous external stimuli such as growth factors, hormons or cytokines. This complex processes comprise recognition on cellular mebrane by receptors, intracellular signalling transduction pathways, activation of numerous transcription factors, and expression of different genes. This is the way of cellular response to microenviroment, as well as regulation of cellular

proliferation and differentiation [1]. In this complex multifacorial nets of signalling transduction pathways from cellular membrane to nucleus, the crutial role have protein kynases, enzymes involved in methabolic pathways, protein phosphorilation, transport and activation, as well as in degradation of proteins. Changes in components of signalling transduction pathways can result in malignant cell transformation. In normal cells signalling transduction pathway is precisly regulated. In tumor cells, crucial molecules of this complex signaling transduction pathways can be changed by different mechanisms, envolving expression of some oncogenes, leading to abnormal signalling transduction pathways, inhibition of apoptosis, uncontrolled tumor cells proliferation, angiogenesis, tumor invasion and metastazing [2]. Activation of some oncogenes (e.g. ErbB2, PI3K, Akt, Myc,), or loss of function of some tumor supressor genes (TP53, or PTEN), resulting in changes in signalling pathways sach as PI3K/Akt/mTOR, or raf/MEK/ERK are implicated to be involved in carcinogenesis of breast cancer [3]. Certain components of signalling transduction pathways can be targeted molecules of so called targeted biological therapy. Understanding of complexities of these dysregulated multiple intracellular signalling cascades in the tumor cells is essential for the developing of novel potential molecular therapeutic targets [4].

Personalized therapy of malignant deseases, including breast cancer is, according to the definition, optimal therapeutic approach to the patient, taking into consideration his individual, personal characteristics (including genetic), as well as clinical characteristics of the malignant deasease, involving pathohystological and molecular abnormalities of certain tumor. With the devolopment of molecular oncology methods, especially with DNA microarray analyses, genetic profiling of each individual tumor is possible. Two biggest international projects of systematic genomic analyses of tumor samples are currently ongoing: The Cancer Genome Atlas – NIH project in USA, and International Cancer Genomic Consortium in the rest of the world (3). With these molecular genetic analyses, numerous genetic changes in breast cancer have been found, some of them are considered as „driving" genes, but the real role of some genetic changes in carcinogenesis remans to be determined [5].

According to the recommendations of St. Gallen conference (St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer, 2013) it is obligatory to determine major subtypes of breast cancer on the basis of immunohystochemical analysis of estrogene and progesterone

receptors, HER-2 receptors and Ki-67 proliferation index on the tumor tissue samples [6]. The therapeutic basis for luminal A and luminal B subtypes of steroide receptor positive breast cancer is hormonal therapy, imunotherapy shoulod be included in the treatment of HER 2 positive subtypes, while chemotherapy is still the basis for treatment triple negative („basal like") subtypes of breast cancer. However, molecular analyses of individual breast carcinoma tissues revealed that each of these subtypes can comprise futher new genetic subtypes of tumors which can deffer in prognosis and response to the therapy. According to numerous studes in the field of breast cancer, a great therapeutic problem in this desease is pronounced heterogeneity of tumor cells among apparently similar tumors, as well as diffent tumor clones in even one tumor. Tumor genom is very unstable, prone to numerous changes and mutations, even during therapy, which can lead to induction of different mecahisms of resistance and survival of mutated clones of tumor cells [3].

Hormonal therapy of steroid receptor positive breast cancer is one of the oldest and most succesful personalyzed therapeutic approach. With hormonal therapy steroide receptor expression on tumor cells is modulate or downregulate and/or hormone synthesis is blocked, resulting in decreased activation of estrogen signalling pathway. However, it has been shown that there is possibility of parallel activation of different signalling transduction pathways in breast cancer cells together with steroide receptor pathway (e.g. signalling pathways of EGFR, and PI3K/Akt/mTOR) which can be activated in resistance to hormonal therapy [7]. We block one signalling pathway with targeted therapy, but tumor cells activate different compensatory mechanisms and other numerous signalling pathways. This is the basis for therapeutic concept of necessity of parallel blocking of different signalling pathways – such as hormonal therapy together with mTOR inhibition in breast cancer patients (e.g. BOLERO-2 clinical trial of addition of mTOR inhibitor everolimus to aromatase inhibitor exemestan in the treatment of hormone receptor pozitive advanced breast cancer patients) [8,9]. Immunotherapy is the mainstain for the treatment of HER-2 pozitive breast cancer [10]. However, it has been shown that significant percent of HER-2 positive breast cancer does not respond to immunotherapy [11]. Different expression of TOPO2A enzyme in the group of HER 2 positive breast cancer could be one of the reasons of heterogeity. Tumors with mutation of HER-2, instead of HER-2 amplification could be another subgroup [12]. Second and third generations of anti-HER-2

therapies are in clinical studies, as well as so called „dual blocking" of ErbB2 pathway (e.g. anti HER2/neu receptor antibody together with tyrosine kinase inhibitors, as well as different combinations of chemotherapy, HER-2 blocking and blocking of some other signalling pathways by targeted agents [13]. A recent molecular anlyses of triple negative breast cancer (TNBC) revieled that different subgroups can be identified, defined by mesenchymal features, immune system-related genes, DNA damage response genes and activated androgen receptor signalling [14]. Potential novel therapeutic targets will be defined on the basis of this heterogeneity, like PARP inhibitors in deficiencies in the BRCA1 gene pathway [13].

In conclusion, we can say that reliable prognostic and predictive parametars for breast cancer, or biomarkers for identification of different tumor subpopulations are still widely needed [1,15]. A great progress on the way of personalisation in the therapy of breast cancer has been already achieved, but because of enormous genetic instability and heterogeneity, breast cancer is still largely unknown and the subject of numerous investigations.

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Sažetak

Personalizirano liječenje raka dojke – signalni putovi i ciljano liječenje raka dojke

Personalizirana terapija karcinoma dojke obuhvaća optimalni terapijski pristup, uzimajući u obzir pacijentove osobne karakteristike, kao i kliničke karakteristike pojedine maligne bolesti, uključujući patohistološke i molekularne abnormalnosti svakog pojedinog tumora. Razvojem metoda molekularne onkologije omogućeno je genetičko profiliranje svakog individualnog tumora. Pored osnovnih subtipova karcinoma dojke temeljem ekspresije steroidnih receptora, HER-2 receptora i čimbenika proliferacije Ki-67, a zbog velike hetrogenosti i nestabilnosti genoma tumorskih stanica, nalaze se i brojni drugi subtipovi. Neke od tih genetičkih promjena smatraju se tzv. pokretačkim genima odgovornim za poremećenu regulaciju ključnih signalnih puteva u stanici uključenih u staničnu proliferaciju, angiogenezu, apoptozu, invaziju ili metastaziranje. Određene komponente signalnih puteva su ciljne molekule tzv. ciljane biološke terapije. Razumijevanje kompleksnosti mehanizama ovih poremećenih prijenosa signala u tumorskim stanicama ključno je za razvoj novih potencijalnih meta ciljane biološke terapije karcinoma dojke.

***Ključne riječi*:** karcinom dojke; prijenos signala u stanici; personalizirana terapija.

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