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GLUTATHIONE S-TRANSFERASES EXPRESSION IN CARCINOMA OF URINARY BLADDER

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Summary: The glutathione S-transferases (GSTs) superfamily comprises multiple isoenzymes (α, μ, π, θ), with an important role against potential carcinogens in normal cells. In tumors, increased expression of GSTs is generally related with resistance to chemotherapy. GSTM1 and GSTP1 have potential regulatory roles in the activity of some members of mitogen-stimulating protein kinases (MAPK). It is believed that GSTs/regulatory kinases interactions depend on cell redox balance. However, the relationship between GST expression and apoptosis or antioxidant potential of transitional cell carcinoma of urinary bladder (TCC) has not been investigated. In this study, tumor samples and surrounding normal uroepithelium were obtained from 46 patients with TCC of urinary bladder. We determined the activity and expression of GST (Western blot, immunocytochemistry), apoptosis (TUNEL), as well as the activity of enzymes involved in regeneration of glutathione (γ-glutamyl-cistenyl synthetase, γ-GCS, glutathione reductase, GR) and antioxidant enzymes (glutathione peroxidase, GPX; superoxide dismutase, SOD). GSTP1 and GSTM1 were expressed in normal uroepithelium of patients with TCC (45/45 and 23/45, respectively). In tumors, significant upregulation of overall GST activity ($p < 0.001$), expression of GSTP1 ($p < 0.001$) and GSTM1 ($p < 0.05$) were found. Moreover, GSTP1 expression correlated with tumor grade ($p < 0.05$). In addition to cytoplasmatic localization of GSTM1 and GSTP1, we also found nuclear GSTP1 in tumor cells. Increased GSTP1 expression, as well as its nuclear localization, inversely correlated with the apoptotic index ($p < 0.05$). TCC cells had upregulated enzymatic antioxidant potential judging from increased tumor activity of γ-GCS, GR, as well as GPX and SOD. Moreover, GR activity correlated with GSTP1 expression. We concluded that increased expression of GSTP1 and GSTM1 could have an important role in TCC progression and chemoresistance. Therefore, it can be

EKSPRESIJA GLUTATION S-TRANSFERAZA U KARCINOMIMA MOKRAĆNE BEŠIKE

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Kratak sadržaj: Glutation S-transferaze (GST) su superfamilija enzima (α, μ, π, θ), koji u zdravim ćelijama imaju zaštitnu ulogu od potencijalnih kancerogena. U tumorima, povećana ekspresija GST se najčešće vezuje za rezistenciju na hemoterapiju. GSTP1 i GSTM1, pored katalitičke uloge, imaju i potencijalnu ulogu u regulaciji aktivnosti mitogenom-aktiviranih protein-kinaza (MAPK), uključenih u indukciju apoptoze. Smatra se da interakcija između GSTM1, GSTP1 i regulatornih kinaza zavisi od redoks balansa u ćeliji. Međutim, veza između ekspresije GSTP1 i apoptoze, kao i antioksidantnog potencijala u karcinomima prelaznog epitela mokraćne bešike do sada nije ispitivana. U ovom istraživanju korišćeni su uzorci tumorskog i okolnog zdravog uroepitelijuma 46 pacijenata s karcinomom bešike. Određivana je aktivnost i ekspresija GST izoenzima (imunoblot, imunocitohemija), apoptoza (TUNEL), kao i aktivnosti enzima sinteze i regeneracije glutationa (γ-glutamilcistein sintetaza, γ-GCS; glutation reduktaza, GR) i antioksidantnih enzima (glutation peroksidaze, GPX; superoksid dizmutaze, SOD). Pokazano je da su u zdravom uroepitelijumu pacijenata s karcinomom bešike eksprimirani GSTP1 (45/45) i GSTM1 (23/45). U tumorskom tkivu zabeleženo je značajno povećanje aktivnosti ukupne GST ($p < 0,001$), ekspresije GSTP1 ($p < 0,001$) i GSTM1 ($p < 0,05$). Štaviše, utvrđeno je da nivo ekspresije GSTP1 zavisi od stepena maligniteta tumora ($p < 0,05$). Za razliku od GSTM1, koja je imunocitohemijskom analizom detektovana samo u citoplazmi, prisustvo GSTP1 je pokazano i u jedru tumorskih ćelija. Ekspresija GSTP1, kao i prisustvo ovog izoenzima u jedru, značajno su negativno korelirali sa apoptotskim indeksom (AI) ($p < 0,05$). Na osnovu povećanih aktivnosti γ-GCS i GR, kao i GPX i SOD, u tumorskom tkivu, može se zaključiti da ćelije karcinoma bešike imaju povećan enzimski antioksidantni potencijal. Štaviše, aktivnost GR korelira s nivoom ekspresije GSTP1. Na osnovu ovih rezultata može se zaključiti da povećana

speculated that treatment of GSTP1 inhibitors, together with cytostatic drugs, targeting both apoptosis and chemoresistance, could be the new approach for TCC therapy.

Key words: glutathione S-transferases, apoptosis, redox balance, transitional cell carcinoma, urinary bladder, chemoresistance

ekspresija GSTP1 i GSTM1 može imati važnu ulogu u progresiji, kao i nastanku hemorezistencije karcinoma prelaznog epitela. U tom smislu, primena inhibitora GSTP1, zajedno sa citostaticima, može predstavljati novi pristup u terapiji karcinoma bešike.

Ključne reči: glutation S-transferaze, apoptoza, redoks balans, karcinom prelaznog epitela, mokraćna bešika, hemorezistencija