

PERSONALIZED APPROACH TO THE THERAPY OF BREAST CANCER

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Summary

Personalized therapy of breast cancer is optimal therapeutic approach to the patient, taking into consideration his personal characteristics, as well as clinical characteristics of the malignant disease, involving pathohistological and molecular abnormalities of certain tumor. With the development of molecular oncology methods, genetic profiling of each individual tumor is possible. Beside the major subtypes of breast carcinoma based on steroid 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 signaling transduction pathways involving in cell proliferation, angiogenesis, apoptosis, invasion or metastasis. Certain components of signaling transduction pathways can be targeted molecules of so called targeted biological therapy. Understanding of complexities of these dysregulated multiple intracellular signaling cascades in the tumor cells is essential for the developing of novel potential molecular therapeutic targets.

KEY WORDS: *breast cancer, signalling pathways, personalized therapy.*

PERSONALIZIRANI PRISTUP LIJEČENJU RAKA DOJKE

Sažetak

Personalizirana terapija karcinoma dojke obuhvaća optimalni terapijski pristup, uvažavajući pacijentove osobine i kliničke karakteristike maligne bolesti, uključujući patohistološke i molekularne abnormalnosti tumora. Razvojem metoda molekularne onkologije omogućeno je genetičko određivanje svakog individualnog tumora. Pored osnovnih podtipova karcinoma dojke temeljem izražajnosti steroidnih receptora, HER-2 receptora i čimbenika proliferacije Ki-67, a zbog velike heterogenosti i nestabilnosti genoma tumorskih stanica, nalaze se i brojni drugi podtipovi. 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 ciljane molekule tzv. ciljane biološke terapije. Razumijevanje složenosti mehanizama poremećenih prijenosa signala u tumorskim stanicama ključno je za razvoj novih mogućih meta ciljane biološke terapije karcinoma dojke.

KLJUČNE RIJEČI: *rak dojke, prijenos signala u stanici, personalizirana terapija*

The normal cells, as well as the tumor cells have capability to respond to the numerous external stimuli such as growth factors, hormones or cytokines. This complex processes comprise recog-

niton on cellular membrane by receptors, intracellular signalling transduction pathways, activation of numerous transcription factors, and expression of different genes. This is the way of cellular re-

sponse to microenvironment, as well as regulation of cellular proliferation and differentiation (1). In this complex multifactorial nets of signaling transduction pathways from cellular membrane to nucleus, the crucial role have protein kinases, enzymes involved in metabolic pathways, protein phosphorylation, transport and activation, as well as in degradation of proteins. Changes in components of signaling transduction pathways can result in malignant cell transformation. In normal cells signaling transduction pathway is precisely regulated. In tumor cells, crucial molecules of this complex signaling transduction pathways can be changed by different mechanisms, involving expression of some oncogenes, leading to abnormal signaling transduction pathways, inhibition of apoptosis, uncontrolled tumor cells proliferation, angiogenesis, tumor invasion and metastasizing (2). Activation of some oncogenes (e.g. ErbB2, PI3K, Akt, Myc,), or loss of function of some tumor suppressor genes (TP53, or PTEN), resulting in changes in signalling pathways such 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 target 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 diseases, 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 disease, involving pathohistological and molecular abnormalities of certain tumor. With the development 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 remains 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 immunohistochemical analysis of estrogen 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 steroid receptor positive breast cancer is hormonal therapy, immunotherapy should 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 further new genetic subtypes of tumors which can differ in prognosis and response to the therapy. According to numerous studies in the field of breast cancer, a great therapeutic problem in this disease is pronounced heterogeneity of tumor cells among apparently similar tumors, as well as different tumor clones in even one tumor. Tumor genome is very unstable, prone to numerous changes and mutations, even during therapy, which can lead to induction of different mechanisms 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 successful personalized therapeutic approach. With hormonal therapy steroid receptor expression on tumor cells is modulated or downregulated and/or hormone synthesis is blocked, resulting in decreased activation of estrogen signaling pathway. However, it has been shown that there is possibility of parallel activation of different signaling transduction pathways in breast cancer cells together with steroid receptor pathway (e.g. signaling pathways of EGFR, and PI3K/Akt/mTOR) which can be activated in resistance to hormonal therapy (7). We block one signaling pathway with targeted therapy, but tumor cells activate different compensatory mechanisms and other numerous signaling pathways. This is the basis for therapeutic concept of necessity of parallel blocking of different signaling pathways – such as hormonal therapy together with mTOR inhibition in breast cancer patients (e.g. BOLERO-2 clinical trial of ad-

dition of mTOR inhibitor everolimus to aromatase inhibitor exemestan in the treatment of hormone receptor positive advanced breast cancer patients) (8,9).

Immunotherapy is the mainstay for the treatment of HER-2 positive 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 heterogeneity. 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 analyses of triple negative breast cancer (TNBC) revealed 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).

CONCLUSION

In conclusion, we can say that reliable prognostic and predictive parameters for breast cancer, or biomarkers for identification of different tumor subpopulations are still widely needed (1,15). A great progress on the way of personalization 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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