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MOLEKULARNI MEHANIZMI PRIJEMA I ODOZGOVAĆEĆE EUKARIOTA NA SIGNALNE IZ SPOUNE SREĆINE

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Sinopsis:

Homeostaza je ravnotežno stanje metaboličkih procesa koje obezbeđuje optimalno funkcionisanje organizma. Organizam odgovara na odstupanja od ovog stabilnog stanja pokretanjem kompleksnog niza lokalnih i sistemskih reakcija koje zajedno čine tzv. akutno fazni odgovor (AFO). AFO je evolutivno konzervisan mehanizam usmeren ka reuspostavljanju normalnog funkcionisanja organizma tokom infekcija, tkivne povrede, hemijskog tretmana i neoplastičnih bolesti. Inicijacija i tok AFO uključuju koordinisanu seriju događaja kao što je oslobađanje citokina, hemotaksija leukocita, aktivacija endotelijalnih ćelija i adrenalno-hipofizna preganja koja obezbeđuje neophodne metaboličke signale kojim deluje na ciljane organe. Jetra je važan učesnik AFO obzirom da se u njoj pod uticajem proinflammatoryh citokina kao što su Tumor nekrotični faktor α , Interleukin-1 β i Interleukin-6 indukuju proinflammatorye promene u sintezi brojnih proteina. Krajnji rezultat se ogleda u povećanoj sintezi i aktivaciji

aktivacije za jetru karakterističnih transkripcionih faktora koji povratno regulišu ravnoge gene među kojima i gene za akutno fazne proteine (AFP).

Akutno fazni proteini predstavljaju heterogenu grupu ciklinskih proteina koji su uključeni u reuspostavljanje homeostaze putem svojih aktivnosti. Oni se mogu svrstati u tri kategorije: inhibicija (2-makroglobulin, α 1-antitripsin i α 1-antitripsin), aktivacija sinteze kompleksa i modulacija imunog odgovora (fibrinogen, C-reaktivni

protein, serum albumin, komplement C3, urolizinski glikoprotein) i funkcionalni

vezivači i transporteri (hepatoglobulin, lipoproteini, transferrin). Koncentracija AFP u ciklusu je uvek jednaka u odgovoru na različite stresogene stimuliše što sugerisuje da je njihova sinteza regulisana specifičnim profilom inflamatornih medijatora koji se aktiviraju na određeni stimulus. Raznovrsnost u smeru, intenzitetu i trajanju promena nivoa AFP-a istice potrebu za kompletnim razumevanjem načina njihovog regulisanja.

Dodatkovo saznajemo o tome kako su geni za AFP modulirani proinflammatorym citokinima tokom AFO bazirajući se na istraživanjima na promotorskom nivou. Ekspresija gena za AFP je uglavnom kontrolisana na transkripcionom nivou i zavisa je od regulatornih interakcija između cis-delujućih DNK sekvenci i specifičnih transkripcionih faktora i DNK vezujućih proteina. Pored sveprisutnih transkripcionih faktora uključuju se i bazalni transkripcioni masineriji svih tipova ćelija, ćelije jetre sadrže dodatne faktore prisutne u ograničenom broju tkiva. Oni pripadaju familijama transkripcionih faktora C/EBP, STAT i NF- κ B. Složenost njihovog učesca u regulaciji ekspresije gena za AFP proizilazi iz činjenice da različiti aktivni članovi svake od ovih familija imaju slična mesta vezivanja za DNK na kojima mogu menjati jedni drugima, i svaki transkripcioni faktor može delovati samostalno ili sinergistički antagonistima sa jednim ili više faktora i kofaktora koji pak pripadaju istoj ili različitoj familiji. Kooperativne interakcije transkripcionih faktora kao i njihove postranslacione modifikacije tipa fosforilacije/defosforilacije glikozilacije/deglikozilacije su neophodne za ostvarivanje određenog nivoa ekspresije gena karakterističnog za ćelije jetre tokom AFO.

DNK vezujućih proteini koji regulišu su transkripciju gena za α 1-P prisutni su i u jedarnoj plazmi i u jedarnom strukturu jedarnog matriksa. Stoga se smatra da je jedarni matriks, kao trodimenzionalna proteinska mreža koja prozima jedro, potencijalno uključena u organizaciju procesa transkripcije. Ovakva uloga jedarnog matriksa ogledala bi se u

funkcionala lno j loka li zacija i gena i prikupljanju i pozicioniranju genskih regulatornih faktora unutar jedra odnosno, u formiranju "ode ljaka " u kojima bl se u odredeno vreme i na jednom mestu nasli svi potrebli ucesllci procesa transkripcije. Na jedarnom- matriksu jetre identifikovatti su transkripcioni faktori: C/EBPa , C/EBP , CIBBP8, STAT 1 , STAT3, STAT 3 i NF-kB p65 koji imaju značajnu ulogu u regulaciji ekspresije gena za AFP. Asocijacija identifikovanih transkripcionih faktora sa jedarnim matriksom je dinamična jer podleže promenama , , 7avisnosti od

... fiziološkog stanja organ izma, odražavajući tako promene u ekspresiji koje karakterisu bazalno stanje i inflamaciju. Detektovanje asocijacija *trans-faktora* sa jedarnim matriksom predstavlja mehanizam skoncentrisavanja genskih regulatornih faktora u blizini aktivnih gena u funkciji optimalne transkripcije. Time se ukazuje na postojanje funkcionalne veze između jedarne strukture - jedarnog matriksa i ekspresije gena.

Micronizni koji kontrolisu ukupnu aktivnost brojnih transkripcionih faktora jetre tokom AFO kao i mehanizmi koji specifično kontrolisu transkripciju određenog gena za AFP su još nedovoljno poznati i predmet su brojnih istraživanja kod nas i u svetu. Razumevanje pomenutih mehanizama je od posebnog značaja za uspostavljanje terapijske kontrole AFO koja je neophodna u nekim životno-ugroženim situacijama kao što je slučaj sa prekomernom produkcijom tumorskog nekrotičnog faktora u uslovljavanju. Isto tako, upoznavanje izmenjenih transkripcionih

... događaja u jetri tokom AFO je od važnosti u prevenciji patoloških stanja koja su povezana sa prevelikom produkcijom određenog AFP-a što je često slučaj u nekim hroničnim inflamatornim bolestima.

MOLECULAR MECHANISMS OF EUKARYOTIC CELL PERCEPTION OF AND RESPONSE TO ENVIRONMENTAL SIGNALS

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Synopsis:

Homeostasis is the state of metabolic equilibrium supporting the optimal functioning of an organism that is actively maintained by complex biological mechanisms. An organism responds to deviations from this stable situation by a coordinated sequence of systemic and metabolic changes, or by local changes such as inflammatory reactions, collectively known as the acute phase response (APR). The APR is an evolutionarily conserved mechanism aimed at reestablishing an organism's normal functioning during infection, tissue injury, chemical irritation and neoplastic disease. The initiation and progression of the APR involves a coordinated series of events, including cytokine release, endothelial-cell activation, leukocyte chemotaxis, alteration of the temperature set-point and activation of the adrenal-pituitary axis which provide the necessary metabolic signals to responding organs. The liver is a major partner in APR and the blood-borne proinflammatory cytokines such as Tumor Necrosis Factor α , Interleukin-1/2 and Interleukin-6 trigger transient changes in the synthesis of numerous proteins in this organ. The result is an up- or down-regulated synthesis and/or activation of liver-enriched transcription factors that in turn regulate genes coding for secreted acute phase proteins (APP).

Acute phase proteins represent a heterogeneous group of circulating proteins which are involved in the restoration of homeostasis

through their actions that can be grouped into three categories: inhibition of proteases (α₂-macroglobulin, α₁-antitrypsin and α₁-antichymotrypsin), complement activation, or modulation of the immune system (fibrinogen, C-reactive protein, serum amyloid A, complement component C3, α₁-acid glycoprotein), and binding and transport function (haptoglobin, hemopexin, transferrin). The plasma concentrations of APPs do not increase uniformly under different stress conditions suggesting that their synthesis is regulated by stressor-specific patterns of production of inflammatory mediators. The diversity in direction, extent and timing of changes in hepatic APP levels stresses the need for a complete understanding of how such changes are regulated.

Our current knowledge of how these genes are modulated by APR and pro-inflammatory cytokines largely rests on studies made at the promoter level. The expression of genes coding for APPs is mostly controlled at the transcriptional level and depends on the regulatory interactions between cis-acting DNA sequences and specific transcription factors and DNA-binding proteins. Besides the ubiquitous transcription factors involved in the basal transcription machinery of most cell types, the hepatocyte contains other factors that are prominent in only a limited number of cell types. These transcription factors mostly include some members of the CAAT/enhancer binding protein (C/EBP) Signal Transducer and Activator of Transcription (STAT), and Hepatocyte Nuclear Factor (HNF)-6 families. Variably active members of the transcription factor family can replace each other at a given binding site and a transcription factor can act either alone or synergistically/antagonistically with one or more other factor(s) or cofactors that belong or do not belong to the same family. The cooperative interaction of transcription factors as well as their posttranslational modifications such as phosphorylation/dephosphorylation or glycosylation/deglycosylation are

required to achieve the levels of expression characteristic of acute phase liver cells.

DNA binding proteins that regulate APP gene transcription reside in both the nucleoplasmic and nuclear matrix compartments of the nucleus. The nuclear matrix is a nascent organizing, three-dimensional proteinaceous network of the nucleus that coordinates many nuclear processes, including transcription. It is assumed that the nuclear matrix provides a structural base for the spatial and temporal gathering of the participants of transcription by functionally localizing genes and concentrating and positioning gene regulatory proteins in specific nuclear compartments. Transcription factors (HNF-1α, HNF-1β, HNF-1γ, HNF-1δ, HNF-1ε, HNF-1ζ, HNF-1η, HNF-1θ, HNF-1ι, HNF-1κ, HNF-1λ, HNF-1μ, HNF-1ν, HNF-1ξ, HNF-1ο, HNF-1π, HNF-1ρ, HNF-1σ, HNF-1τ, HNF-1υ, HNF-1φ, HNF-1χ, HNF-1ψ, HNF-1ω, HNF-1x, HNF-1y, HNF-1z, HNF-1aa, HNF-1ab, HNF-1ac, HNF-1ad, HNF-1ae, HNF-1af, HNF-1ag, HNF-1ah, HNF-1ai, HNF-1aj, HNF-1ak, HNF-1al, HNF-1am, HNF-1an, HNF-1ao, HNF-1ap, HNF-1aq, HNF-1ar, HNF-1as, HNF-1at, HNF-1au, HNF-1av, HNF-1aw, HNF-1ax, HNF-1ay, HNF-1az, HNF-1ba, HNF-1bb, HNF-1bc, HNF-1bd, HNF-1be, HNF-1bf, HNF-1bg, HNF-1bh, HNF-1bi, HNF-1bj, HNF-1bk, HNF-1bl, HNF-1bm, HNF-1bn, HNF-1bo, HNF-1bp, HNF-1bq, HNF-1br, HNF-1bs, HNF-1bt, HNF-1bu, HNF-1bv, HNF-1bw, HNF-1bx, HNF-1by, HNF-1bz, HNF-1ca, HNF-1cb, HNF-1cc, HNF-1cd, HNF-1ce, HNF-1cf, HNF-1cg, HNF-1ch, HNF-1ci, HNF-1cj, HNF-1ck, HNF-1cl, HNF-1cm, HNF-1cn, HNF-1co, HNF-1cp, HNF-1cq, HNF-1cr, HNF-1cs, HNF-1ct, HNF-1cu, HNF-1cv, HNF-1cw, HNF-1cx, HNF-1cy, HNF-1cz, HNF-1da, HNF-1db, HNF-1dc, HNF-1dd, HNF-1de, HNF-1df, 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are important in the regulation of liver APP gene expression during the APR. were identified on the nuclear matrix. The association of these transcription factors with the nuclear matrix is dynamic. It undergoes changes in a physiological state-related manner, thus reflecting differential gene expression during basal conditions as well as in inflammation. The observed association of *trans-factors* with the nuclear matrix is in correlation with its proposed role in concentrating gene regulatory proteins near their target sites for optimal gene transcription.

Our understanding of the modulations that control the net activity of the whole array of hepatic transcription factors during the APR is still in its infancy, as is our understanding of the mechanisms that specifically control the transcription of a given APP gene. Progress in these fields will pave the way for the improved therapeutic control of the APR that is required in life-threatening situations such as a sepsis associated overproduction of tumor necrosis factor-α and resulting multiple organ failure. Likewise, a better knowledge of the APR-modulated transcriptional events in liver may help one to prevent the pathological events associated with overproduction of a given APP that takes place in some chronic inflammatory diseases.