UDK 577.1 : 61

ISSN 1452-8258

JOURNAL OF MEDICAL BIOCHEMISTRY

Published by
The Society of Medical Biochemists of Serbia
Belgrade

J Med Biochem

Vol. 37 • No 2 • 2018

JOURNAL OF MEDICAL BIOCHEMISTRY

available online at
http://www.dmbj.org.rs/jmb
http://www.degruyter.com/view/j/jomb

The Journal of Medical Biochemistry
is a member of

Committee on Publication Ethics

COPE

www.publicationethics.org

European Association of Science Editors

EASE

www.ease.org.uk

WAME
world association of medical editors

www.wame.org

Journal of Medical Biochemistry
is covered by the following indexing and abstracting service:
PubMed, Science Citation Index Expanded (SciSearch®, Thomson Reuters),
Journal Citation Reports / Science Edition, (JCR, Thomson Reuters), EBSCO Publishing, EMBASE / Excerpta Medica,
Elsevier BIOBASE / Current Awareness in Biological Sciences, Current Awareness in Biomedicine,
Chemical Abstracts Service, ChemWeb, CAB Abstracts, Global Health,
DOAJ (Directory of Open Access Journals), Summon,
Bowker International Serials Database, Bulletin Scientifique,
SCOPUS, VINITI: All-Russian Institute of Scientific and Technical Information,
Referativnyi Zhurnal, National Library of Serbia, KoBSON

JOURNAL OF MEDICAL BIOCHEMISTRY

Publication dates: March, June, September, December

Editorial Office

Society of Medical Biochemists of Serbia,
Vojislava Ilića 94B/7, 11050 Belgrade, Serbia

FARMAKOGENOMIKA U KONTROLI RAKA

Marija Hiljadnikova-Bajro

Institut za primenjenu biohemiju, Farmaceutski fakultet, Univerzitet Ćirilo i Metodije, Skoplje, Makedonija

Kao drugi vodeći uzrok smrtnosti u svetu, odgovorne za 1 od 6 smrtnih slučajeva ili 8,8 miliona smrtnih slučajeva u 2015. godini, maligne bolesti postale su značajno opterećenje za ljudsko zdravlje. Statistike raka u svetu za 2012. godinu procenjuju incidencu vecu od 14000000. Na osnovu mortaliteta i statistika prevalence, procenjuje se da u svetu ima oko 33 miliona ljudi sa dijagnozom raka. Kako je rak bolest starenja i rizik od raka se povećava sa godinama, može se očekivati da će brzi razvoj medicine i farmacije produženjem životnog veka, neizbežno dovesti i do povecane incidence raka u buducnosti. Prema tome, očekuje se da će broj novih slučajeva porasti za oko 70% u naredne dve decenije, što zahteva dodatne pristupe u kontroli bolesti. Pojava molekularnih tehnika uvodi genetsku analizu u laboratorijsku procenu malignih bolesti i čini je vrlo perspektivnom. Primena genetske analize kod karcinoma obično je povezana s procenom rizika od naslednog kancera, ali klinička primena genetske analize danas podrazumeva i DNK testiranje germinativnih ćelija na nasledne karcinome, testiranje za postavljanje dijagnoze i praćenje stečenih maligniteta kao što su hematološki, kao i prognostičko i prediktivno farmakogenetsko testiranje. Ovaj rad se fokusira na biomolekularne mehanizme koji čine osnovu kliničke primene farmakogenetike u onkologiji, tj. prognostičkom DNK profilisanju kod tumora i prediktivnom DNK profilisanju germinativnih ćelija u lečenju karcinoma. FDA/EMA je odobrila nove obećavajuće markere i o njima će biti reči. Biće elaborirana genetička analiza EGFR, KRAS, ALK, BCR/ABL, KIT, BRAFV600E u pogledu njihove vrednosti u prognoziranju efikasnosti ciljanih antikancerogenih agenasa, kao i najnovijih pristupa u prevazilaženju otpornosti na lekove protiv raka, identifikovanjem odgovornih genetskih promena u malignim celijama. Pored toga, sumira se klinički značaj nekoliko markera, uključujuci DPID, TPMT i UGT1A1 sa osvrtom na prognoziranje toksičnosti lečenja. PharmGKBdatabase će biti predstavljen kao resurs znanja za farmakogenomiku koji obezbeđuje pouzdane podatke koji se koriste za istraživanje ili kliničku primenu u skladu sa principima »precizne« medicine. U protekloj deceniji, biomolekularne analitičke tehnologije prešle su sa »singleplex« na »mutiplex« testiranje. Brzi razvoj sekvenciranja sledeće generacije je revolucionirao genomiku i učinio je dostupnijom, tako da se može očekivati da će razvoj molekularnih tehnologija uparenim sa bioinformatikom neminovno ubrzati otkrivanje novih

PHARMACOGENOMICS IN CANCER MANAGEMENT

Marija Hiljadnikova-Bajro

Institute for Applied Biochemistry, Faculty of Pharmacy, University SS Cyril and Methodius, Skopje, Republic of Macedonia

Being the second leading cause of death globally and responsible for nearly 1 in 6 deaths or 8.8 million deaths in 2015, malignant diseases have become a formidable burden on human health. The 2012 worldwide cancer statistics estimates an incidence higher than 14000000. Based on the mortality and prevalence statistics, it is estimated that there are about 33 million people in the world alive diagnosed with cancer. As cancer is a disease of ageing and the risk of getting cancer increases with age, it can be anticipated that the rapid development of medicine and pharmacy leading to extended human lifespan will inevitably produce higher cancer incidence in future. Hence, the number of new cases is expected to rise by about 70% over the next two decades requiring additional efforts in management of the disease. The emergence of molecular techniques has introduced genetic analysis in laboratory evaluation of malignant diseases and made it quite promising in this regard. Application of genetic analysis in cancer management is usually associated with the risk evaluation in hereditary cancer, but clinical application of genetic analysis today implies germline DNA testing for hereditary cancer syndromes and testing for diagnosis and monitoring of acquired malignancies like the hematological ones, as well as prognostic and predictive pharmacogenetics testing. This work focuses on the biomolecular mechanisms underlying the clinical application of pharmacogenetics in oncology i.e. prognostic tumor DNA profiling and predictive germline DNA-profiling in cancer treatment. The FDA/EMA approved as well as novel promising markers will be addressed. The genetic analysis of EGFR, KRAS, ALK, BCR/ABL, KIT, and BRAFV600E will be elaborated regarding their value in prognosing the effectiveness of targeted anticancer agents, as well as the latest advances in avoiding anticancer drug resistance by identification of the responsible genetic alterations in the malignant cells. Furthermore, the clinical significance of several markers including DPYD, TPMT and UGT1A1 with relevance to predicting treatment's toxicity will be summarized. The PharmGKBdatabase will be presented as a pharmacogenomics knowledge resource providing reliable data to be used for research or clinical application in concordance with the principles of precision medicine. Within the last decade, biomolecular analytical technologies have shifted from singleplex towards mutiplex testing. The rapid development of the next generation sequencing has revolutionized genomics and made it more available, so it is can be anticipated that the

biomarkera u kontroli raka. Identifikacija robustnih farmakogenetskih markera značajno će uticati na trenutne farmakološke pristupe i pomoć u razvoju novih, efikasnijih i manje toksičnih tretmana.

POLIMORFIZMI GENA ZA ADIPOCITOKINE I RIZIK ZA POJAVU KOLOREKTALNOG KARCINOMA

Ana Ninić[1], Marija Mihajlović[1], Miron Sopić[1], Vesna Spasojević-Kalimanovska[1], Nataša Bogavac-Stanojević[1], Željka Stjepanović[2], Aleksandra Stefanović[1], Ivan Jančić[1], Dejan Zeljković[3], Bratislav Trifunović[3], Aleksandra Zeljković[1]

[1]Univerzitet u Beogradu – Farmaceutski fakultet, Beograd
[2]Medigroup Opšta bolnica, Beograd
[3]Klinika za Opštu hirurgiju, Vojno-medicinska akademija, Beograd, Srbija

Mnoge epidemiološke studije su ukazale da postoji važna uloga gojaznosti u riziku i razvoju kolorektalnog karcinoma (CRC). Zajednička karakteristika gojaznosti i CRC-a je hronična subklinička inflamacija. Adipocitokini, sintetisani u masnom tkivu, imaju ulogu u razvoju i progresiji CRC-a koja i dalje nije u potpunosti jasna. Smanjeni nivoi adiponektina (ADIPOQ) u serumu su u korelaciji sa razvojem i progresijom kancera i u obrnutoj su korelaciji sa markerima inflamacije. Faktor nekroze tumora alfa (TNFα) stimuliše malignu proliferaciju celija i indukuje inflamatorne puteve koji stimulišu karcinogenezu. Iako rezistin (RETN) igra važnu regulatornu ulogu u inflamatornim bolestima, njegova uloga u metaboličkim poremećajima još uvek nije jasna. Cilj studije je bio da se utvrdi da li polimorfizmi pojedinačnog nukleotida (SNP) i koncentracije proteina adipocitokina predstavljaju prediktivne faktore rizika za pojavu CRC-a. Uzorci krvi 187 zdravih osoba i 105 pacijenata sa CRC-om su genotipizirani za ADIPOQ rs266729 (-11377C/G), RETN rs1862513 (-420C/G), TNFα rs1800629 (-308G/A) i adiponektinski receptor 1 rs7539542 (+10225C/G) polimorfizme. Koncentracije adipocitokina su određene ELISA testovima. Nije bilo značajnih razlika u distribuciji genotipova, za svaki od testiranih polimorfizama, između pacijenata sa CRC-om i kontrolne grupe. Multivarijantna logistička regresija je pokazala da su koncentracije rezistina nezavistan prediktor za pojavu CRC-a ($p<0,05$) kada se testiraju u Modelu sa svim ispitivanim polidevelopment of high throughput molecular technologies paired with bioinformatics will inevitably speed up the discovery of new biomarkers in cancer management. Identification of robust pharmacogenetics markers will significantly impact the current pharmacological approaches and aid in development of new, more effective and less toxic treatments.

GENE POLYMORPHISMS FOR ADIPOCYTOKINES AND THE RISK FOR COLORECTAL CANCER DEVELOPMENT

Ana Ninić[1], Marija Mihajlović[1], Miron Sopić[1], Vesna Spasojević-Kalimanovska[1], Nataša Bogavac-Stanojević[1], Željka Stjepanović[2], Aleksandra Stefanović[1], Ivan Jančić[1], Dejan Zeljković[3], Bratislav Trifunović[3], Aleksandra Zeljković[1]

[1]University of Belgrade – Faculty of Pharmacy, Belgrade, Serbia
[2]Medigroup General Hospital, Belgrade, Serbia
[3]Clinic for General Surgery, Military Medical Academy

Many epidemiological studies indicated an important role of obesity in colorectal cancer (CRC) risk and development. The common hallmark of obesity and CRC is chronic subclinical inflammation. Adipose tissue-synthesized factors, known as adipocytokines, have roles in regulation of CRC development and progression which still remains controversial. Decreased adiponectin (ADIPOQ) serum levels correlate with cancer development and progression and are inversely associated with markers of inflammation. Tumour necrosis factor alfa (TNFα) stimulates malignant cells proliferation and induce the inflammatory pathways that enhance carcinogenesis. Although resistin (RETN) plays an important regulatory role in inflammatory diseases, its role in metabolic dysregulations is still unclear. We aimed to determine whether adipocytokines' single nucleotide polymorphisms (SNP) and protein concentrations represented predictive factors for CRC susceptibility. Blood samples from 187 apparently healthy persons and 105 patients with CRC were genotyped for ADIPOQ rs266729 (-11377C/G), RETN rs1862513 (-420C/G), TNFα rs1800629 (-308G/A) and adiponectin receptor 1 rs7539542 (+10225C/G) polymorphisms. Adipocytokines' concentrations were determined by ELISA tests. There were no significant differences in genotype distributions for each of tested SNPs between CRC patients and control subjects. Multivariate logistic regression analysis demonstrated independent prediction of protein RETN concentrations on CRC diagnosis ($p<0.05$) when tested in